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Novel calcium encapsulated mesocellular siliceous foams for crystal growth in dentinal tubules

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ABSTRACT

Objectives: The aim of this study was to investigate the novel mesocellular siliceous foams (MCF) containing $CaCO_3$ nanoparticles (denoted as CMCF) combined with phosphoric acid could occlude dentinal tubules through the formation of biomimetic crystal barrier.

Methods: Ultrastructures of MCF and CMCF were examined by transmission electron microscopy (TEM). Elemental components were analyzed with energy dispersive X-ray spectrometry (EDX). CMCF was mixed with distilled water, 10%, 20% and 30% phosphoric acid then applied on dentine discs. Crystals were characterized by X-ray powder diffractometry (XRD). The sealing efficacy of the dentinal tubules was examined by scanning electron microscopy.

Results: TEM images showed MCF presented a pore size of approximately 30.0 nm and CMCF contained abundant nano-$CaCO_3$. Sealing efficacy showed that CMCF, when reacted with 30% phosphoric acid, would form crystals in the dentinal tubules to a depth of 83.2 ± 17.6 μm at an occlusion percentage of 75.6 ± 12.8% on average; both occlusion percentage and depth were higher than those obtained with 10% or 20% phosphoric acid ($p < 0.05$). The results of XRD and EDS indicated that the crystal growth in the dentinal tubules could be transformed into the biomimetic crystals.

Conclusion: This study showed that the CMCF with 30% phosphoric acid could effectively occlude the dentinal tubules through the formation of biomimetic crystal barrier.

Clinical significance: The novel CMCF combined with phosphoric acid may have potential for the treatment of dentine hypersensitivity.

1. Introduction

Teeth exhibiting symptoms of dentine hypersensitivity have open (patent) tubules at the dentine surface that extend to the pulp, where a neural response is triggered via a hydrodynamic mechanism [1,2]. Dentine hypersensitivity can be defined as a short, sharp pain arising from exposed dentine by the loss of enamel or cementum due to erosion, wear/attrition, tooth fracture, cervical abrasion, or periodontal diseases [3]. According to the hydrodynamic theory, when fluid flow within dentinal tubules is altered by stimuli (i.e., air-blow, thermal, tactile, osmotic, evaporation, or chemical), the fluid movement causes the deformation of nerve endings at the Raschkow plexus, which leads to stimulus transmission and causes dentine hypersensitivity [2]. The alternations in the dentinal fluid flow and pulp hemodynamics may be responsible for the variations in dentine hypersensitivity that occur over time [3]. In addition, an increased number and width of patent dentinal tubules may increase the severity of dentine hypersensitivity [4–6]. Evidence suggests that patients suffering the painful symptoms of dentine hypersensitivity may decrease their quality of life by altering their diet and even reducing social contact [7,8].

It is now widely recognized that the reduction in dentine permeability achieved by the occlusion of tubules could be effective for treating dentine hypersensitivity [9–11]. Examples of current dentinal tubule occlusion treatment include the use of strontium chloride [12], iontophoresis/sodium fluoride [13,14], potassium nitrate, potassium oxalate [15], glass-ionomer cement, dentine bonding agents [14], and laser treatment [16]. Although exposed dentinal tubules can be sealed or occluded, which subsequently reduces dentinal permeation and demineralization, such effects are short-lived as the forming materials are not constituents of natural dentine [17]. Some researches focused on

