Synthetic Hydroxyapatite as a Biomimetic Oral Care Agent

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Purpose: Human tooth enamel consists mostly of minerals, primarily hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, and thus synthetic hydroxyapatite can be used as a biomimetic oral care agent. This review describes the synthesis and characterization of hydroxyapatite from a chemist's perspective and provides an overview of its current use in oral care, with a focus on dentin hypersensitivity, caries, biofilm management, erosion, and enamel lesions.

Sources: Reviews and original research papers published in English and German were included.

Results: The efficiency of synthetic hydroxyapatite in occluding open dentin tubules, resulting in a protection for sensitive teeth, has been well documented in a number of clinical studies. The first corresponding studies on caries, biofilm management and erosion have provided evidence for a positive effect of hydroxyapatite either as a main or synergistic agent in oral care products. However, more in situ and in vivo studies are needed due to the complexity of the oral milieu and to further clarify existing results.

Conclusions: Due to its biocompatibility and similarity to biologically formed hydroxyapatite in natural tooth enamel, synthetic hydroxyapatite is a promising biomimetic oral care ingredient that may extend the scope of preventive dentistry.

Key words: biofilm management, caries, erosion, dentin hypersensitivity, synthetic hydroxyapatite

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Teeth are highly mineralised, rigidly organised structures which represent the hardest tissue in the human body. They have remarkable mechanical properties, such as fracture toughness and high load resistance. In general, teeth are composed of two types of differently structured hard tissues (Fig 1). The inner part of a tooth consists of dentin, a bone-like biomineral consisting primarily of hydroxyapatite nanocrystals with about 20 wt% organic matrix which is mainly composed of proteins. Shape and size of the hydroxyapatite crystallites in dentin are very similar to those described in bone. They have a platelet-like crystal morphology with dimensions of about 35 x 25 x 4 nm, i.e. they are much smaller than the hydroxyapatite crystallites found in enamel and their spatial arrangement is much more random.[41] Within the dentin, µm-sized tubuli are present that radially point outwards towards the tooth surface. The outer layer of a tooth consists of enamel, which forms a complex microstructure of µm-sized hydroxyapatite crystallites, with proteins making up only a few percent of the composition. The smallest inorganic building units of enamel are hydroxyapatite crystallites with a needle-like crystal morphology. These crystallites are thin (approximately 50 nm) and long (up to 100 µm), tightly packed and strictly organised in crystallite bundles, denoted as enamel prisms. Chemically, the crystallites in dentin and enamel both consist of carbonated calcium-deficient hydroxyapatite (dahllite). The boundary zone between dentin and enamel is called dentin-enamel junction. Dentin and enamel have different mineral contents, as determined by thermogravimetry, with dentin containing about 70 wt% hydroxyapatite and enamel about 97 wt% hydroxyapatite.[12,24,41,42,43,45,55,56,57,88,107,121,187]

Out of all calcium phosphate phases, hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, is the most prominent calcium phosphate mineral in nature.[41] It is also the most common mineral found in mammalian teeth and bones (thus also human). Hydroxyapatite has a hexagonal crystal structure with lattice parameters $a = 9.430$ Å and $c = 6.891$ Å.[41] Pure hydroxyapatite appears white in colour. However, geological hydroxyapatite often displays different colours because of substitution of calcium with transition metals within the apatite lattice. From a mechanical point of view, hydroxyapatite has an elasticity modulus of about 10 GPa and a compressive strength of about 100 MPa.[41] Within the hexagonal crystal structure of such a biological apatite, small

