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Specialized channels to control the kinetics of ion release in hydrophobic resin

Chul Ho Park · Sung Chul Hong · Bum-Soun Im · Myung-hwan Oh · Jonghwi Lee

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Abstract Fluoride, as a model ion, has been clinically used to inhibit the development of secondary carious lesions at the interfaces of restored teeth and demineralization. Controlling of its release kinetic is important in the dental restorative composites with respect to enhance biological activities without side effects. To introduce the channels into composites as specialized channels for continuous and controllable fluoride release, this paper suggests the one-dimensional structure with controllable functions. This specialized structure is generated by the novel development of a coaxially aligned tri-nozzle electrospinning technique. The fluoride source, comminuted sodium fluoride nanoparticles, was encapsulated in poly (methyl methacrylate) sheath. Tuned fluoride release was achieved by hydrophilic poly(acrylic acid) incorporated with the NaF nanosuspension with a hollow structure introduced using an inner fluid (ethylene glycol) in the tri-nozzle system. The structures of the multi-functionalized channels were preserved during UV curing of the polymeric dental restorative composites. The resulting composite resins show long-term release profiles controllable by both poly(acrylic acid) content and the hollow structures, which are based on fluoride diffusion and water ingress. Therefore, the functionalized channel can be applied to control the long-term release of ions in hydrophobic matrix at desirable kinetic.

C. H. Park · J. Lee (✉)
Department of Chemical Engineering and Materials Science, Chung-Ang University, 221, Heukseok-dong, Dongjak-gu, Seoul 156-756, South Korea
e-mail: jong@cau.ac.kr

S. C. Hong
Department of Nano Science and Technology, Sejong University, 98 Gunja-dong, Gwanjin-gu, Seoul 143-747, South Korea

B.-S. Im
Department of Dental Biomaterials Science, School of Dentistry, Seoul National University, Yeongeon-dong, Jongno-gu, Seoul, South Korea

M. Oh
Vericom R&D Center, Anyang-si, Kyunggi-do, South Korea

Introduction

The 13th most common element in the earth's crust, fluoride (F), has a high affinity to calcified tissues. Since it prevents the development of secondary carious lesions at the interfaces of restored teeth and demineralization, its use in dental restoration is an important research subject [1, 2]. Three factors are responsible for its anticariogenic effect. The first being the formation of fluoroapatite which has a solubility lower than that of hydroxyapatite, thus reducing demineralization. Second, it enhances remineralization. Finally, F inhibits carbohydrate metabolism in dental plaque. In 1984, the World Health Organization set the maximum fluoride concentration in drinking water to 1.5 ppm to avoid dental fluorosis, and in 1986, the US Environmental Protection Agency established a maximum primary contaminant level of 4 ppm based on the avoidance of skeletal, but not dental, fluorosis. Therefore, it is important to balance fluoride release from dental restorative composites in order to optimize biological activities without side effects.

The kinetics of F release from dental restorative composites depends on the physical processing parameters and composition of chemical materials. While commercial polymer composites release almost negligible amounts, glass-ionomer cements release relatively high amounts with initial burst release behavior. This results mainly from

the polymer matrix resins' hydrophobicity and the hydrophilicity of glass-ionomer cements [3–7]. Negligible and fluctuating releases were problems examined in this research. Even though several equations have been reported to explain and estimate the kinetics of fluoride release from commercialized dental restorative resins, experimental data typically vary with the physical processing parameters, such as mechanical mixing variables, powder/liquid ratio, surface area, or porosity [7–9]. Therefore, a method of well-controlled F release from dental restorative composites would help reduce clinical problems.

Until now, F has been heterogeneously dispersed in polymer dental composites without any hierarchical release channels. This paper suggests a novel solution that uses continuous one-dimensional channels of core–sheath structure in polymer composites to guide water and F diffusion. If specialized channels for the diffusion of hydrophilic fluoride are introduced into a hydrophobic polymer resin, well-controlled, continuous fluoride release may result without significant fluctuations and associated problems. Also, engineering the structure and composition of the channels can optimize fluoride release profiles.