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the use of bioactive glass for treating exposed dentine promoted by phosphoric acid or CO_2 laser [18,19]. They produced biomimetic crystals (i.e. DCPD, $CaHPO_4{\cdot}2H_2O$ or DCPA, $CaHPO_4$) on dentine surfaces. However, the crystal depth in dentinal tubules was not addressed. In addition, the use of CO_2 laser may cause the damage of dentine structure [20]. Recently, a number of home-use dental care commercial products claim to occlude exposed and open dentinal tubules [21–23]. Regardless of whether the occlusion agents are provided in-office or as home care products, currently available agents cannot withstand the stresses of the oral environment and thus degrade over time [24,25]. It is desirable to develop biomaterials that are capable of more effective and longer-lasting dentinal tubule occlusion [3,26]. Our previous studies have shown that sol-gel dicalcium phosphate bioglass (DP-bioglass) mixed with 30% phosphoric acid can produce monocalcium phosphate monohydrate (MCPM, $Ca(H_2PO_4)_2{\cdot}H_2O$) to occlude dentinal tubules to a depth of 60 μm [27,28]. Although the biocompatibility of the sol-gel DP-bioglass paste was highly beneficial [29], the long reaction time and low occlusion percentage may limit the practicality of sol-gel DP-bioglass and could compromise clinical outcomes.

In this study, we reported the synthesis of mesocellular siliceous foams (MCF) with $CaCO_3$ nanoparticles encapsulated, denoted as CMCF. The MCF acted as a Ca^{2+} carrier and reservoir. The addition of phosphoric acid resulted in the formation of CMCF-phosphate (CMCF-P) and created a supersaturated environment of calcium and phosphate ions on the exposed dentine surface.

The aim of this study was to investigate the ability of CMCF-P to occlude dentinal tubules. The null hypotheses tested are as follows: (1) No precipitation or crystal formation is formed in dentinal tubules after application of CMCF-P on dentine surface. (2) The CMCF-P does not occlude the dentinal tubules.

2. Materials and methods

2.1. Synthesis of CMCF (manufacturer's detail)

A Ca-SiO_2 nanocomposite with a Ca/Si molar ratio of 1/1 was synthesized via the following impregnation process. First, 0.5 g of calcined mesocelluar siliceous foams was mixed with an aqueous solution of 0.84 g of $CaCO_3$ and 0.1 g of oxalic acid; the mixture was then dried at 100 °C. The obtained powder was calcined at 400 °C to form CMCF. Briefly, calcined mesocellular siliceous foams were manufactured as follows. A surfactant solution (1.4 g of P123 ($EO_{20}PO_{70}EO_{20}$) (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany) in 50.0 g of water) was added to 4.0 g of toluene at 40 °C and stirred to form an oil/water (*o/w*) emulsion. An acidified sodium silicate solution was prepared by dissolving 5.5 g of sodium silicate in 300.0 g of water at 40 °C. The *o/w* emulsion was added to the silicate solution after the pH value was adjusted to 5.0. The obtained gel solution was hydrothermally treated at 100 °C for 24 h. The product was calcined in air at 560 °C for 8 h to form the MCF.

2.2. SEM, TEM and XRD examination

The ultrastructural features of the MCF and CMCF were examined under a transmission electron microscope (TEM, Hitachi, Model H-7100, Tokyo, Japan). Energy dispersive X-ray spectroscopy analysis (EDX) was carried out with a Phoenix EDAX X-ray analyzer (EDX, 100-nm resolution, Model Phoenix, EDAX Inc., Mahwah, NJ, USA) attached to the TEM for determination of the Ca/Si ratio in the CMCF. The CMCF powder was then mixed with distilled water, 10%, 20%, or 30% phosphoric acid at a powder-liquid mixing ratio of 0.06 g / 0.18 mL to form the CMCF-W or CMCF-phosphate (CMCF-P). CMCF-P_{10} refers to a sample of CMCF reacted with 10% phosphoric acid; CMCF-P_{20} refers to CMCF reacted with 20% phosphoric acid; CMCF-P_{30} refers to CMCF reacted with 30% phosphoric acid. In addition, CMCF-W refers to CMCF reacted with distilled water.

The CMCF produced with various phosphoric acid concentrations were examined with a scanning electron microscope (SEM, 15 Kv, Topcon ABT-60, Tokyo, Japan) equipped with the analySiSR 3.0 imaging system (Soft Imaging System, Munster, Germany). The crystal phases of CMCF-P and CMCF-W were characterized using an X-ray powder diffractometer (XRD, Rigaku Denki Co. Ltd, Tokyo, Japan) with CuKα radiation and a Ni filter. The scanning range was set to $2\theta = 10^{\circ}$–60° with a scanning speed of 4°/min. The acceleration voltage was 30 kV, and the current was 20 mA. The relative amounts of the different phases were determined from the relative intensities of the characteristic diffraction peaks of each phase.

