Polyethylene-glycol coated maghemite nanoparticles for treatment
of dental hypersensitivity

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A B S T R A C T
Dental hypersensitivity is a common oral problem that is directly related to the number and the diameter
of dental tubules. Therefore, the occlusion of the tubules using compounds capable of penetrating and
precipitating into dental tubules may result in a long-lasting remedy to this problem. In this in-vitro
study, the ability of polyethylene-glycol coated maghemite nanoparticles for treating dental hypersensi-
tivity was investigated. Due to their superparamagnetic characteristics, these nanoparticles are
susceptible to navigation inside the dental tubules via an external magnetic field. The experiments were
performed in various durations for the purpose of determining the optimum time for the effective
occlusion of dental tubules. Our findings showed that the polymer-coated maghemite nanoparticles
exhibited a significant potential for reducing the permeability of dental tubules by occluding the open
tubular area after a 120 min.

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1. Introduction

Dental hypersensitivity is defined as “a short sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic, or chemical and which cannot be ascribed to any other form of defect, pathology, or disease” [1]. In other words, it means a painful response to stimuli(s) that is not normally associated with pain [2]. The main cause of dental hypersensitivity is open dental tubules (microscopic channels in the dentin), which serve as direct links between the external environment and the pulp. Previous studies have demonstrated that the dental tubules in hypersensitive dentins are larger in both number and diameter compared to non-sensitive dentin [3]. Therefore, it can correctly be assumed that the severity of dental hypersensitivity is related to the number and width of dental tubules.

Dental tubule occlusion is one of the principal strategies for the treatment of dental hypersensitivity which involves the use of compounds that can precipitate inside the tubules and plug their orifices. However, the micron-sized diameter of dental tubules presents a physiological limitation for diffusion of large therapeutic compounds. Therefore in this protocol, fine particle size is crucial as it allows a faster and deeper deposition of particles inside the dental tubules. Based on this fact, several biomaterials have been synthesized in the nanoscale for treatment of dental hypersensitivity, including gold [4], hydroxyapatite [5], carbonate apatite [6], calcium oxide–mesoporous silica [7], and nanolipid carriers [8]. Although these agents have yielded promising results, the navigation of such nanoparticles inside the tubules remains a challenge [9].

In this research, we have studied the possibility of using polyethylene-glycol coated maghemite nanoparticles (PEG-MNPs) for treating dental hypersensitivity. We assumed that the maghe-
mite nanoparticles (MNPs) could be navigated inside the tubules via an external magnetic field. The PEG coating acts as a protective layer for minimizing the aggregation and biofouling of MNPs in physiological conditions for long periods [10–12]. The biocompat-
ibility of both PEG and maghemite compounds makes the PEG-MNPs attractive candidates for the fast and effective treatment of dental hypersensitivity.

2. Materials and methods

Maghemite nanoparticles were synthesized via the modification of the recipes described in literature [13,14]. In our method, the synthesis was performed in an aqueous medium and air atmosphere (instead of nitrogen) for a more facile production of nanoparticles. In a typical synthetic process, 1.0 mL of 2 M ferrous sulfate heptahydrate (FeSO₄·7H₂O) and 3.5 mL of 1 M ferric
chloride (FeCl₃) were mixed in 25 mL of distilled water, and then 25 mL of ammonium hydroxide (NH₄OH, 33% NH₃ in water) solution was added dropwise under vigorous stirring. After 2 h, the synthesized maghemite nanoparticles were separated using a magnetic field, washed with ethanol, and dried in 80 °C for 24 h.

Fig. 1. (a) TEM image of PEG-MNPs synthesized by "graft-to" method. (b) A typical specimen before treatment. The smear layer is completely removed and dental tubules are open (magnification: 2260 ×).

Fig. 2. Two different tubular occlusion modes by PEG-MNPs in M60 specimens, before rinsing with water: (a) intra-tubular precipitation and (b) superficial obliteration (magnification: 4000 ×). EDX analysis of particles (c) attached to the tubular walls and (d) obliterated the tubular openings.
For the synthesis of PEG-MNPs, the “graft-to” method was used according to a previously described protocol [12]. Briefly, the surface-modified nanoparticles were firstly prepared by stirring the as-synthesized MNPs and 3-aminopropyl triethoxysilane (APTES) in toluene at 80 °C for 24 h. Then, the obtained particles were mixed with carboxyl-terminated PEG in toluene at 80 °C for another 24 h. The synthesized nanoparticles were washed with ethanol and dried at 50 °C for 48 h to produce surface-functionalized MNPs possessing sufficient stability in aqueous solutions. The morphology and particle size of PEG-MNPs were analyzed using a Transmission Electron Microscope (TEM; LEO Libra 120).

