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Preparation of fluoride substituted apatite cements as the building blocks for tooth enamel restoration

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ABSTRACT

Fluoride substituted apatite cement (fs-AC) was synthesized by using the cement powders of tetracalcium phosphate (TTCP) and sodium fluoride (NaF), and the cement powders were mixed with diluted phosphoric acid (H_3PO_4) as cement liquid to form fs-AC paste. The fs-AC paste could be directly filled into the carious cavities to repair damaged dental enamel. The results indicated that the fs-AC paste was changed into fluorapatite crystals with the atom molar ratio for calcium to phosphorus of 1.66 and the F ion amount of 3 wt% after self-hardening for 2 days. The solubility of fs-AC in Tris–HCl solution (pH 6) was slightly lower than hydroxyapatite cement (HAC) that was similar to the apatite in enamel, indicating the fs-AC was much insensitive to the weakly acidic solution than the apatite in enamel. The fs-AC was tightly combined with the enamel surface because of the chemical reaction between the fs-AC and the apatite in enamel after the caries cavities was filled with fs-AC. The extracts of fs-AC caused no cytotoxicity on L929 cells, which satisfied the relevant criterion on dental biomaterials, revealing good cytocompatibility. The fs-AC had potential prospect for the reconstitution of carious lesion of dental enamel.

1. Introduction

Dental caries is a prevalent chronic and world-wide oral disease [1]. As a non-living tissue, the main composition of mature enamel is inorganic apatite so dental enamel is scarcely self-repaired by living organisms after substantial mineral loss [2]. Traditional clinical practice has recommended complete removal of softened and discolored dentin (demineralized carious dentin) to eliminate infected tissue and create a hard foundation to support a proposed restoration such as composite resin or metal alloys, which result in poor adhesion between the repair materials and enamel at the interface during the restoration, and this technique is far from ideal, because excessive sound dentin is removed [3–5]. Obviously, reconstitution of carious dentin is a more desirable clinical approach than the traditional clinical practice. It has been proved that fluoride could not only improve the acid resistance of apatite crystals effectively (a certain concentration) but also inhibit metabolism of bacterial [6]. Yamagishi et al. reported a paste of fluoridated hydroxyapatite that could be used to repair early carious lesion, and the apatite paste could be bond to the surfaces of the dental enamel [7]. However, this method may limit its application in the restoration of badly carious lesion of dental enamel, such as carious cavities.

Hydroxyapatite biomaterials are promising candidates for reconstruction of calcified tissue, such as human tooth and bone, because they are the main inorganic components of dentin and bone minerals [8]. However, the native structure of enamel is too complex to be remodeled, and the synthesized apatite biomaterials (such as bioceramics) often have different from the natural ones [9]. The human tooth is protected by enamel that is composed of apatite crystals, acid-forming bacteria cause microscopic damage to the enamel, creating carious cavities, which cannot be repaired by the restorative materials (such as amalgam, ceramics, or polymer composites) because these materials without viscidity do not adhere (bond) perfectly to the enamel surfaces owing to the differences in chemical composition and crystal structure [10]. In order to further restoration of badly carious lesion of dental enamel, such as carious cavities, in this study, a paste of fluoride substituted apatite cement (fs-AC) with good viscosity was synthesized, and the fs-AC pastes could be directly filled into the carious cavities and adhered with dental enamel surfaces to repair the damaged enamel.

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2. Materials and methods

2.1. Preparation and characterization of fs-AC

The fluoride substituted apatite cement consisted of the cement powders and cement liquid. The cement powders were composed of tetracalcium phosphate ($Ca_4(PO_4)_2O$, TTCP) and sodium fluoride (NaF), and cement liquid was diluted phosphoric acid (H_3PO_4) with the concentration of 17% (v/v). TTCP was synthesized by a solid-to-solid reaction between calcium phosphate and calcium carbonate at a temperature of 1500 °C for 8 h. The TTCP was grounded in a planetary ball mill for 1 h, followed by sieving through 120 meshes to obtain TTCP powders [11].