2.3. Sealing efficacy in dentinal tubules

With NTUH IRB (National Taiwan University Hospital Institutional Review Board) approval and informed consent of patients, a total of fifty intact human molars were collected and stored in 4 °C of 0.4% thymol solution (w/v). A precision diamond saw (ISOMET® 2000, BUEHLER® LTD., Lake Bluff, IL, USA) was used to expose the flat dentine surface perpendicular to the long axis of the tooth and to obtain 1-mm-thick dentine discs via apical cuts. All discs were pretreated with 17% EDTA for 1 min to expose the opening of the dentinal tubules and were then cleaned in an ultrasonic cleaner (Enshine Scientific Co., Taiwan). The specimens were then divided into five groups (N = 10) for surface treatments with (1) CMCF-W, (2) CMCF-P_{10}, (3) CMCF-P_{20}, (4) CMCF-P_{30}, or (5) MCF-P_{30}. The treatment of MCF-P_{30} group was used to investigate whether dentinal tubules would be occluded without the additional large amount of calcium supply (i.e., from CMCF). The test materials were applied over the dentine discs with a microbrush (Microbrush International, Grafton, WI, USA) 3 times (3 min/time). After 10 min, the material was rinsed out from the dentine surface with pH = 9 water and then stored in artificial saliva for 24 h at 36 °C. The treated dentine disc was then split to evaluate the sealing quality within the dentinal tubules. The depths and percentage of precipitate occlusion in dentinal tubules were examined by SEM. We examined three areas randomly in each sample and then averaged the obtained occlusion depth and percentage (n = 10). Statistical comparisons of the obtained occlusion depth and percentage were performed using one-way ANOVA and the *post hoc* Tukey's test, with the statistical significance set as $\alpha = 0.05$.

3. Results

3.1. TEM/EDX examination of MCF and CMCF

The ultrastructure of MCF demonstrated a uniform foam-like nanopore with approximately 30.0 nm in diameter (Fig. 1A). After impregnation of $CaCO_3$, the dark-spot appearance indicated the existence of $CaCO_3$ nanoparticles confined within MCF (Fig. 1B). The EDX element mapping in CMCF was shown (Fig. 2). The pink color (Ca element) indicated the existence of $CaCO_3$ particle in MCF; the blue color shows the Si element of MCF. From the EDX analysis, the Ca/Si ratio was approximately 0.93, which was close to the expected synthetic components (Ca/Si = 1.0).

3.2. Crystal phase characterization and SEM examination of CMCF-P

Both the pure CMCF (Fig. 3A) and the CMCF-W (Fig. 3B) were identified as amorphous phases, indicating that the $CaCO_3$ was well-dispersed in nano-dimension within the MCF. The major crystal compound in the CMCF-P_{10} was dicalcium phosphate dihydrate (DCPD, $CaHPO_4{\cdot}2H_2O$), which showed the characteristic peaks at $2\theta = 11.6^{\circ}$, 21.0° and 29.3° (Fig. 3C). The crystal phases in the CMCF-P_{20} (Fig. 3D) were principally composed of monocalcium phosphate monohydrate (MCPM, $Ca(H_2PO_4)_2{\cdot}H_2O$) and DCPD, which presented significantly at characteristic peaks at $2\theta = 23.1^{\circ}$, 24.2° and 30.6° mixed with other

