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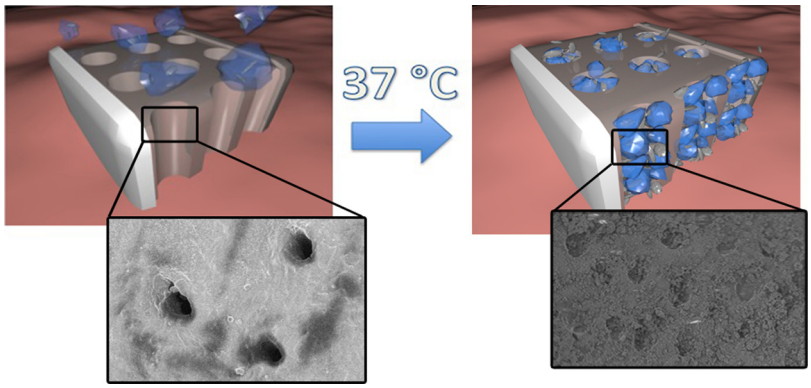
Poly(N-isopropylacrylamide)-hydroxyapatite nanocomposites as thermoresponsive filling materials on dentinal surface and tubules

Paolo Tempesti, Giovanni Simone Nicotera, Massimo Bonini, Emiliano Fratini *, Piero Baglioni *

Department of Chemistry "Ugo Schiff" and CSGI, University of Florence, Via Della Lastruccia 3, 50019 Sesto Fiorentino, Italy

GRAPHICAL ABSTRACT



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ABSTRACT

Hypothesis: Dental decay, as a consequence of exposure to acidic foods and drinks, represents one of the most important tooth pathologies. Recently, enamel and dentinal surface remineralization using hydroxyapatite nano- and microparticles has been proposed; however, commercial remineralizing toothpastes are quite expensive, mostly due to the high costs of hydroxyapatite. Hence, we propose a thermoresponsive hybrid nanocomposite material as filler for tooth defects. The use of thermoresponsive composite particles aims at filling exposed dentinal tubules in response to a change of temperature in the oral cavity. In addition, the presence of the organic matrix contributes to the occlusion of the dentinal tubules, therefore reducing the needed amount of hydroxyapatite.

Experiments: Poly-N-isopropylacrylamide microgels containing different amounts of hydroxyapatite nanoparticles were prepared via radical polymerization in the presence of N-N′-methylenebisacrylamide as cross-linker followed by mechanical grinding. The nano- and microstructure of the hydrogels and their thermal behavior were studied via small-angle X-ray scattering (SAXS), scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). Defected teeth were treated with a dispersion of nanocomposite microparticles to simulate toothpaste action.

Findings: The hydrogels maintain their structure and thermal responsiveness when loaded with an amount of hydroxyapatite nanoparticles up to 2.3% w/w. In addition, the lower critical solution temperature is not affected by the presence of the mineral particles. Exposed dentinal tubules on the surface of test tooth samples were successfully occluded after 15 cycles of treatment with a dispersion of nanocomposite microparticles alternated with washing steps.

* Corresponding authors.
E-mail addresses: fratini@csgi.unifi.it (E. Fratini), piero.baglioni@unifi.it (P. Baglioni).

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1. Introduction

Thermoresponsive polymers are known to exhibit conformational changes because of temperature variations. Block copolymers such as poly(ethylene oxide)-poly(propylene oxide)-poly (ethylene oxide) and poly(N-ethyl oxazoline co-acrylamide), or linear polymers such as poly(N-vinyl caprolactam) and poly-N-isopropylacrylamide (PNIPAm) in water, for instance, undergo a coil-to-globule phase transition from a swollen to a collapsed state when heated above their lower critical solution temperature (LCST) which is typically around or above 32 °C [1–4]. As an example, thermoresponsive polymers, like Pluronic F127 and F68, have been already investigated as delivery systems for various anesthetics targeting the periodontal pocket [2,3]. Together with its biocompatibility [5], the LCST close to the human body temperature represents the main reason for the growing attention on PNIPAm in the biomedical field, especially in view of thermally triggered drug release applications [6]. Recent studies have concluded that no evident collateral effects arise when PNIPAm hydrogels are added to cells [5] even after internalization in lysosomes [7]. Moreover, the cytotoxic response is usually correlated to commercially available PNIPAm where it is likely associated to the presence of impurities in the polymer matrix (monomer, radical initiator) rather than on the polymer itself [5].

PNIPAm is often used as a thermoresponsive matrix in various composite materials, embedding either inorganic or organic micro- and nanoparticles, that are then used in fields such as optics [8,9], chromatographic separation [10], tissue engineering [11] and biomedicine [12]. Among inorganic fillers [13–15], hydroxyapatite (HAP) has attracted most of the interest in the design of synthetic bone replacement materials: in fact, the mineral component of natural bone tissue (which represents 60–70% of its total dry weight) almost entirely consists of HAP [16].

Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] is the main mineral component of teeth as well, constituting the 95% w/w and 75% w/w of enamel and dentin, respectively [17]. HAP is a bio-ceramic that can be resorbed and support the formation of new dental tissue, allowing the tooth to repair its defects, due to its ability of integrating similar chemical structures [18]. It is already been used as a remineralizing agent in commercially available toothpastes, such as UltraDEX®, MEGASONEX®, or BioRepair®. HAP action in those formulations mainly consists in the filling of dentinal tubules whose exposure is due to the partial loss of the enamel layer [19].

Even though the market prices (typically significantly higher than conventional toothpastes) have limited their markets up to now, the advantage in their performances over HAP-free formulations is evident [20]. The high market prices for HAP-containing products are mostly due to production costs of good quality hydroxyapatite, thus requiring to reduce both HAP costs and amounts needed in the toothpaste to achieve the required effectiveness. In the first case, research has been devoted to obtain hydroxyapatite particles from natural sources with respect to the more expensive synthetic products [21,22], while in the second case there are no reports on the improvement of HAP effectiveness in filling dentinal cavities and further research is required [23].

In this paper, we describe a method for synthesizing a smart nanocomposite material by embedding HAP nanoparticles within PNIPAm hydrogels to improve their adhesion and entrapment within dentinal tubules. While the literature reports few papers where PNIPAm networks are combined with HAP to form composite particles [24–26], to the best of our knowledge there are no scientific reports describing the inclusion of HAP particles within bulk PNIPAm hydrogels. The obtained composite is ground to obtain microparticles whose size fits well that of dentinal tubules. The thermoresponsiveness of the polymeric network introduces a control over the volume occupied and the chemical affinity of the composite particles. The material is designed so that the shrinking of the polymer matrix (triggered by the temperature of the oral cavity) results in the hydrophobization of the nanocomposite and the subsequent sedimentation of the particles on the tooth surface. In addition, the filling of the tubules could be highly enhanced by the reduced size of the particles when in their collapsed state (see Fig. 1). This novel composite material can be readily dispersed in commercial formulations, potentially matching the performances of already existing remineralizing toothpastes, but with reduced costs as a result of the lower amount of HAP needed. Lastly, the thermoresponsiveness of the polymeric network and the potential to release an embedded active molecule could be extended towards different applications, such as pore filling material for on-demand drug releasing membranes [27].

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPAm, Sigma-Aldrich, 97%, M.W. 113.16 g/mol), N,N′-methylenebisacrylamide (MBAm, Fluka, ≥98.0%, M.W. 154.17 g/mol), N,N,N′,N′-tetramethylethylenediamine (TEMED, Sigma-Aldrich, ~99%, M.W. 116.2 g/mol) and ammonium persulfate (APS, Sigma-Aldrich, ≥98.0%, M.W. 228.2 g/mol) were used without further purification. Commercial HAP was received as a gift in the form of an aqueous dispersion (NanoXIM CarePaste®, Fluidinova S. A., Portugal). The concentration in HAP was 25.5% w/w as obtained by thermogravimetry (see Fig. S1 in the Supplementary Material). Water was purified by a Millipore Organex system (R ≥ 18 MΩ cm).

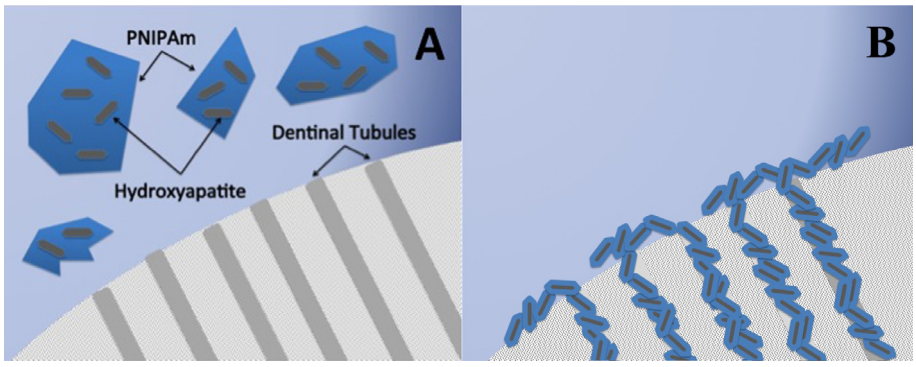

Fig. 1. Graphical representation of the proposed work: tooth samples with exposed dentinal tubules are treated with a dispersion of PNIPAm-HAP composite microparticles. At 25 °C the microgel is in its swollen state and hardly enters the tubules (A), while at 37 °C the shrinking leads to the occlusion of the dentinal tubules (B).