The fs-AC with self-hardening (self-setting) property was prepared by mixing the cement powders (5 g TTCP + 0.46 g NaF) with cement liquid (3.2 mL diluted H_3PO_4) to form a cement paste. The fs-AC paste was placed into stainless steel molds with the size of Ø10 mm × 2 mm. After stored in beakers in a constant temperature oven at 37 °C and 100% relative humidity (r.h.) for 2 days, the pre-hardened fs-AC solid mass sample was obtained. We prepared hydroxyapatite cement (HAC) (as a control), which contained tetracalcium phosphate as cement powder and diluted phosphoric acid (17% H_3PO_4) as cement liquid without sodium fluoride. The HAC was prepared by mixing the cement powder with liquid to form cement paste, and the following process was similar to the preparation of fs-AC.

In order to confirm that the F ion entered into the apatite crystal lattice while did not adsorb on the surfaces of apatite cement, the experiments were done as follows: the pre-hardened fs-AC and HAC samples were grounded into powers, respectively. The power samples were then immersed in deionized water for 24 h and the water was changed one time at 12 h. Finally, these samples were dried at 120 °C for 24 h to obtain fs-AC and HAC power samples, which were characterized by X-ray diffraction (XRD; Rigaku Co., Japan), and Fourier transform-infrared spectroscopy (FT-IR; Magna-IR 550, Nicolet, American).

2.2. Solubility of fs-AC

The solubility of the fs-AC was characterized by the weight loss ratio (wt%) in Tris–HCl solution at different time, and the hydroxyapatite cement (HAC) was used as a control. After setting for 2 days and dried at 50 °C for 24 h, the fs-AC and HAC samples (Ø10 mm × 2 mm) with initial weight (W_i), were put in 400 mL of Tris–HCl solution (pH 6, adjusted by diluted HCl) with a weight-to-volume ratio of 0.5 g/mL. The solution was continuously shaken in a water bath at 37 °C. At different time, the fs-AC and HAC samples were removed from the Tris–HCl solution, cleaned with water, dried at 50 °C for 24 h and its new weight (W_t) was recorded. It was then re-immersed into a fresh Tris–HCl solution at the same weight-to-volume ratio followed by continuous shaking. The weight loss ratio of the fs-AC and HAC samples at different time was calculated. Three samples of each kind of cement were tested and the average value was recorded.

2.3. Cytotoxicity of fs-AC

L929 cells were used to test the cytotoxicity of the fs-AC, which was carried out by using the fs-AC extracts in contact with L929 cells according to International Standard Organization (ISO/EN 10993-5), and hydroxyapatite cement (HAC) was used as a control. To prepare the fs-AC extracts, a stock solution of 200 mg/mL was first prepared by adding 5 g fs-AC (after setting for 2 days and dried at 50 °C for 24 h) into DMEM culture medium. After incubation at 37 °C for 24 h, the mixture was centrifuged and the supernatant was collected. Subsequently, the extracts were sterilized by filtration through 0.2 μm filter membranes for cell cultured experiments.

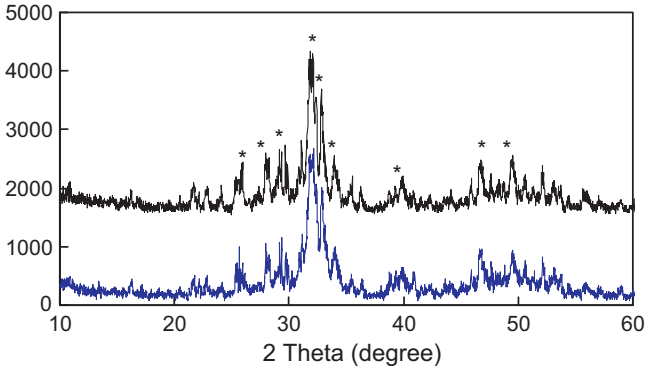

Fig. 1. XRD of fs-AC (a) and HAC (a) after hardening for 2 days, * represents apatite.