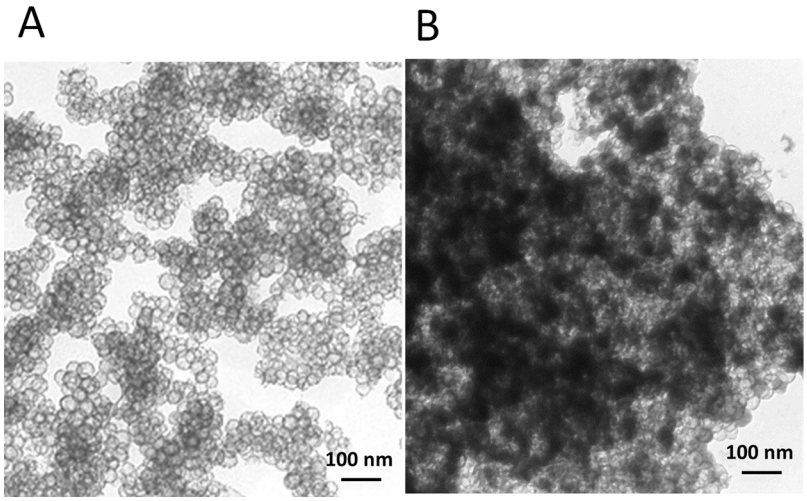

Fig. 1. TEM examination of mesocellular siliceous foams (MCF) composite. (A) MCF with pore size of approximately 30.0 nm in diameter. (B) calcium encapsulated mesocellular siliceous foams (CMCF), the dark-spot appearance within MCF indicates the presence of nano-sized $CaCO_3$.

peaks at 2θ = 11.6°, 21.0° and 29.3°. The major crystal phase in the CMCF-P_{30} was MCPM. SEM micrographs of the product from CMCF-W showed amorphous clusters (Fig. 4A). Formation of crystals was noted while CMCF was mixed with phosphoric solution (Fig. 4B-D).

3.3. Sealing efficacy in dentinal tubules

The dentine surface treated with CMCF-W showed less occlusion in the dentinal tubules; only amorphous precipitates covered the dentine surface (Fig. 5A). When the dentine discs were treated with the other CMCF-P mixtures, prominent crystal growth in the dentinal tubules was noted regardless of the H_3PO_4 concentration (Fig. 5B-F). However, the CMCF-P_{10} group showed only shallow precipitates in the dentinal tubules (Fig. 5B). Interestingly, higher concentrations of H_3PO_4 promoted deeper and more complete crystal growth in the dentinal tubules (Fig. 5E and F). The MCF-P_{30} group (i.e. no calcium carbonate encapsulated) showed no occlusion of dentinal tubules (Fig. 5G) but severe erosion appeared (Fig. 5H). A quantitative measurement of the sealing efficacy indicated that CMCF-P_{30} performed at significantly higher efficiencies in occluding the dentinal tubules, with crystal growth reaching an average depth of 83.2 ± 17.6 μm and an occlusion percentage of up to 75.6 ± 12.8% when compared with CMCF-W, CMCF-P_{10} and CMCF-P_{20} materials ($p < 0.05$).

4. Discussion

The exposure of dentinal tubules is a critical step toward dentine hypersensitivity, pathogenesis of dental caries, along with pulp and periapical diseases [30]. Bacterial invasion of the dentinal tubules has

