Materials Research Express

PAPER

Practical evaluations of bioactive peptide-modified Fluorapatite/PLGA multifunctional nano-clustery composite against for root caries restorations to inhibit periodontitis-related pathogens in periodontitis care

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Abstract

Periodontitis noted as dental care disease, which occur the inflammatory process in the teeth tissues surrounding which has the response to bacterial accumulation. The main objectives of the present investigations were to improve the multifunctional nanocomposite with PLGA@fluorapatite and enhance the bactericidal inhibitory efficiency against periodontitis-related pathogens. The peptide modified fluorapatite@PLGA nanocomposite were synthesized and physico-chemically characterized. The observed analytical results demonstrated rod-like nanoparticles formation with favorable human cell compatibility and toxicity against bacterial pathogens. In addition, the use of FA and PLGA dual agents in the composite achieved the greatest reduction in the biofilm growth and the metabolic activity of polysaccharide production. The CFU count in the biofilms was reduced by nearly 3 orders for periodontal pathogens. Therefore, the new modified peptide PLGA-FA composite promising in the root caries restorations to inhibit periodontitis related pathogens.

1. Introduction

Periodontitis is a dental infectious disease linking a connection between the bacterial organism in a subgingival plaque and host immune responses. Though multi-species and single species biofilm formations have been existed in a different kind of infections on the dental implants [1–4]. The teeth surrounded by host mediated soft and hard tissues. This is determined disease with the number of substantial decrease rate in the occurrence of periodontitis in the globe regions in 1991–2010. In the year of 1999, 35% of individuals lesser than 30 years gets the symptoms of periodontitis in the United states [5–8]. The occurrence of periodontal increase furthermore with age. Above 65 age adults with 70% were diagnosed with some form of periodontal disease increase with their age. In the environmental triggers, dental caries and periodontal disease showed complex interaction between resident microorganisms and the host [9–12].

When the dental disease affects due to the host microorganism is out of balance in the composition of individual’s resident oral cavity. Population in aging increase in the word as senior citizen. These people were affected by root caries disease usually having reduced saliva flow due to gingival recession. When the crown caries compared with root caries reactive faster while the cemented has higher solubility than enamel. It’s complicated to root caries to its obscure location in the early stage. Once a cavity was producing in the root area, it’s necessary to filling therapy on the cavity. This root caries treated with composite ceramic restoration (class V) [13–17]. However, it is hard to clean and supply pockets for periodontal bacterial plaque accumulation in the subgingival margins class V restoration treatment. To overcome this treatment will intensify growth of periodontits and improve the loss of the tooth’s addition. But regrettably the presently available resin based on
class V restorative tends to accumulate more biofilms and plaque. Which was verified that bacterial plaque is the initial factor of periodontal, which is affected by biofilms including species of porphyromonas gingivalis (P. gingivalis) and aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans). Microbial resistance is need for the predominant bacterial disease [18–20]. For that purpose to improve novel compounds and approaches for microbial control. Some of the antimicrobial peptides propose significant properties against to conflict microbial pathogens. This antimicrobial peptides in acquisition was vulnerable strains is slower and less common compared with developed against other antimicrobial agents. The outer surface of bacterial membranes was positive charged and capacity to accept an amphipathic structure thought to improve the attraction of peptides for negatively charged phospholipids on it. Cytoplasm targets were affected by the peptide interferes with the membrane integrity. Invertebrates, synthesized antimicrobial peptides were secreted from phagocytic cells and epithelia for it are contributed to natural immunity. By the oral cavity studies, it was occupied with various microorganisms, having wide selection peptides. It plays a significant role in maintain for complex ecological homeostasis [21–23]. For the drug delivery system, need bio compatible and biodegradable peptides and composites. For the past few years, biodegradable material obtained from natural or synthetic organ. Some of them predigested vivo, either enzymatically or non-enzymatically [24, 25]. To fabricate biocompatible, toxicologically safe by products to laminated through normal metabolic pathways. Synthetic polymer includes the relative hydrophobic material such as α-hydroxyacids (PLGA). Complex sugar (hyaluronan, chitosan) and inorganics (hydroxyapatite) were naturally occurring polymers [26, 27].