The cells were seeded on a 96-well plate and incubated for 24 h. Then, the culture medium was removed and replaced by 50 μL of extracts and 50 μL of DMEM medium supplemented with 10% FCS. The DMEM with 10% FCS (without extract supplement) was used as a blank control. After incubation for 24 h, MTT test was carried out to test cell viability. In brief, 100 mL of 0.5 mg/mL 3-(4,5)-dimethylthiahiazo (-z-y1)-3,5-dipheny-tetrazoliumromide (MTT) solution was added into each well. After additional incubation for 4 h, dimethyl sulfoxide (DMSO) was added to stop the reaction between MTT and cells. The optical density (OD) was measured by a microplate reader at the wavelength of 492 nm.

2.4. Restoration of enamel carious cavities

Human teeth with big enamel carious cavities were degreased with absolute ethanol, and etched with 17% phosphoric acid for about 30 min. The fs-AC pastes were filled into the enamel carious cavities immediately before the phosphoric acid solution dried. After the tooth samples with enamel carious cavities were filled with the fs-AC pastes, the as-prepared tooth samples were stored in beakers in a constant temperature oven at 37 °C and 100% relative humidity (r.h.) for 2 days. The tooth samples with fs-AC repair the enamel carious cavities were sectioned perpendicular to the dental crown using a diamond saw, and interface between the enamel and fs-AC was examined by using scanning electron microscope (SEM, JSM-6360LV, JEOL). The surface morphology and microstructure of the fs-AC filled into the dental enamel carious cavities were also examined with SEM.

3. Results

3.1. XRD analysis

The phase compositions and crystal structure of the hardened fs-AC and HAC were characterized by powder XRD as shown in Fig. 1. It can be seen that the diffraction peaks of the two samples at $2\theta = 25.7°, 28°, 29°, 31.8°, 32.4°, 33.5°, 39°, 46.8°, 49.5°$ and $52.6°$ were ascribed to apatite both in Fig. 1a and b. Clearly, all of the peaks can be readily indexed to a pure hexagonal phase, which was in accordance with apatite structure. The XRD results indicated that the hardened fs-AC and HAC were all apatite structure. The presence of HAC could be attributed to the chemical reactions as follows [12]:

$$5Ca_4(PO_4)_2O + 2H_3PO_4 \rightarrow 2Ca_{10}(PO_4)_6(OH)_2 \quad (HA)$$

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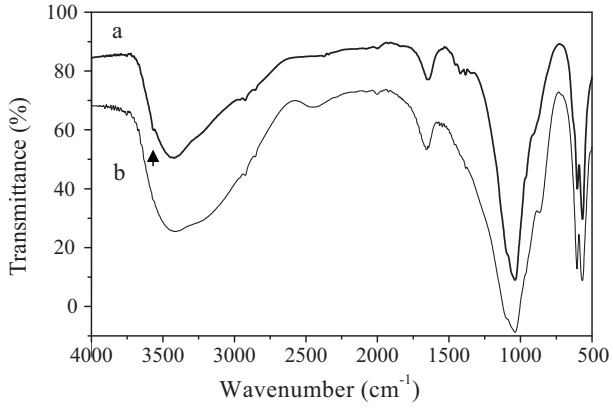

Fig. 2. IR of fs-AC (a) and HAC (b) after hardening for 2 days.

The presence of fs-AC could be attributed to the chemical reactions as follows:

$$5Ca_4(PO_4)_2O + 2H_3PO_4 + 4NaF \rightarrow 2Ca_{10}(PO_4)_6F_2 \quad (FA)$$

3.2. IR analysis

Fig. 2 shows the IR analysis of the hardened fs-AC and HAC. The absorption bands at 1071 and 950 cm^{-1} were ascribed to PO_4^{3-}. The two peaks at 1431 and 1750 cm^{-1} and the broad band from 2800 to 3750 cm^{-1} were attributed to the absorbed water. The band at 876 cm^{-1} might correspond to the vibration of P–O–H from PO_4.

The OH-specific peaks were found at around 3571 cm^{-1} and 632 cm^{-1} in Fig. 2a, revealing that the HAC was hydroxyapatite (HA). However, it was found that no OH-specific peaks appeared at around 3571 cm^{-1} and 632 cm^{-1} in Fig. 2b, indicating that no HA present in the finally hardened product of fs-AC because –OH group was replaced by F group to form FA ($Ca_{10}(PO_4)_6F_2$). The results of the IR analysis were in accordance with the XRD of the fs-AC.