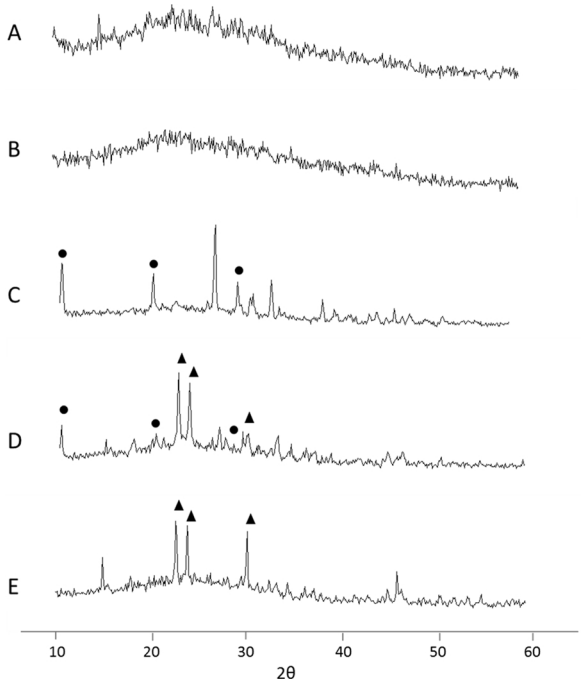

Fig. 3. XRD crystal characterization. (A) CMCF powder; (B) CMCF-W; (C) CMCF-P_{10}; (D) CMCF-P_{20}; (E) CMCF-P_{30}. (●) DCPD, $CaHPO_4{\cdot}2H_2O$, (▲) MCPM, $Ca(H_2PO_4)_2{\cdot}H_2O$.

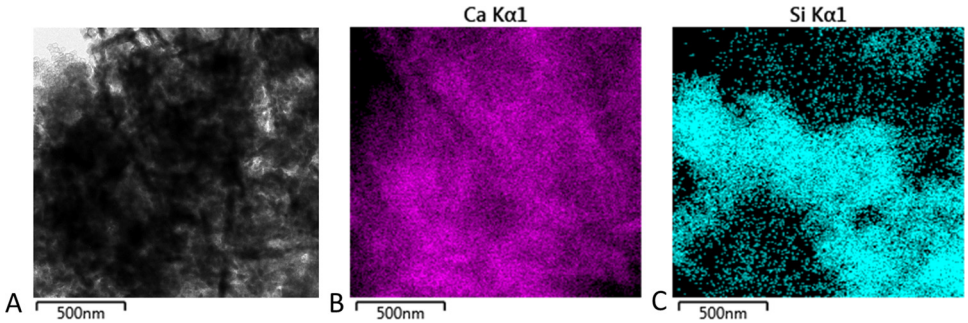

Fig. 2. TEM/EDX examination of CMCF composite. (A) TEM of CMCF (B) EDX mapping: Ca (pink color) in CMCF (C) EDS mapping: Si (blue color) in CMCF (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