Recently, various developments in the drug delivery and antibiotics production system, such as including gels, implants, fibers and film forming. These formulation for periodontal pockets to maintained in the scaling process to retain antibiotics for prolonged duration. When approaches with synthetic implants such as nylon fibers, acrylic, ethylcellulose strips were used. It requires removal by surgery, when burst release of active agents was experiential after the direction of films and gels. Polymer with nanoparticles was analyzed as potential substitute active agents for drug delivery, due to their approved safety and biocompatibility. Metallic nanoparticles have the antimicrobial activity against the pathogens. FDA-approved polymers PLGA have established biocompatibility and flexible tuning of physical [28–31]. PLGA and PGA were the copolymer of polyester. These two polymers were the best drug delivery with their respective design, activity and biocompatible nature. The PLG having asymmetric α-carbon. It was described as D or L form in the stereo chemical aspects. But some time it showed as S and R form (24). To prevent the root caries many works have been carried out. Using fluoride solution, tooth paste, fluride gel, varnishes, chlorhexidine solution or varnish. Moreover, these temporary treatments were success depends on the patient’s condition. Coating on tooth roots, with make a bond with adhesives and composite in the cavities. This principle composite used for cavity restoration for their excellent aesthetic and direct filling capability [32–35].

Fluoride was recognized as effective material for control dental caries. In the dental hard tissues, fluoride acts as competent agent to control dental caries through topical effect by inhibiting demineralization in teeth. Compared to daily used self-care products such as tooth paste, mouth wash, deposition of fluoride act as well-established caries protective role. But this agent was unfavorable, due to vital function of saliva makes it difficult to maintain cariostatic concentrations of fluoride in the oral fluids. It leads to suboptimal fluoride regimens particularly in patients at the risk of developing. It showed that the efficiency of fluoride regimen depends on the dosage and ability of the treatment to utilize fluoride activity on demineralization [36–39]. In the commercial market varnishes and fluoridated gels have been introduced to prolong contact time between fluoride and tooth surface. However, for the professional application, intake of excessive fluoride contains high concentration of fluoride leads to risk to the patients. Oral intake of bioadhesive tablets was another form of releasing fluoride. By Applying oral mucosa, leads to local irritation to the patients. For the dental restoration, as prepared composite having fluoride in order to protect against recurrent caries following a restoration. Conveniently, professional intervention and the despite of fluoride reservoirs, insertion of these materials requires limited to patients risk to leads failure in restoration. When in the developed system in microparticles have been studied for controlled delivery of fluoride. For the vitro studies, biocompatible polymeric microparticles used as drug delivery. It reveals that enhances fluoride retention in the oral cavity and promotes its time dependent release to produce different potential oral care products [40–43].

Gel applying was easy to fast drug release rate for the site action, adhere to large area of mucosa in dental pockets. The antibiotic concentration was maintaining, due to their bio-adhesive characteristics. Some of the polymers such as PLGA, chitosan, PLG, were used to prepare the gels. The evaluation of antibacterial activity against porphyromonas gingivlis pathogens showed time plants with 24% PLG showed a better inhibition zone when compared with commercial control drugs. Which was locally delivered antimicrobial drug doxycycline hyclate [16, 44, 45]. The aim of the future work, we plan to modified peptide with Fluoraprite–PLGA composite. Our goal was to improve pervious invitro work to assess the in vivo efficiency and safety using as daily applied formulation product such as mouth wash, gels.
2. Materials and methods

Commercial grade bioactive peptide and the liquid (Fuji II, GC gold label, GC international, Tokyo, Japan) were used for gel preparation. Hydrated calcium nitrate [Ca(NO₃)₂ 4H₂O], diammonium hydrogen phosphate [(NH₄)₂HPO₄], ammonium fluoride (NH₄F), absolute ethanol (C₂H₅OH) and ammonium hydroxide (NH₄OH) were employed. Poly lactic acid, glycerol, Dimethyl sulfoxide, dichloromethane were parched from sigma Aldrich, china. All the chemicals in this research were of analytical grades and applied as obtained from.