3.3. Elemental composition

The chemical elemental composition of the fs-AC was further characterized by EDS. The EDS spectrum (Fig. 3) shows that the fs-AC contained Ca, P and F elements. Furthermore, the EDS results reveal that the fs-AC had an average Ca/P ratio of 1.66, which was closely similar to that of HA (Ca/P = 1.67). The amount of F ions in fs-AC was 3 wt%, which was almost similar to that of F ion in fluorapatite. Combined with the results of XRD, IR and EDS analysis,

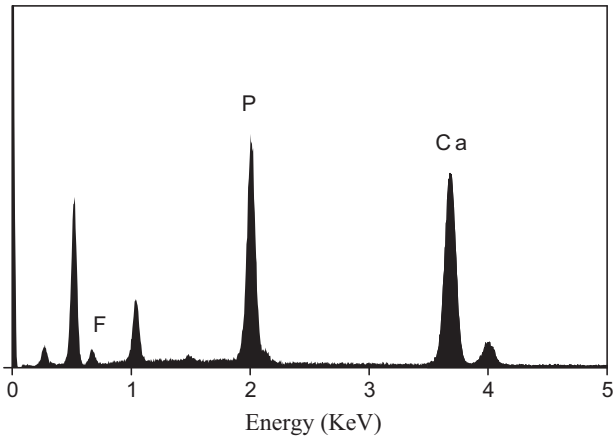

Fig. 3. EDS of the fs-AC after hardening for 2 days.

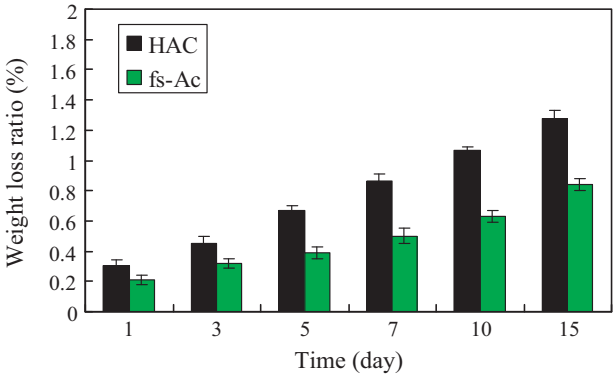

Fig. 4. Weight loss ratios of fs-AC and HAC after immersing in Tris–HCl solution over time.

it could be suggested that the produced fluoridated apatite cement was fluorapatite (FA).

3.4. Solubility in Tris–HCl solution

The solubility of the fs-AC and HAC samples in Tris–HCl solution was characterized by their weight loss ratio after immersing into the solution. Fig. 4 shows the weight loss ratio of the fs-AC and HAC immersing in the acidic Tris–HCl solutions (pH 6) for various time periods. It was found that the weight loss ratio of the fs-AC was slightly lower than HAC throughout the soaking. The weight loss ratio of the fs-AC was 0.84 wt% while HAC was around 1.28 wt% by the end of the experiment, indicating the solubility of fs-AC was slightly lower than the HAC. The results suggested that the fs-AC was much insensitive to the acidic solutions than that of HAC.

After self-hardening for 2 days, the fs-AC was changed into fluorapatite and HAC was changed into hydroxyapatite, respectively. Hydroxyapatite bioceramic and hydroxyapatite cement were biocompatibility and have been used for bone repair in clinic for many years, and hydroxyapatite is the main composition of dental enamel. In this experiment, we want to testify that the fs-AC with 3 wt% F had lower solubility and was much insensitive to the weakly acidic solutions than HAC (as a control) because previous study showed that fluoride can improve the acid resistance of apatite effectively.