In several fiber-producing methods recently available, electrospinning was selected because it can produce many structures of unlimited length with controlled dimensions [10, 11]. When a high electric field is applied to a viscous solution in a spinneret, electric charges accumulate on the surface of the meniscus. The accumulated charges are accelerated under the electric field, and eventually the meniscus adopts a cone-shape, referred to as Taylor-cone [12]. If the repulsive forces among the charges overcome the surface tension above the Rayleigh limit, the jet stream is disintegrated into a mist of very small droplets. For high viscosity solutions, the breakup droplets are elongated into fine fibers [13–16]. Electrospinning can allow the encapsulation of bioactive materials such as antibiotics, anticancer therapeutics, proteins, DNA, and growth factors by using coaxial nozzles for two separate fluids or by direct blending of components in polymer solutions [11, 13].

Even though coaxial electrospinning can continuously encapsulate fluoride ions and fabricate one-dimensional structures, there still remains the challenge of controlling the kinetics of F release for biological activity. Since dental restorative matrix resins are hydrophobic, the sheath material of F-containing fibers should be hydrophobic in order to be compatible in the matrix resin. An inner hydrophilic channel is necessary to induce F diffusion leading to the design of core–sheath structured fibers. Despite such fibers, F diffusion inside the hydrophobic sheath materials might be restricted. Therefore, the specific functionalization of inner structures of fibers is needed to guide fluoride release. Electrospinning using a customized spinneret of three coaxially aligned nozzles can make the core structure act as a F diffusion channel with a poly (methyl methacrylate) sheath to provide protection and compatibility with the matrix resins. This study presents the possibility of implementing coaxial tri-nozzle electrospinning for advanced channel structures and functions by testing the performances of resulting fibers as F-releasing channels for polymer dental restorative materials.

Experimental

Materials

Poly(methyl methacrylate) (PMMA, 96,000 and 350,000 g/mol), sodium fluoride (NaF), and poly(acrylic acid) (PAA, 1,800 g/mol) were received from Sigma-Aldrich (USA). *N*,*N*-Dimethylformamide (DMF), ethanol (EtOH), and ethylene glycol (EG) were purchased from Ducksan Pure Chem. (South Korea). Tetramethylurea (TMU) was received from Tokyo Chem. (Japan). A polymer restorative resin (DenFil®), which consists of 2,2-bis-[4-(methacryloxypropoxy)-phenyl]-propane (Bis-GMA), tri-(ethylene glycol)dimethacrylate (diluter), camphorquinone (photo-initiator), 2-(dimethylamino)ethyl methacrylate (co-initiator), and *N*,*N*′-methylene bis(acrylamide) (UV cross-linker), were provided by Vericom (South Korea). All reagents were used as received.

Coaxial tri-nozzle electrospinning

PMMA (4 g) at a 1:1 weight ratio of the two molecular weights was dissolved in 15 mL of 2/1 DMF/TMU (v/v). NaF nanosuspension was prepared by wet ball milling. Briefly, 40 wt% NaF in DMF was comminuted with ZrO_2 beads (diameter: 1 mm) in a 60 mL round glass vial at 100 rpm for 6 days. PAA was dissolved in the NaF nanosuspension at a desired concentration.

The experimental conditions for coaxial tri-nozzle electrospinning are shown in Table 1. Figures 1 and 2 are diagrams of the electrospinning apparatus and resulting fiber structures. The three stainless steel nozzles had 15/19/26 outer/middle/inner gauges (I.D.: 1.64/0.72/0.24 mm, O.D.: 2.10/1.08/0.64 mm, respectively). All solutions were placed in 5 mL syringes (Becton, Dickinson and Company, USA) and continuously transported by a KD Scientific KDS100 syringe pump (USA) with a control step rate of 10 μL/h. A positive direct current was applied to the outer nozzle using a Convertech SHV model (South Korea). It ranged from 0 to 60 kV with a 0.2 mA maximum current, dependent upon the flow rate and solution properties (i.e., conductivity, concentration, or type of organic solvent). The ground-to-nozzle distance (working distance) from the tip of a nozzle to the aluminum foil ground was 40 cm. To make unlimited fibers, all solutions were continuously electrospun for 30 min. EG,