2.1. Synthesis of fluorapatite
For first step of solution synthesis, 80 mmol hydrated calcium nitrate (Ca (NO₃)₂4H₂O was dissolved in 50 ml of ethanol in a beaker. For the next process, another part of solution was prepared by using 50 mmol of diammonium hydrogen phosphate [(NH₄)₂HPO₄] taken in a beaker with distilled water to make as 0.5 M solution. Both the solution carried out continues stirring to reach transparency for 2 h. After that the aqueous solution was added drop wise at the rate of 6 ml per minute to alcoholic solution with constant stirring. In the final step 17.1 mmol ammonium fluoride (NH₄F) solution was added to that solution drop wise. The pH of the solution was maintained up to 10 to added ammonium hydroxide as drop wise to the above solution. The solution was stirred at ambient temperature for 1 h. Milky white precipitate was obtained. This settled precipitate were centrifuged and washed with ethanol for five times, dried at 85 °C for 6 h. After that the powder subsequently grinded with pestle mortar. Composite powder was calcinated at 600,700,800 °C at the rate of 1 h intervals. Finally the ratio of the composite as Ca: P: F as 6:4:2 ratios were obtained. It was designated as FA (36).

2.2. Modification on peptide
Peptide was modified by on its surface with PLGA and FA. It was prepared by single one pot emulsion technique. PLGA with 50:50 monomer ratio.100 mg of PLGA was dissolved in 2 ml dichloromethane (DCM) for overnight. On the second day 3 ml of 4% polyvinyl alcohol (PVA) was mixed with 3 ml of 6 mg ml⁻¹ avidin-palmitate. 3 ml of PLGA-DCM solution was added drop wise to the above mixture to overtaxing. The synthesized Fluorapatite powder 10 g was added to 60 ml of PVA for 3 h to evaporate residual DCM. After the evaporation, the FA solution was centrifuged at 13000 rpm at 4 °C. The supernatant was discard and the precipitate. It was resuspended in 10 ml of phosphate buffer saline for about 30 min on a rotator. FA precipitate was washed with 5 ml of distilled H₂O, frozen at 80 °C. Finally modification on peptide was done with FA (37).

2.3. Gel preparation
For preparing gel, commercially available mouth gel was used as control. Gel mixed for three methods, gel with FA powder, Gel with PLGA, Gel with PLGA modified peptide using FA. All the sample was mixed well and blended for 30 min.

2.4. Sample preparation
In vitro method, sample was prepared by 10 healthy adult donors. The saliva was collected from the donors. Who was selected donors, for the past 3 months having dentition without active caries or periopathology, and without the use of antibiotics naturally(38,39).The condition to collect saliva, donor should not brush teeth for 24 h and also abstained from food and drink intake for 2 h prior donating. Stimulated the saliva was collected on paraffin chopping and kept on ice. Same volume of 10 donor saliva was combined. It was diluted in the concentration of sterile glycerol for about 70% and kept at −70 °C. Was the human saliva as microcosm model for the dental plaque. In vitro studies, saliva is ideal for growing dental plaque microcosm biofilm. This method having the advantage of maintain much of the complexity and heterogeneity of dental plaque (40).

2.5. Bacterial growth strain
P.gingivalis (ATCC33277) was grown with in Trypticase soy broth (Difco Laboratories Inc., Livonia, MI, USA) supplemented with 0.4% (w/v) yeast extract, 1 μg ml⁻¹ menadione, and 5 μg ml⁻¹ hemin. The medium was reduced for 24 h under anaerobic conditions (10% CO₂ 10% H₂ and 80% N₂). The P.gingivalis was subsequently in ovulated and grown an aerobically for 48 h at 37 °C(41).