3.5. Cytotoxicity

The effects of the fs-AC extracts on L929 cells cultured for 24 h are shown in Fig. 5. It can be seen that there was no obvious differences for optical density (OD) value between the fs-AC and HAC (OD represents cell viability). HAC with excellent biocompatibility has been applied as bone cement in clinic for many years. More-

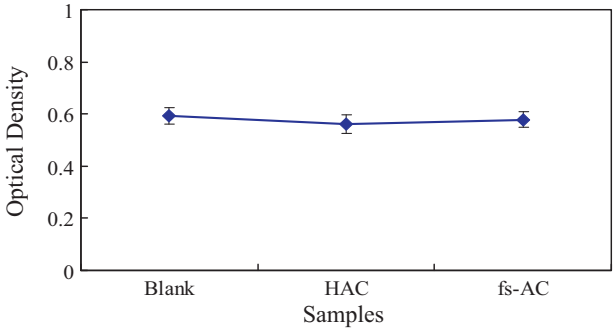

Fig. 5. Effects of the fs-AC extracts on L929 cells cultured for 24 h. The experimental group compared with the blank and HAC control group.

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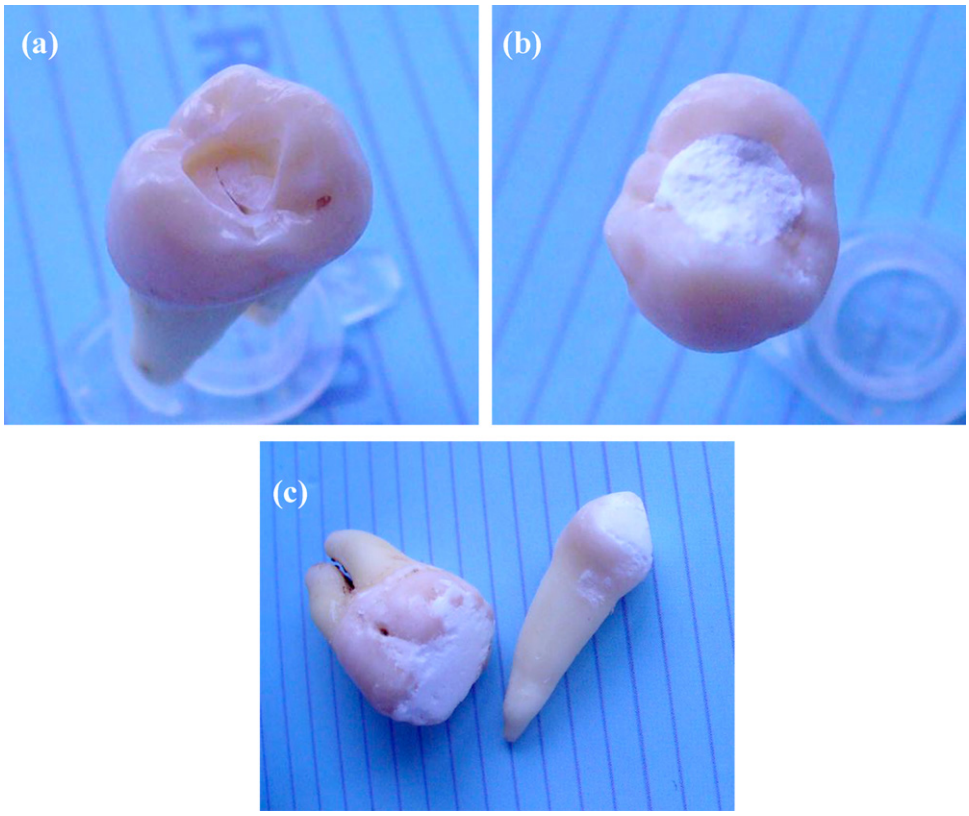

Fig. 6. Photos of the human dental enamel carious cavities before (a) and after (b and c) filled with fs-AC.

over, no significant differences for OD value were found between the fs-AC and blank control. The results suggested that the extracts of fs-AC caused no cytotoxicity on L929 cells, indicating fs-AC had good cytocompatibility.

3.6. Restoration of enamel carious cavities

Fig. 6 shows the photos of the human tooth enamel carious cavities filled with the fs-AC. It was found that the tooth enamel carious cavities were repair by the fs-AC. Fig. 7 exhibits the distinct interface morphologies of the dense fs-AC and enamel by SEM. The SEM images (under different magnifications) showed the transversely section of the fs-AC applied to the enamel carious cavity. The microstructure of the restored enamel revealed no obvious structural gap at the interface between the fs-AC and the enamel region. This showed that the newly-form fs-AC had properly integrated with the tooth enamel.