Table 1 Experimental conditions for coaxial tri-nozzle electrospinning

Abbreviation	Inner fluid (flow rate: 0.1 mL/h)	Middle fluid (0.2 mL/h)	Outer fluid (8 mL/h)	NaF content[a] (wt%)
F-fiber	–	NaF nanosuspension	PMMA solution	16 ± 5
FA-fiber	–	PAA (0.1 g) in 1 mL of NaF nanosuspension	PMMA solution	14 ± 5
FA2-fiber	–	PAA (0.2 g) in 1 mL of NaF nanosuspension	PMMA solution	12 ± 5
H–F-fiber	EG	NaF nanosuspension	PMMA solution	15 ± 5

[a] TGA measurement

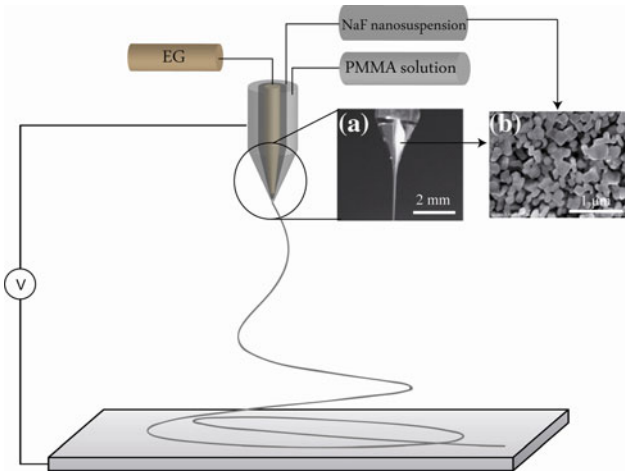

Fig. 1 Coaxial tri-nozzle electrospinning. Photonic image of the menisci of three fluids (**a**); and SEM image of NaF nanoparticles (**b**)

used as the inner fluids for the H–F fibers, was removed by ethanol washing for 30 min and repeated rinsing. To remove residual solvents, all samples were dried in ambient conditions for 1 day, and then in a vacuum oven for 2 days.

Specimen preparation

Bis-GMA composite resins with 1 wt% fibers (1 × 1 cm^2 nonwoven) were prepared in a tube (5.25/5 mm diameter/length). A vacuum oven removed any trapped air bubbles after mixing for 12 h. The mixtures were then cured for 24 h with a Spectroline UV lamp (8 W, 50 Hz, 0.17 AMPS, USA), operating at a wavelength of 365 nm. After cross-linking, all samples were bathed in ethanol for 1 min to remove any residual reagents on their surfaces. The samples were then dried in a vacuum oven for 1 day.

In vitro F release test

Cross-linked cylindrical samples (5.25/2 mm diameter/height), possessing sandpapers (P1000) polished surfaces, were immersed in distilled water (2 mL) in 15 mL centrifuge tubes (Medical Co., South Korea) at 37 ± 4 °C. After extracting the solutions, fresh water was refilled into the tubes. The concentration of released fluoride was measured by a fluoride specific electrode (Orion, 96-09) with the Orion 5 meter of Thermo Scientific (USA). Before fluoride measurements, a TISAB II buffer solution (Orion Res., USA) was added to the fluoride-released solutions at a 1:1 volume ratio. F releases from fibers (several pieces of 0.2 × 0.2 cm^2, 2.2 g) immersed in the 1:1 TISAB/water v/v solution (20 mL) were directly measured by the fluoride specific electrode at 37 ± 4 °C.

Characterization

A Hitachi S-4800 scanning electron microscope (SEM, Japan) was used to characterize the fibers and composites