2.6. Dental microcosm biofilm formation and live/dead assay
The collected sample was added with glycol from the stock solution with 1:40 dilution, to growth medium as inoculums. As the growth of bacterial medium contains mucin(type II, porcine, gastric) at the concentration of 3.5 g l⁻¹ bacteriological peptone, 2.0 g l⁻¹ tryptone, 1.0 g l⁻¹ sodium chloride, 0.35 g l⁻¹ potassium chloride;0.2 g l⁻¹ calcium chloride, 0.2 g l⁻¹ cysteine hydrochloride, 0.1 g l⁻¹ hemin, 0.001 g l⁻¹ vitamin K1. Each resin disk was placed into a 24 well plates, 1.5 ml of inoculums was added to each well and incubated at 37°
°C in 6% CO₂ for 8 h. It was transferred to 24 well plates containing fresh medium. After that the disk again transferred in same manner, after 16 h the disk was incubated for 24 h. The mature biofilm on resin shown within 2 days of incubation (42). Bacterial grown biofilms were rinsed with buffer saline (PBS) live or dead stained using the Backlight live or dead viability kit. The green fluorescence shows that the iodide produce with propiodium in the stained dead bacterial disk. This disk was analysis by using randomly chosen field of view photo graphed from disk for each group.

2.7. MTT activity

MTT assay was prepared from 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide. The grown resin disk was transferred into 24 well new plate of MTT assay. It was colorimetric assay, which was measures the enzymatic reduction on MTT, it results yellow tetrazole to formazan. Each well was added with (0.5 mg ml⁻¹ MTT in PBS) and incubated at 37 °Cin 4% CO₂ for 2 h. The reduce bacterial MTT to purple formazan due to metabolically activated. Disk was transferred to new 24 well plates, and 1 ml of DMSO was added to solubilize the formazan crystals. It was mixed gently at room temperature in dark and incubated for 20 min. Then 200 l of DMSO solution from each well was collected and absorbance at 540 nm was measured via microplate reader. A higher absorbance is related to higher formazan concentration, which indicates a higher metabolic activity in the biofilm (39).

2.8. Infection authentication

From the collected oral sample S. gordonii and P. gingivalis colonization were confirmed by the gingival of upper minces 15 cm sterile polyester tipped applicator (Puritan Medical product) after 14 days of last oral infection. Then the sample were added to 10 ml of collected saliva for the streptococcal species enrichment and trypsin case soy broth supplemented with 0.4%(w/v) yeast extract, 1 µg ml⁻¹ mendione, 5 µg ml⁻¹ heminto were selected for P. gingivalis samples incubating at 37 °C for 24 h under anaerobic conditions. The resulting cells shows by PCR using S. gordonii and P. gingivalis specific primers (43).

2.9. Counts for CFU

Each composite were made twenty-four disks. Each bacterial species loaded on six disks. After 2 days of culturing the biofilms were formed as described above. The disk was transferred into vials with 2 ml cysteine peptone water. By scraping and sonication the biofilms were harvested out. The suspension of biofilm were serially diluted, spread on to agar plates and incubated at 37 °C for 48 h at anaerobic condition as per the ATCC standard. After that the number of colonies was counted by colony counter and used with dilution factor to calculate CFC counts (44).

3. Result and discussion

3.1. XRD analysis

Synthesized Fluorapatite x-ray diffraction using Cu Kα1 radiation with a wavelength of 1.55 Å. All the samples were analysis in the 2θ angle range of 20°–60° at a scan rate of 0.05° min⁻¹. The XRD analysis was carried out for both before and after calcinations of fluorapatite. In the figure 1(a) shows the FA nanoparticles was calculated at 500,600,700 °C. In the figure it can be observed the resulting pattern of samples showed amorphous before calcinations. Compared with pure material, it was showed the synthesized nanoparticle after the calcinations at 700 °C were formed in crystalline. In the JCPDS No 03-0736 data matches shows the sharp peak at 22.5 nm matches with (002), (211), (213) plane. Using the Scherrer formula the crystalline structure of the FA was calculated as 22.5 nm as hexagonal structure (45). In the figure 1(b) shows the FA contained composite, after mixing with PLGA. Figure (a) shows commercial gel without adding composite, it does in shows any sharp or strong peaks in the xrd pattern. Were as in figures (b) and (c) shows predominantly sharp peaks related to crystalline apatite structure in the peak between 20° and 45°. There obtained peak results were conformed to previous report (46).