The teeth specimens were selected from freshly extracted human molars. A number of eight teeth were sectioned horizontally from the cervical area using a water-cooled saw in order to obtain disc-shaped samples with thicknesses of 2 mm from each tooth. The sample surfaces were demineralized using citric acid containing 20%w/v ethylenediamine tetraacetic acid (EDTA) at room temperatures for a period of 10 min. Then, the discs were ultrasonicated for 30 min and rinsed with distilled water to remove residual smear layer and to open dental tubules. The disc-shaped samples were randomly divided into four groups, namely, M30, M60, M90, and M120, for the purpose of investigating the effect of treatment duration on the occlusion ratio of dental tubules (30, 60, 90, and 120 min, respectively).

For filling the tubules with nanoparticles, each specimen was incubated in 5 mL of water containing 100 mg PEG-MNPs, and an external magnetic field was applied in order to direct the nanoparticles to move inside the tubules. Then, the specimens were removed from suspension, rinsed with distilled water, and dried in air. The specimen surfaces were analyzed using a Scanning Electron Microscope (SEM; Phenom world desktop machine). Energy-Dispersive X-ray spectroscopy (EDX; FEI Quanta 250) was also performed for elemental analysis of the precipitates inside the tubules.

3. Results and discussion

Fig. 1a shows a TEM image of the synthesized nanoparticles. The diameter of the nanoparticles was mostly smaller than 25 nm, which was suitable for filling the dental tubules. The photomicrograph of a typical untreated specimen is shown in Fig. 1b, which presents a smooth dentin surface without any smear layer covering the tubules’ orifices.

Fig. 2 shows the SEM images of the M60 samples before rinsing with water. This figure presents two significant modes of tubular

![Image](image-url)
occlusion by PEG-MNPs before rinsing the surface. The majority of dental tubules were occluded (i.e. filled) by nanosized maghemite precipitates (Fig. 2a), while some agglomerates with approximately similar diameters to that of the tubules could obliterate (i.e. block) the dental tubule openings (Fig. 2b). EDX analysis (Fig. 2cd) confirmed that these precipitates contain iron (Fe) element. Some other elements, including calcium (Ca), phosphorus (P), sulfur (S), aluminum (Al), sodium (Na), and magnesium (Mg), were also detected due to their presence in the mineral content of the underlying dentine. However, after rinsing with water, the agglomerated particles were mostly removed from the specimens’ surfaces due to the insufficient penetration inside the tubules. This fact indicates that the tubules might not be occluded by micросized particles for a long-term period. Moreover, these particles may reduce the diffusion rate of nanosized particles inside the dental tubules. Therefore, the precise control of the particle size distribution of PEG-MNPs is necessary for an effective occlusion of dental tubules.

Fig. 3 shows the SEM images of the dentine surfaces after treatment with PEG-MNPs in different durations. These images show the attachment of some precipitates to the tubular walls, which confirm that the dental tubules remain occluded after rinsing with water (Fig. 3a–d). In particular, the specimens treated with nanoparticles for 120 min showed a high occlusion level of dental tubules (Fig. 3d).

According to the “hydrodynamic theory”, the fluid movement within the dental tubules is the main cause of dental hypersensitivity. On the other hand, Poiseuille–Hagen equation states that the fluid movement in a tubule is proportional to the fourth power of tubular radius and the pressure difference between the two ends of the tubule[7]. This present study provided the understanding of the potential of PEG-MNPs for occlusion of the dental tubules’ orifices which in turn would reduce the dentin’s permeability and fluid movement within the dental tubules. Therefore, according to the hydrodynamic theory and Poiseuille–Hagen equation, these nanoparticles may reduce the hypersensitivity pain by decreasing the number or the diameter of opened dental tubules.

The PEG-MNPs possess the potential to act as biomedical carriers for other potential treatment opportunities in dentistry, such as dental renaturalization. These nanoparticles might also be used to penetrate into teeth structures in order to acquire energy, sense, and manipulate their surroundings within a short time, offering a quick and permanent cure for patients.

4. Conclusion

In this study, the permeability of polyethylene-glycol coated maghemite nanoparticles into dental tubules was examined via an external magnetic field. Moreover, the effect of exposure time to external magnetic field on the occlusion ratio of the tubules was also investigated. The results of this study provide a confirmation of the research hypothesis that polyethylene-glycol coated maghemite nanoparticles are able to occlude the open dental tubules, and could be used in dental hypersensitivity treatments due to a relatively fast diffusion and tight sealing of the tubules. These nanoparticles could also be synthesized by various other biocompatible coatings, such as silicate or hydroxyapatite in order to evaluate their effectiveness for more durable treatment of dental hypersensitivity.

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