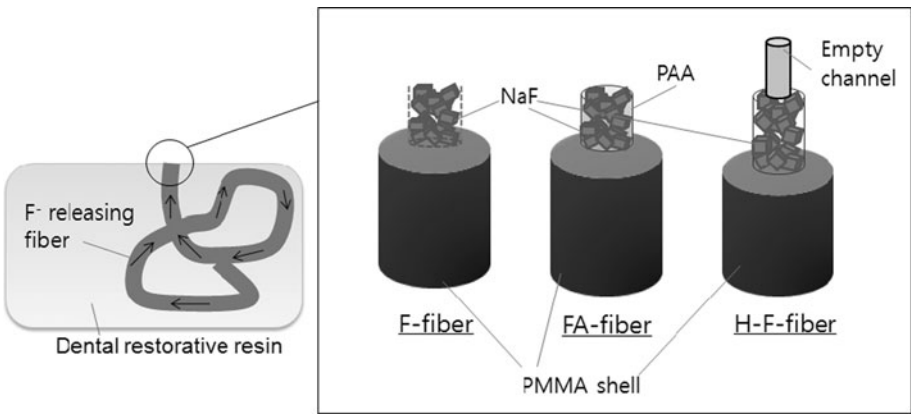

Fig. 2 Fiber structures and F release mechanism

with Pt coating. Fracture images of the fibers and composites were obtained from samples cryo-fractured in liquid nitrogen for at least 15 min. For thermal gravimetric analysis (TGA) of NaF, all the samples were dried in a vacuum at room temperature for more than 24 h before tests in which the remaining NaF contents of fibers were measured. TGA (Q50 TA instruments, USA) was performed in an oxygen environment at a heating rate of 10 °C/min.

Results and discussion

Coaxial tri-nozzle electrospinning

Steady F release requires the proper selection of materials and solvents, and stable electrospinning conditions. PMMA was used as a sheath because it has been used for dental restorative resins and also has a relatively high miscibility with Bis-GMA matrices [17]. Electrospinning requires PMMA and NaF to be dissolved in an organic solvent and water, respectively. If PMMA is dissolved in a water-miscible organic solvent, both it and NaF can be precipitated at the interface between the inner and outer fluids. Precipitation destabilizes coaxial electrospinning leading to irregular encapsulation and fiber structures. Although successful electrospinning of various water-in-oil emulsions with a chloroform sheath solution has been reported without the problems of phase separation or precipitation [18], it created non-uniform fibers in the initial trials of this work.

To overcome these drawbacks, NaF was dispersed in an organic solvent, DMF (a good solvent of PMMA, but a poor one of NaF), instead of water. NaF was first mixed with DMF and ball milled for 6 days to produce homogeneous NaF nanosuspensions (~100 nm). This was accomplished without the support of ionic or steric stabilization because DMF can stabilize the surface energy of NaF nanoparticles without added stabilizer (Fig. 1b). The resulting NaF nanosuspensions were then stably electrospun (Fig. 1a).

Despite stable coaxial electrospinning, DMF (b.p. 157 °C) was not sufficient to fabricate uniform core–sheath structures as inhomogeneous surfaces and exposed NaF particles on the surfaces of fibers were often observed (Fig. 3a). Homogeneous consolidation is critical in electrohydrodynamic jetting for the determination of physical properties such as porosity, core–sheath structure, diameter, shape, and diffusion barrier properties, of resulting fibers and particles [19]. Figure 3a shows how DMF could not provide enough solidification time for uniform encapsulation because of its relatively high vapor pressure. Figure 3b (F-fiber) shows fibers of relatively uniform diameter with particles of NaF visible on their cryo-fractured surfaces. In this case, TMU (b.p. 178 °C) was used together with DMF to increase the overall solidification time, resulting in NaF nanoparticles more uniformly encapsulated in PMMA. When PAA was incorporated into the core NaF nanosuspension (FA-fiber), a similar structure to the F fibers was obtained (Fig. 3c). They have diameters of about 5 ± 0.6 μm.

When each EG, NaF nanosuspension and PMMA as the inner, middle and outer fluids (which is H–F-fiber) were continuously transported through the tri-nozzle spinnerets, a hollow structure was successfully synthesized in the center of fibers (Fig. 3d). The magnified image shows the