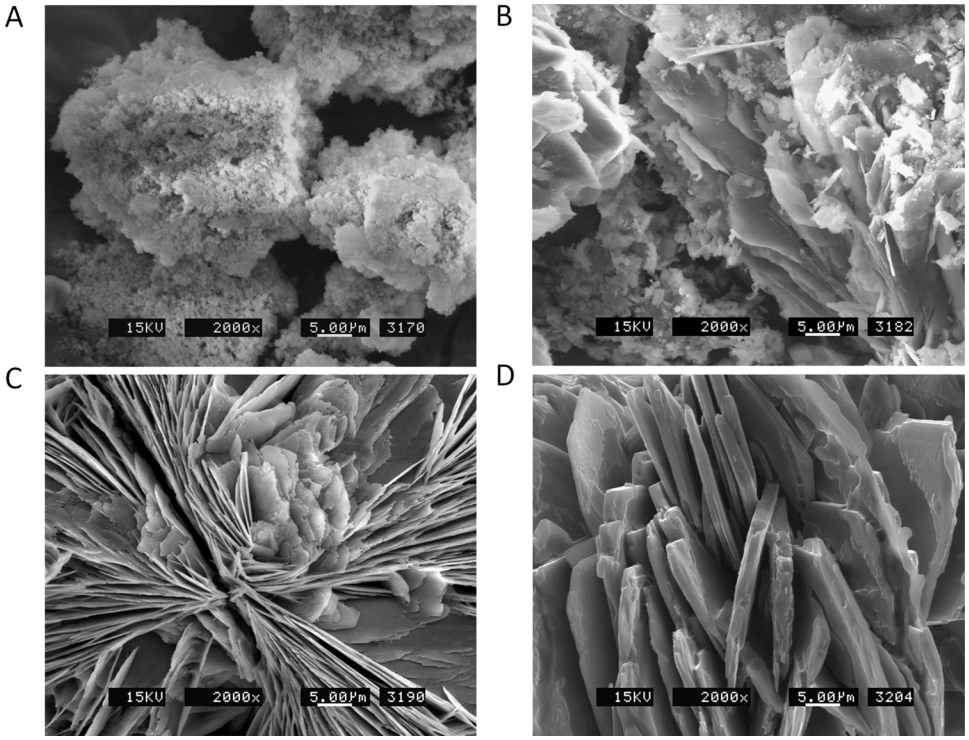

Fig. 4. SEM micrographs of crystal growth of CMCF reacted with distilled water or phosphoric acid. (A) CMCF-W (B) CMCF-P_{10} (C) CMCF-P_{20} (D) CMCF-P_{30}.

also been regarded as a potential source of persistent infection, which may cause recurrent diseases such as periradicular lesions and late failure of endodontic treatment or retreatment [31,32]. Thus, the occlusion of dentinal tubules is an important means for preventing bacterial invasion and reducing the permeability of dentinal tubules which may result in dentine hypersensitivity. The results showed that CMCF-P_{30} could effectively occlude the dentinal tubules. Crystal growth reached about 83.2 ± 17.6 µm into dentinal tubules. Therefore, the null hypotheses were rejected.

Several studies have aimed to create calcium phosphates to occlude dentinal tubules because of their similarity to the main component of dentine [33–37]. Imai and Akimoto used disodium phosphate with a calcium chloride solution on the dentine surface, which resulted in a rapid precipitation of calcium phosphate [33]. Unfortunately, the crystals did not grow in the dentinal tubules to form a sustained occlusion. Ishikawa et al. proposed the use of a supersaturated acidic solution containing Ca^{2+} and PO_4^{3-} to prevent rapid precipitation on the dentine surface from blocking the patent dentinal tubules [35]. However, this shallow apatite crystal formation only occluded the exposed dentinal tubules to a depth of 4–10 µm and could not guarantee a positive clinical outcome. Wang et al. developed a collagen/calcium dual-affinitive peptide with nano-hydroxyapatite (HAp) for sealing dentinal tubules [37]. However, the penetration into the dentine (approximately 5 µm in depth) did not extend as far as expected, although a HAp layer formed on the dentine surface. The shallow deposition of HAp on dentine surface may provide neither long lasting occlusion and protection nor effective reduction of dentine permeation on exposed dentinal tubules [38].

In the present study, we synthesized a MCF as a carrier to restrict nano-$CaCO_3$ particles. The nanoscale foam structure encapsulated plenty of nano-$CaCO_3$ particles (Fig. 2B). The reaction rate is partially pH-dependent, however; the use of higher concentration H_3PO_4 usually leads to a sustained release of calcium ions and produces biomimetic calcium phosphates which have similar mineral composition of tooth [39]. When CMCF reacts with the H_3PO_4 (to form CMCF-P), nanopores of mesocellular siliceous foams can release an abundance of Ca^{2+}; a supersaturation of Ca^{2+} and PO_4^{3-}, H_2PO_4-, or HPO_4^{2-} forms on the dentine surface, which allows the precipitate goes deeper into the dentinal tubules. At a lower (i.e., pH = 4.5–4.7 of CMCF-P_{30} or pH = 5.0–5.5 of CMCF-P_{20} material), H_2PO_4- ions may play a dominant role of leading ions, allowing the acidic MCPM to precipitate deeper into dentinal tubules. When the dentine surface remained in a high pH state (for example, treating by the pH = 6.0–6.8 of CMCF-P_{10}), HPO_4^{2-} ions become dominant to form the DCPD near the dentine surface in which orifices of dentinal tubules are blocked by the resulting crystals. Dentine hard tissue is mainly composed of HAp in which calcium ions from dentinal hard tissue may also participate in the precipitation in dentinal tubules. However, there is no occlusion within dentinal tubules in the MCF-P group (Fig. 5G and H). This finding proved that (1) no calcium phosphates precipitated in dentinal tubules without enough amount of calcium ions source (MCF-P treatment); (2) the main source of calcium which formed the precipitate in dentinal tubules is mainly from CMCF-P surface treatment. The abundance of Ca^{2+} ions released from CMCF promoted a continuous precipitation of crystals in the dentinal tubules.