3.2. FTIR analysis

For the FTIR analysis were used with 4000–400 cm⁻¹ at 4 cm⁻¹ resolution after averaging 40 scan to analysis them chemical functional groups of the composite. In the figure 2 shows the FTIR spectra of nano FA particle. The peaks show at 982, 1052 and 1104 cm⁻¹ are due to the phosphate stretching vibration and bands at 475,577,605 cm⁻¹ belongs to bending vibration on phosphate (47). When the formation of FA the peaks at 3570 and 630 cm⁻¹ is disappeared. It reveals that the presence of stretching and bending hydroxyl ion vibration in FA sample. The peak at 753 cm⁻¹ showed that hydroxyl groups in the apatite structure are replaced and saturated with fluoride (46). In the hydroxyapatite, the hydroxyl groups were substituted with fluoride ions. It ravels that
the stretching mode of OH moved to new band that arises from OH...F bond formation. It shows the OH bands were completely removed in FA. It reveals that substantial amount of fluoride ions was replaced with hydroxyl groups.

### 3.3. TEM observations

The morphology of the sample was analysed by transmission electron microscopy. The sample was dispersing with few drops of FA on carbon film supported copper grids. The TEM and SAED pattern of calcinated FA nanoparticle are shown in figures 3 (a) and (b) respectively. The FA nanoparticle shows flower like morphology. The crystalline size of the calcinated FA was analyses by Clemex software. The estimated size of FA nanoparticle is about 32 nm. The SAED pattern conformed the formation of hexagonal FA crystals, which is agreed to XRD
data. The reflection of experimental patterns is attached to appropriate ring positions. Where the determination of powder electron diffraction displays higher intensity: (213), (211) and (210) were shown in the figure 3(b). The reflections are broadened and diffused, due to smaller particle size of FA.

3.4. Biofilm live/dead staining analysis

Figure 4 shows the 2nd day biofilms on commercial mouth gel as control in (figure 4(a)). The saliva collected from the donor was infected by S. gordonii and P. gingivalis. In the top of the biofilm shows, primarily alive few dead bacterial colonies, some were dead colonies at the bottom of the film due to less nutrition compared with FA potential limitation to deposit salivary proteins on the surface could decrease the efficacy of the contact inhibition. Thus, it reduces the antibacterial efficiency (49). Beside the root surface coating method prevent caries to apply gel, can potentially use to bond restoration in tooth cavity. The gel with PLGA, FA, modified peptide PLGA-FA has succeeded to protein repellant, antibacterial, demineralization capabilities without compromising the dentin bond strength. The biofilm formation produces acid and enzymes to cause tooth decay. The gel with modified peptide FA has the prospective to inhibit secondary caries. When the tooth decay is
removed, it is usually not possible to completely remove all the bacteria in the cavity. Therefore, as prepared tooth cavity need more carious tissues with residual could be left over. Uncured prime with the gel composition has direct contact with the tooth structure and flow into dentinal tubules to kill the residual bacteria. It was noticeable in the vitro study without the complications of oral environment such as saliva flow, food debris and wears in vivo. For the benefits to the patients in vivo studies, precaution has been taking care.

The 2-day of CFU counts of biofilms on composites are plotted in figure 5. Every species has dissimilar CFU on the control composites, a few having close to $10^{10}$ CFU/disk, were some with less than $10^6$ CFU/disk. The commercial composite and the investigational composite control had similar CFU (p > 0.2) for each species. Adding FA or PLGA unaccompanied into the composite decreased the CFU (p > 0.06). The composite with dual agents, 4%FA + PLGA, reduced the CFU of different species differently, few may slightly < 4log and the other by > 4log. The CFU of S.gordonii, P.gingivalis on biofilms of modified peptide PLGA-FA were reduced to 0.007%, 0.008%, 0.009% and 0.013% respectively, of the respective CFU on control commercial gel. The metabolic activity of commercial gel and the FA, PLGA had similar value (p > 0.1) shows in figure 6. When the incorporation PLGA and FA alone shows reduced metabolic activity of the biofilm compared to control. In the case of modified peptide PLGA-FA had the least metabolic activity of biofilms for these two S.gordonii and P. gingivalis periodontal pathogens (p < 0.04). The figure 7 results shows that the commercial gel and the FA, PLGA alone had similar polysaccharide amounts (p > 0.1) for the modified peptide PLGA-FA was much less than control sample (p < 0.04). These results showed that modified peptide PLGA-FA have the potential to inhibition on periodontal pathogens and their synthesis of extracellular matrix.