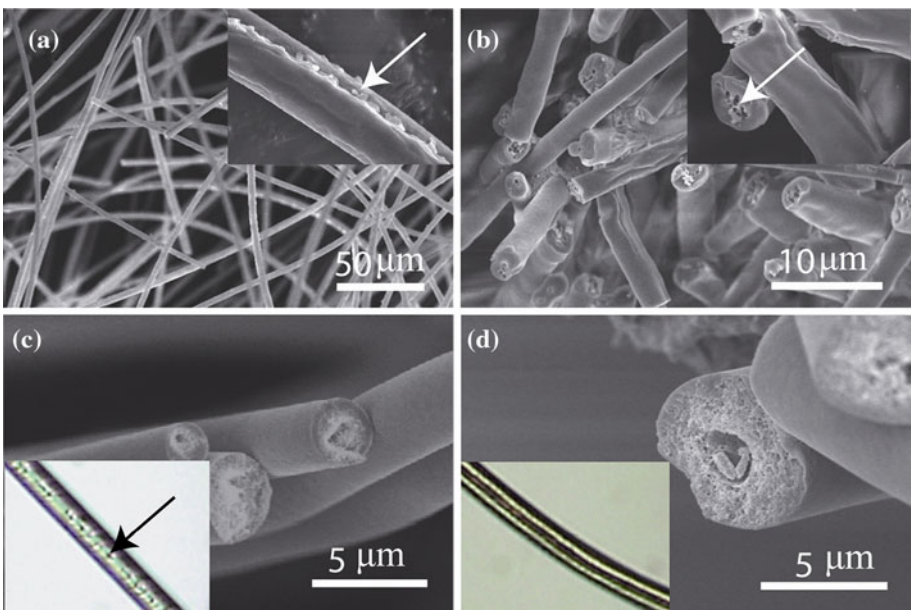

Fig. 3 SEM images of: F fibers with DMF (**a**), and DMF/TMU (**b**); FA fibers (**c**); and H–F fibers (**d**). The *insets* are the magnified SEM images (**a**, **b**); and optical microscopy images (**c**, **d**). The *arrows* indicate the NaF nanoparticle clusters