The surface morphology and microstructure of fs-AC filled into the enamel carious cavities after self-hardening for 2 days were examined by SEM as shown in Fig. 8. It can be seen that the SEM image of the fs-AC layer on the enamel surface, which contained conspicuously elongated apatite crystals that had grown on the tooth enamel surface. The homogeneous rod-like crystals had a typical apatite hexagonal cross section of approximately 400 nm in length and 50 nm in diameter.

4. Discussions

The restoration of the carious cavities of dental enamel by using synthetic apatite was always suggested in dental research [13]. However, the native structure of dental enamel is too complex to be remodeled, and the synthesized apatite crystallites often have different from the natural ones, which result in poor adhesion between the synthetic apatite and enamel at the interface during the restoration [14]. In order to further repair badly

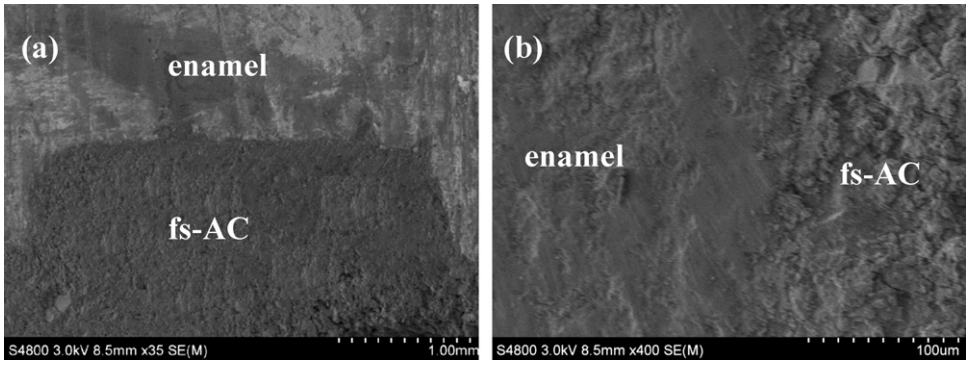

Fig. 7. SEM images of the transversely section of the fs-AC applied to the human tooth enamel carious cavities under different magnifications: (a) 35× and (b) 400×.

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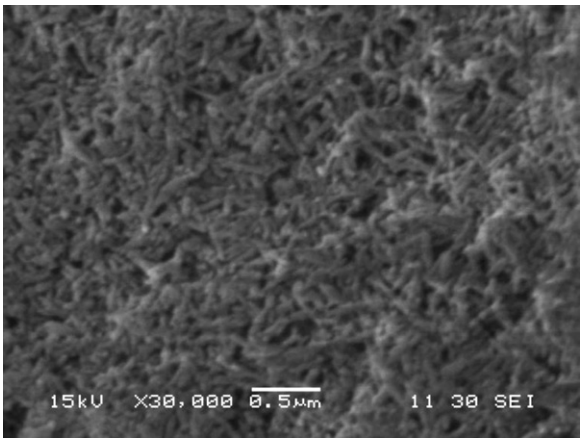

Fig. 8. SEM images of the surface morphology/microstructure of fs-AC on the enamel surfaces after hardening for 2 days.

carious lesion of dental enamel (carious cavities), a paste of fluoride substituted apatite cement (fs-AC) was synthesized in this study. The fs-AC paste could be directly filled into the carious cavities to restore damaged enamel. It was found that the fs-AC crystals could be formed on the surface of human teeth with tight contact to the enamel (fs-AC closely bond to the enamel apatite). According to the analysis of XRD, IR and EDS, the results indicated that the fs-AC was finally changed into fluorapatite (FA), which had a Ca/P ratio of 1.66 and the F ion amounts of 3 wt%. The mixed powders of TTCP (basic) reacted with phosphoric acid solution (acidic) to form cement paste that first changed into hydroxyapatite (acidic–basic neutralization reaction), then, hydroxyapatite reacted with sodium fluoride to form fluorapatite.