An advanced nanotechnological strategies for the treatment of root caries in periodontitis care could be signified by the effective drug delivery approaches and direct delivery of drug and anti-bacterial compounds into the periodontal pocket through facile nanof ormulation. To attain such outcome, biocompatible polymeric formulation with nanof illers could represent as an exciting drug-vehicle. The drug delivery of these nano-formul ated materials have depended on the their size, structures, biodegradation ability and importantly not affected to the therapeutic efficiency of drug and anti-bacterial components. In this present research report, the study was designed for the optimization of novel material formulation to enhance anti-bacterial activity with the components of biocompatible PLA polymeric materials with anti-microbial peptide and dental favored fluorapatite, which was successfully synthesized and applied for the root caries for the first time. This novel strategy and obtained results are clearly established presence of AMP into the PLA polymeric matrix with fluorapatite nanof illers composited form provided improved anti-bacterial efficacy. The anti-bacterial actions of AMP presented composites was already well-known factor and reported in previous studies [46-47]. As previous reports, PLA polymeric nanoparticles have efficient cellular uptake capability and degradation behaviors than its larger polymeric formulations. Besides, PLA polymer has been approved by FDA for numerous applications, due to its biocompatibility with degradable nature under physiological atmosphere.
Generally, degradation rate of the polymers has greatly depended on their hydrophilicity. In the preparation of PLGA polymeric material, lactic acid is more hydrophobic nature than other component of glycolic acid, hence usually PLGA prepared with more lactide-group would be have slower degradation. In this research work, we have used 50:50 PLGA for the drug delivery vehicle, so presented material would have controlled degradation ability and highly suitable for the in vivo treatment, which is a required satisfaction to the treated patients [48].

In addition, the ability of strong adhesion onto the dental surface by prepared drug vehicle is an important factor and major significances in the root caries restoration therapies. In the current investigation, fluorapatite loaded PLGA formulation have greater aptitude to adhere onto the dental surface, due to the effective nanoformulation, appropriate nano-size of the fillers, significantly connected to the enhanced adhesion ability. On the other hand, improving biocompatibility of the prepared composite without conciliatory anti-microbial activity is a major challenge and illogicality in this work. Anti-microbial peptide is an admirable anti-bacterial agent with no

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**Figure 6.** The 2 day metabolic activity of biofilms are plotted for (a) commercial gel (control) (b) gel with PLGA (c) gel with FA (d) gel with modified peptide PLGA-FA (mean ± SD; n = 5) against S. gordonii and P. gingivalis.

**Figure 7.** Shows the production of polysaccharide by biofilms on composites is plotted. (a) Commercial gel (control) (b) gel with PLGA (c) gel with FA (d) gel with modified peptide PLGA-FA (mean ± SD; n = 5) against S. gordonii and P. gingivalis.

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toxicity to normal cells. Similarly, many researchers have proved and reported in literatures about the antibacterial activity of AMP, which provided great inhibitions of various bacterial cells growth in the absence of peptide-resistant mutants growth [49, 50].

4. Conclusions

In this study to evaluate peptide modified with fluoroapatite-PLGA nanocomposite was successfully synthesized against the root caries restorations to inhibit periodontitis pathogens. The composite with 4% modified peptide PLGA-FA exhibits a strong antibacterial capability. In addition, the use of FA and PLGA dual agents in the composite achieved the greatest reduction in the biofilm growth and the metabolic activity of polysaccharide production. The CFU count in the biofilms was reduced by nearly 3 orders for periodontal pathogens. Therefore, the new modified peptide PLGA-FA composite promising in the root caries restorations to inhibit periodontitis related pathogens.

Acknowledgments

All co-author gratefully acknowledging corresponding authors for their support during this research investigation. Thank you

Data availability statement

No new data were created or analysed in this study.

Conflict of Interest

None

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