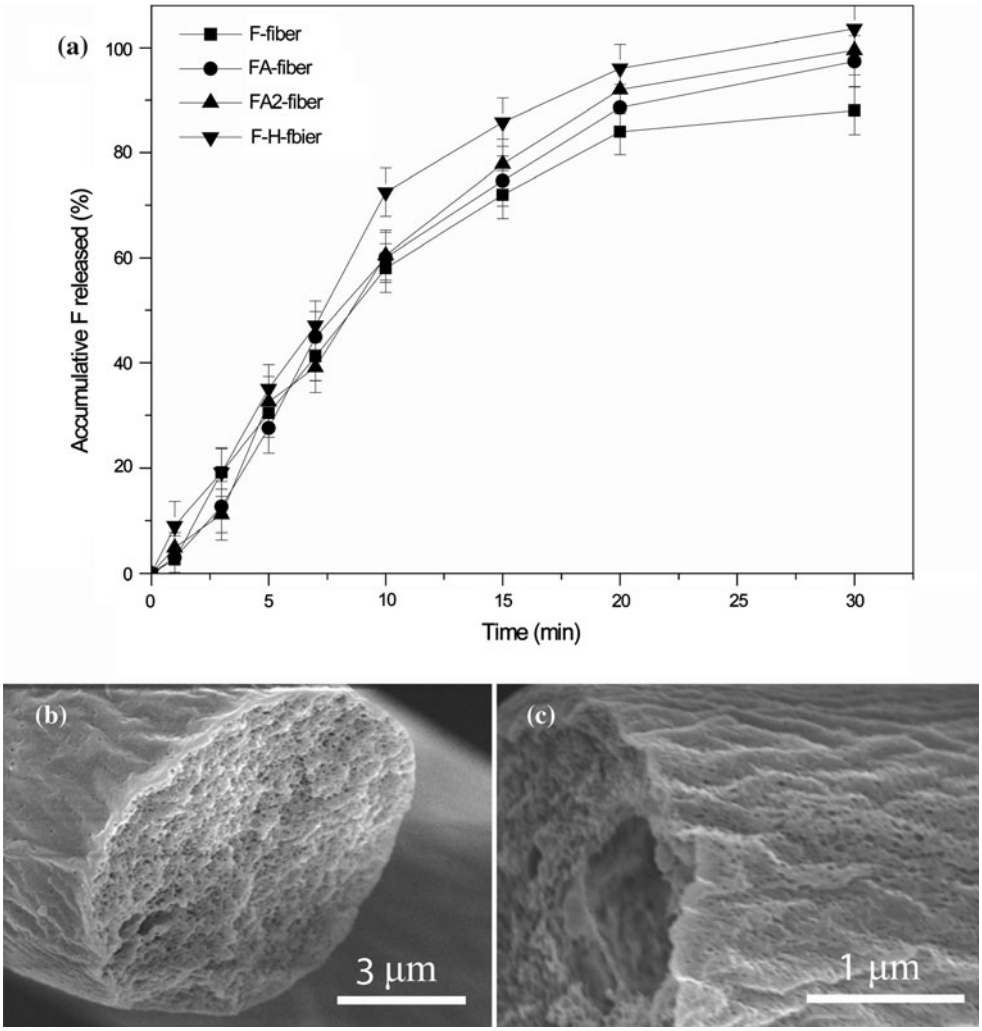

Fig. 4 In vitro release curves of various PMMA fibers in water as a function of the time (**a**); post-release SEM images of FA-fiber (**b**); and H–F-fiber (**c**)

porous nature of the PMMA sheath that was commonly observed in all the fibers. The simple one-step coaxial tri-nozzle electrospinning technique simultaneously encapsulates a water-soluble salt (NaF) and introduces hollow inner structures.

In vitro F release from fibers

The mechanism of fluoride release through the hydrophobic PMMA sheath can be divided into two steps: water ingress and F ion diffusion. Since water ingress depends mainly on the diameter and porosity of the inner core and the hydrophilicity of outer and inner materials, the hydrophilic PAA in the NaF core may aid water's ingress. Subsequently, the absorbed water will dissolve the NaF so that F ions can diffuse through the water. At this point the diffusion constant defined in the Stokes–Einstein relation significantly influences the F release rate [20]. Therefore, incorporation of PAA should enhance water ingress and F diffusion along the one-dimensional channel structure.

However, Fig. 4 shows no significant differences in release rates of F ions for the in vitro tests of all the fibers. Unexpectedly, neither the use of PAA of two different concentrations nor the introduction of hollow structures in the tubes' cores provides any significant change in F release. Only the H–F-fiber showed a marginal increase in F release between 10 and 15 min.

The in vitro release tests of Fig. 4 were performed on chopped fibers. Therefore, in addition to the inner core, any defects on the fibers' surfaces could serve as diffusion channels for water and F ions. The SEM micrographs of Fig. 4b and c show pores on the surfaces and insides of the fibers. Both FA fibers (Fig. 4b) and H–F fibers (Fig. 4c) were porous, although solvents of relatively low vapor pressures were used to achieve homogeneous and complete consolidation during spinning. The pores may have significantly shielded the effects of the incorporation of PAA and the hollow inner structures in the in vitro release experiments.

Although by only a small margin, the F fibers released the smallest amount in Fig. 4. This was confirmed by TGA

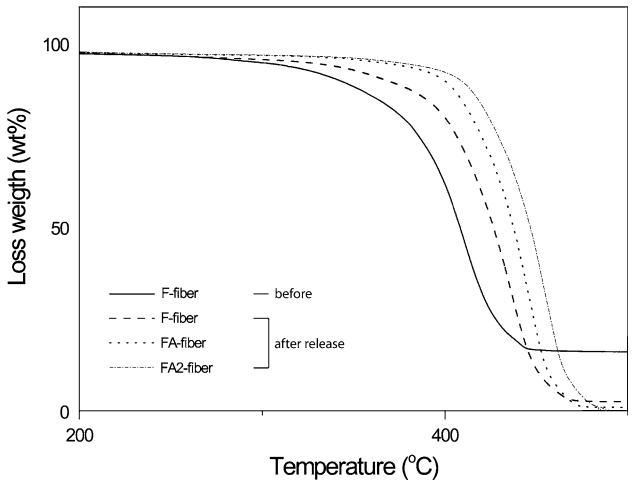

Fig. 5 TGA curves of various fibers before (*solid line*) and after release tests (*dot line*)

investigation. After the release tests, the fibers were vacuum dried for more than 24 h, and then the remaining NaF contents were compared with those of before the release tests. If NaF nanoparticles are effectively engulfed by PMMA, they will not be completely dissolved and released because of PMMA's hydrophobicity. In Fig. 5, the NaF remaining after the release tests was about 5 wt% in the case of F fibers, while ca. 0 and 1.6 wt% NaF remained in FA2 fibers and FA fibers, respectively. This agrees with the results of Fig. 4 and demonstrates that the incorporation of PAA is slightly beneficial for F release.