Based on the XRD findings, the crystal product from CMCF-P_{20} and CMCF-P_{30} was MCPM/DCPD and MCPM (Fig. 3). Thus, we assume that the calcium phosphates formed in dentinal tubules may be related crystals, such as DCPD, MCPM, or TCP-like crystals. It is possible that a crystal phase transformation occurs and that the PO_4^{3-} ions in the dentinal tubules may form TCP-like crystals, which react with the resulting acidic MCPM to form DCPD [40,41]. The chemical reaction of the DCPD-forming calcium phosphate by the MCPM and TCP can be given as follows:

$$Ca_3(PO_4)_2 + Ca(H_2PO_4)_2 \cdot H_2O + 7H_2O \rightarrow 4CaHPO_4 \cdot 2H_2O$$

In addition to TCP, the DCPD can also be easily produced from mixtures of MCPM and HAp [42,43]. The reaction of the formation of DCPD from MCPM and HAp can be given as follows:

$$Ca_{10}(PO_4)_6(OH)_2 + 4Ca(H_2PO_4)_2 \cdot H_2O + 22H_2O \rightarrow 14CaHPO_4 \cdot 2H_2O$$

The pH value increased with the depth of the dentinal tubules which suggested that phase transformations of the DCPD are possible in the

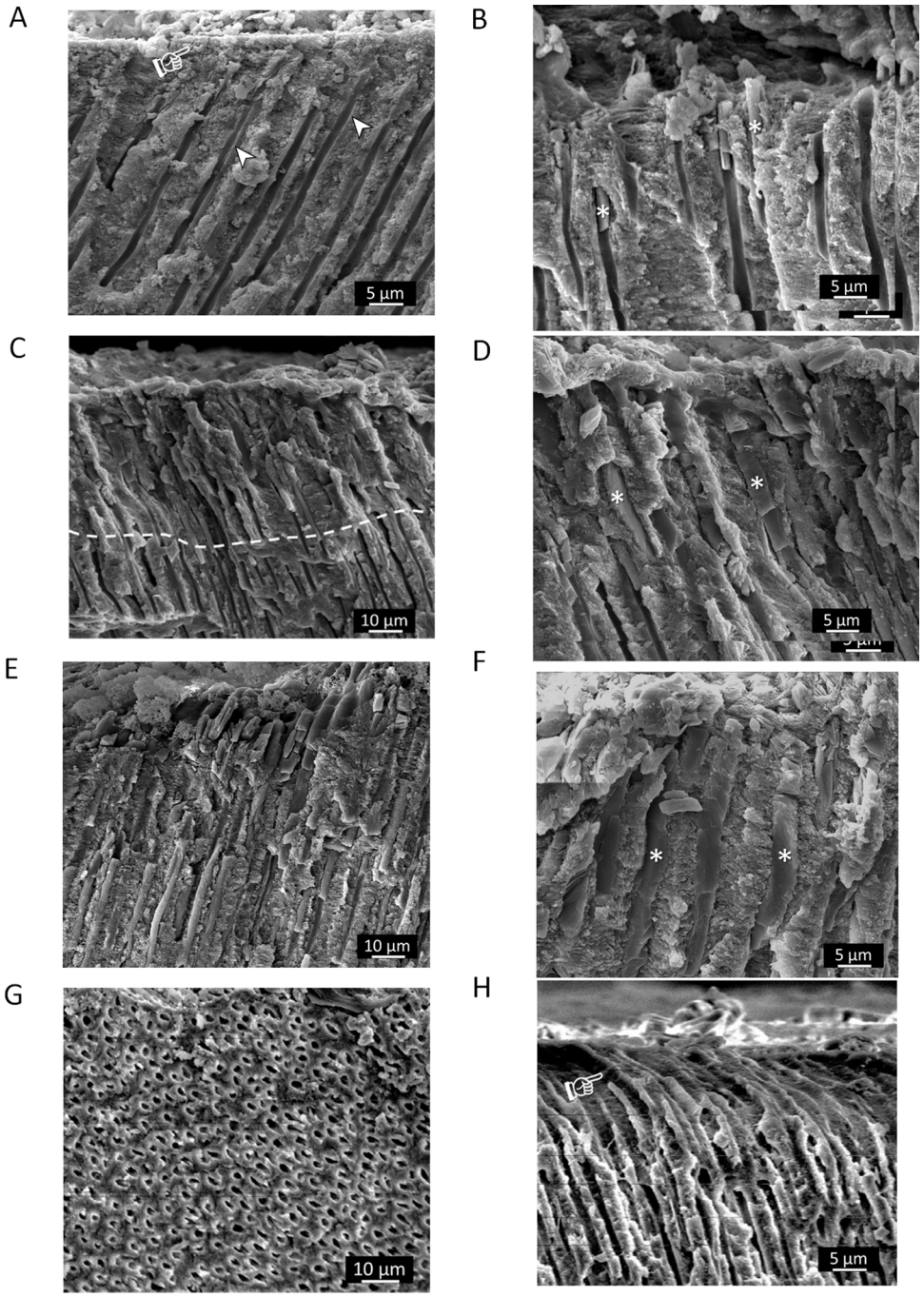

Fig. 5. SEM micrographs of dentinal tubules treatments. (A) CMCF-W group: less occlusion in dentinal tubules (arrowheads). Only amorphous precipitates cover the dentine surface (finger point). (B) CMCF-P_{10} group: shallow crystal growth (less than 30 µm, asterisks) in the dentinal tubules. (C) CMCF-P_{20} group: crystal growth (asterisks) to a depth of 40 µm. (D) Higher magnification of CMCF-P_{20} group. (E) CMCF-P_{30} group: crystal growth to a depth of 80 µm. (F) Higher magnification of CMCF-P_{30} group: integrated crystals grown (asterisks). (G) MCF-P_{30} group: no precipitate on dentine surface. (H) Split dentine of MCF-P_{30} group: dentine erosion (finger point).

physiological pH range between 7.3 and 7.5.