The carious cavities of dental enamel could be repaired by the self-hardening fs-AC because the restorative material was cement and could adhere perfectly to the enamel surfaces owing to the similarity of fs-AC in chemical composition and crystal structure to enamel apatite [15]. In our study, it was found that the fs-AC could be completely filled the porous residual carious dentin. This recovery was caused not only by cement penetration, but also by some chemical reactions between the residual structure (enamel apatite) and the fs-AC (fluorapatite). With this chemical reaction, the fs-AC would adhere perfectly to the enamel surface and repair the enamel carious cavities.

In this study, the results showed the fs-AC was firmly bonded to the surface of the dental enamel because the carious cavities of enamel surfaces etched with 17% phosphoric acid would cause the solution of the apatite in enamel layer. When the fs-AC paste applied on the enamel surface, the fs-AC surface was also partially dissolved, which was conglutinated with enamel surfaces. This means that the fs-AC would chemically reacted with enamel apatite, but this chemical reactions were incomplete, only occurred at the interface between the fs-AC and the enamel surface. Therefore, the results demonstrated that the fs-AC was tightly combined with the enamel surface, and the microstructure of the restored enamel revealed no obvious structural gap at the interface between the fs-AC and the enamel region.

Although dental enamel is not a living part but it has a close chemical structure to apatite, this hard tissue is biologically constructed by living organisms with well-organized structures [16]. The chemical similarity of the apatite for both fs-AC and enamel would ensure the restoration of enamel defects, since it was too complicated to remodel the functions of living organism to induce new enamel apatite on a non-living surface [17]. The fs-AC approximate to the basic building blocks of enamel may be a candidate since the in vitro biomimetic construction of enamel by using fluorapatite had already been achieved [18]. It has been suggested that the fluorapatite was analogous to the subunits of biological apatite [19]. Therefore, the repair of carious cavities of dental enamel could be improved by using the fs-AC.

The human tooth is protected by dental enamel consisting of apatite. Acid-forming bacteria will cause damage to the enamel, creating cavities in the enamel [20,21]. In this study, the solubility of the pre-hardened fs-AC in acidic environment (pH 6) was characterized by using Tris–HCl solution with the extended experimental periods, and the results were expressed as the weight loss ratio of the fs-AC and HAC with time in the acidic solutions. The results revealed that the weight loss ratio of the fs-AC of 0.84 wt% while the HAC was about 1.28 wt% after soaking in Tris–HCl solution for 15 days. The weight loss ratio of the fs-AC was slightly lower than HAC, indicating the fs-AC was much insensitive to the weakly acidic solutions than HAC, which is an apatite similar to enamel apatite. It can be suggested that the underlying enamel surface would be well protected after repaired by the cement since the fs-AC was insensitive to the weakly acidic condition. The results are in accord with previous study that fluoride can improve the acid resistance of apatite crystals effectively [6].

As dental biomaterials for repair the enamel carious cavity, the biocompatibility and biosecurity of the fs-AC are very important. In this study, the cytotoxicity of the fs-AC was determined by using the extracts of the pre-hardened fs-AC co-cultured with L929 cells for 24 h according to the standard from ISO. The results suggested that the extracts of the fs-AC caused no cytotoxicity on L929 cells, indicating the fs-AC had good cytocompatibility, and could be satisfied with the relevant criterion on dental biomaterials.

5. Conclusions

Fluoride substituted apatite cement (fs-AC) was developed to repair the dental enamel carious lesion by filling directly into enamel carious cavity. The result showed that the pre-hardened fs-AC was fluorapatite (FA) with the Ca/P of 1.66 and the F ion amounts of 3 wt%. The fs-AC was tightly combined with the enamel surface because of the chemical reaction between the fs-AC and enamel apatite after the cement filled into the caries cavity of dental enamel. The less soluble fluorapatite cement filling into enamel carious cavity should offer considerable protection against caries since the cement was much insensitive to the weakly acidic solutions. This study confirmed the possibility of applying the fs-AC pastes to directly repair badly carious lesion of the damaged dental enamel, and the fs-AC with good biocompatibility could be used as a substitute for the conventional dental restorative materials. This strategy may have prospective applications in dentistry as it offers an easy but effective method to reconstruct tooth enamel defects that are suffering from mineral loss.

Acknowledgements

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