In vitro F release from composites

Polymer dental restorative resins consist of hydrophobic monomers and cross-linkers. Without connected pores or other diffusion channels, F ions inside the resin matrix could not be released. The introduction of a 1D channel for F release was achieved by incorporating the prepared NaF fibers into a resin matrix. The fibers' ends were exposed to the surface of the dental composites after composite finishing (similar to the finishing of a regular clinical operation). If NaF nanoparticles are effectively surrounded by hydrophobic PMMA, F release will be limited, a possibility for F fibers. Furthermore, since PMMA is not degradable or water-soluble, it can provide sustained release characteristics to the composites.

Composites of fibers and Bis-GMA can have different release profiles compared with pure fibers, depending on structure conservation and dispersity. If PMMA shells could be dissolved with Bis-GMA monomers, functions of specialized channel disappears. Also, if the dispersion of fibers is not uniform, we could not expect statistically averaged and well-controlled release kinetics. Figure 6a reveals that the structure of PMMA shell is well conserved. In addition, the fractured surface shows evidence of crack pinning (tail structures behind fibers), and the fibers seem to have relatively good interfacial strength [21, 22]. Furthermore, the optical microscopy image (Fig. 6b) exhibits that functionalized fibers are well dispersed in hydrophobic resins as well as the hollow structure (Fig. 6b, inset) is not destroyed. Therefore, our fibers can act as specialized channels in hydrophobic resins to offer systemically controllable release kinetics.

Figure 6c shows the release of F from the composites as a function of incubation time. The hydrophobic Bis-GMA resin retards release rates compared with those of Fig. 4. All the release curves show fluoride release slowing following an initial period of fast release of ca. 4 days. Unlike the results of Fig. 4, the incorporation of PAA and hollow structures influence F ion release rates. The amount of PAA significantly affects the release rate and profile. In Fig. 6c, FA2 fibers have the fastest initial release rate and prolonged long-term release afterwards. Less PAA results in a slower release rate. The introduction of hollow structures slightly improved the release rates of F ions, but it was not more effective than using PAA (FA fibers or FA2 fibers vs. H–F fibers). For F fibers, fluoride release after 2 days was negligible. The relatively low released amount and the negligible long-term release behavior of F fibers demonstrate the need for additional PAA phases or hollow structures for effective F release from polymer dental restorative composites.

The introduction of one-dimensional release channels inside Bis-GMA resins facilitated the otherwise impossible release of F ions. PMMA sheaths strengthen the interface between fibers and matrix, but its hydrophobic nature restricts F ion diffusion. Therefore, the use of additional structures inside the fibers was useful. Hollow structures can help the diffusion of F ions. However, if air is trapped, water uptake will create air pressure inside fibers. Furthermore, the hydrophobic PMMA surface hinders the water penetration along the hollow capillaries because of its poor wetting characteristics. Therefore, the use of PAA in the fibers' cores can alleviate both wetting and air problems, apparently a better solution, as FA and FA2 fibers showed the highest release concentrations and rates.

For successful F-releasing polymer dental restorative composites, continuous long-term release is important. In the case of the FA2-fiber composite (Fig. 6c), long-term release after 2 days could be confirmed. As a result, the use of one-dimensional channel structures in polymer dental restorative composites seems to facilitate continuous F ion release. Also coaxial electrospinning might be useful to tune F release profiles by modifying the inner structures of the channels.