In CMCF-P_{10}, the crystal growth in the dentinal tubules was significantly less than that of CMCF-P_{20} and CMCF-P_{30}. One possible explanation for this result is that the lower concentration of H_3PO_4 (10%) and the resulting higher pH led to a faster precipitation of DCPD (Fig. 3C and 4B), inhibiting it from penetrating deeper than the acidic MCPM resulting from CMCF-P_{30}. Thus, to obtain deeper crystallization in the dentinal tubules, higher concentrations of H_3PO_4 may be necessary to overcome the challenges encountered for small, ion-selective dentinal tubules.

Curtis et al. had proposed a nanobioglass to treat the exposed dentinal tubules by the formation of apatite in dentinal tubules to a measured depth of 270 µm [26]. However, they did not mention the control of apatite depth. In our present study, the various concentrations of phosphoric acid can proceed to different precipitated depths (about 31, 48, and 83 µm) in dentinal tubules. We also found dentine surface would not be eroded even when exposed to 30% phosphoric acid. The study conducted by Featherstone et al. could explain this phenomenon: dentine would not be eroded if exposed to supersaturated Ca^{2+} and PO_4^{3-} ions, even at pH values lower than the critical pH value [44]. CMCF-P_{30} provides a similar environment preventing acid erosion during precipitation in dentinal tubules.

5. Conclusion

The synthesized MCF could act as a carrier of nano-$CaCO_3$ particles. The occluding depth in dentinal tubules is controllable by the concentration of phosphoric acid. We believe that the novel CMCF combined with phosphoric acid may have great potential in treating related exposed dentine diseases including dentine hypersensitivity.

Identification of crystal phases in dentinal tubules and the detailed mechanisms of the crystallization will be conducted in further research.

Disclosures

All authors declare no conflicts of interest.

Declaration of interests

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

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