While the results of this study are promising—the system meets the stated design criteria—some issues remain to be optimized. First, the role of the sheath material was not

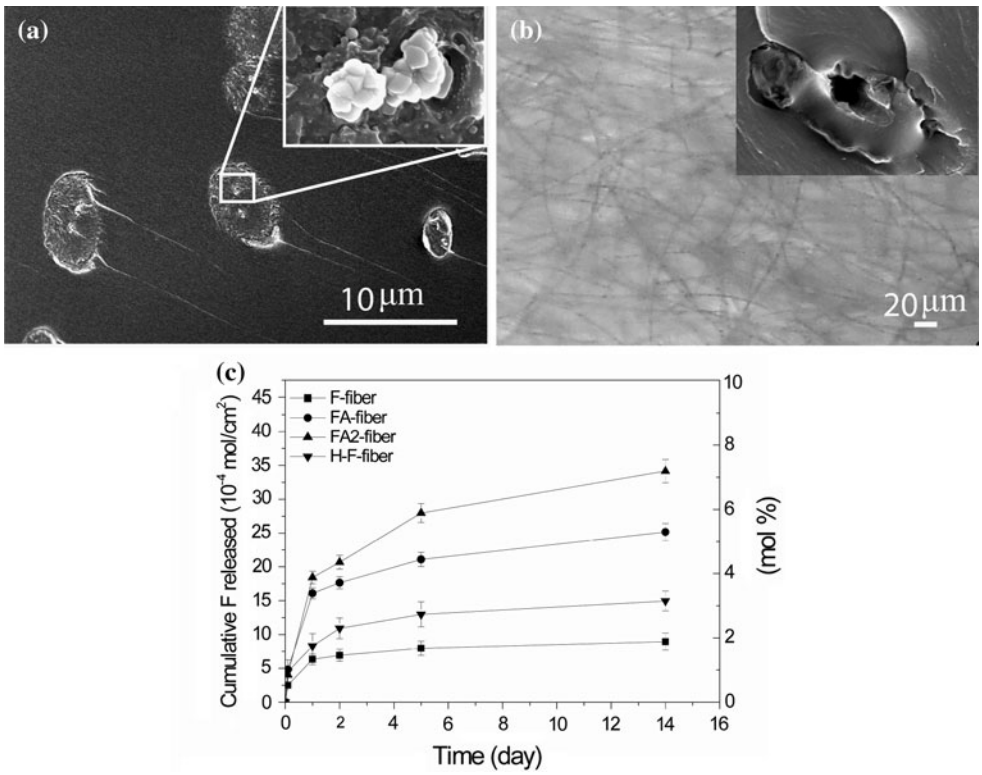

Fig. 6 Cross-sectioned SEM image of F-fiber composite (**a**); and optical image of H–F-fiber composites (**b**). In vitro release curves of various BIS-GMA composite resins in water as a function of the time (**c**)

fully understood. PMMA was chosen after consideration of sheath materials' interfacial adhesion and electrospinning properties. A more systematic study on the sheath materials will elucidate its role in the performance of final dental composites. Furthermore, the lengths and diameters of fibers were not optimized in this experiment, and the reinforcing effect of fibers in the matrix was not explored. Small variations of fibers' diameters (Figs. 3, 4) do not significantly influence release data (Figs. 4, 6). Although fiber content is relatively small, their effects on other properties of dental composites, such as transparency, polish ability, strength, X-ray opacity, workability, and low shrinkage, should also be investigated.

Conclusion

Coaxial tri-nozzle electrospinning successfully fabricated specifically functionalized core–sheath and hollow structures to be introduced as fluoride release channels into polymer dental restorative materials. The fibers' sheaths were PMMA which achieved proper interfacial adhesion with the Bis-GMA matrix. Dental restorative composites of the fluoride-releasing fibers have unique release profiles controlled by the fibers' structures, while in vitro release experiments of fluoride ion release from the fibers was not influenced by their structure. Hollow structures improved fluoride release rates from composites, which were not otherwise active due to the hydrophobic nature of PMMA and Bis-GMA. The introduction of PAA into the fibers' cores further improved the fluoride release, the rate of which increased with increasing content of water-soluble PAA. Long-term continuous release profiles were observed in composites having fibers with PAA structures. The coaxial multi-nozzle electrospinning technique produced well structured advanced fibers, useful for the preparation of fluoride release from polymer dental restorative materials.

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