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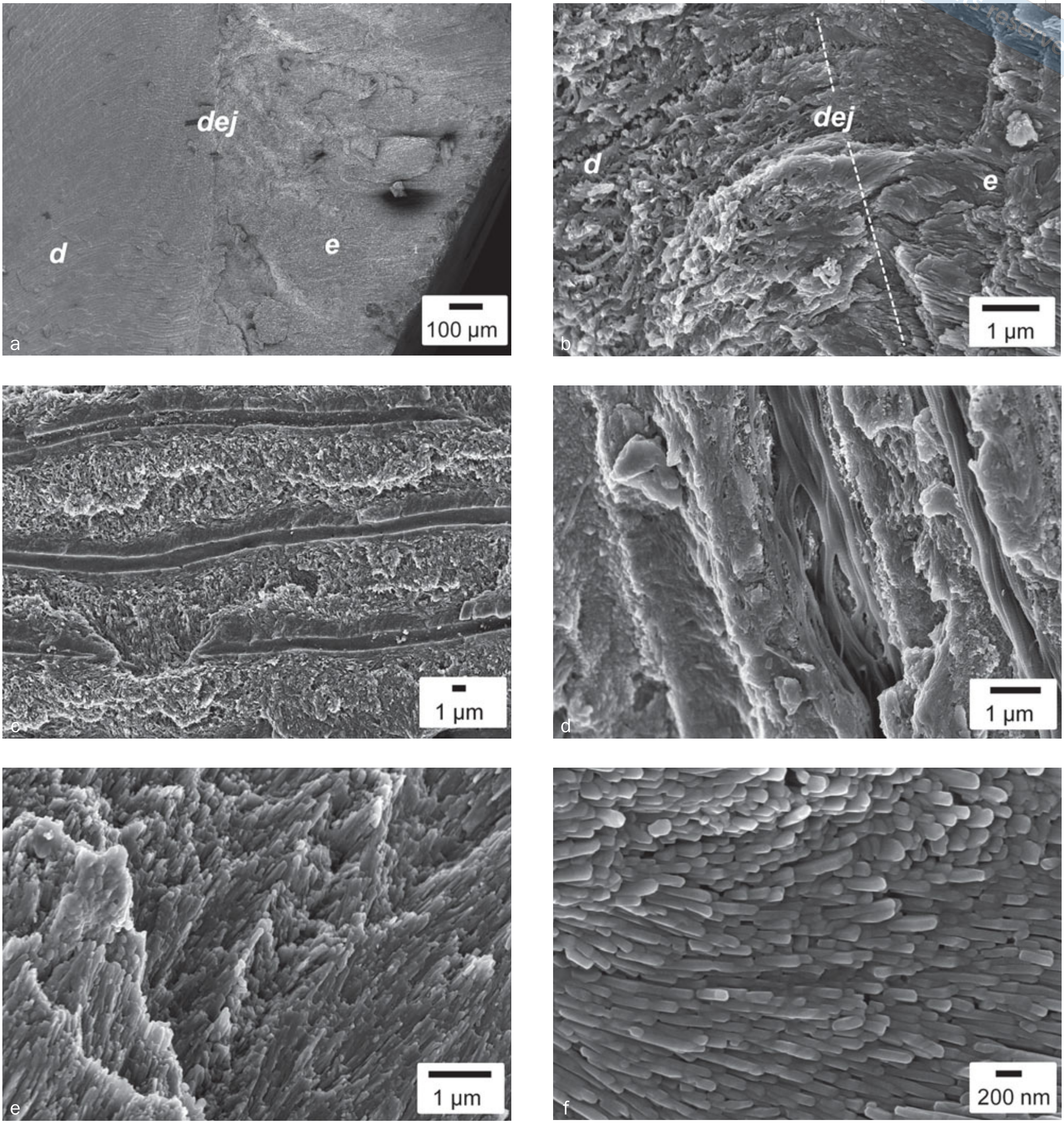

Fig 1 High-resolution SEM images showing the microstructure of a human molar (sagittal fracture). Dentin-enamel-junction dej (a, b), dentin d (c, d) and enamel e (e, f). a: Trajectory of the dentin-enamel-junction; b: Detail of the dentin-enamel-junction showing the interface between highly organised enamel crystallites (right) and porous, less organised dentin (left); c: Dentin microstructure with µm-sized tubuli; d: Organic filaments within dentin tubuli close to the pulpa cavity; e: Needle-shaped crystallites of enamel organised in longitudinal bundles (prisms); f: Structural details of the hydroxyapatite crystallites in enamel (images courtesy of Dr. Helge-Otto Fabritius, Max-Planck-Institut für Eisenforschung GmbH, Düsseldorf, Germany).

amounts of different foreign ions like magnesium, sodium, and especially carbonate are always present.[22,41,107] The substitution of orthophosphate, PO_4^{3-}, by hydrogen phosphate, HPO_4^{2-}, leads to a charge-balancing deficiency within the calcium lattice. Therefore, the mineral in human teeth can be more precisely described as a substituted carbonated calcium-deficient hydroxyapatite.[41]

Several other calcium phosphate phases with different stoichiometry are known.[41,22] Out of all calcium phosphates, hydroxyapatite has the lowest solubility in water at a neutral pH.[41,22] However, hydroxyapatite (like all calcium phosphates) is soluble in acids, which may lead to caries and dental erosion.[5,39,53] It should be noted that hydroxyapatite leads to the release of physiological calcium and hydrogen phosphate ions under acidic conditions:[53]

(I) $Ca_{10}(PO_4)_6(OH)_2 + 8\ H^+ \rightarrow 10\ Ca^{2+} + 6\ HPO_4^{2-} + 2\ H_2O$

Due to the chemical and structural similarity of synthetic hydroxyapatite with hydroxyapatite found in teeth and bones, leading to a high biocompatibility in contact with hard tissue,[163,175,178,179,198] it is widely used in biomedical applications, for example, as bone substitution material, the coating of metallic implants to improve implant biocompatibility, and as a drug-delivery agent.[14,15,68,102,109,114,144,172,179,185,186,193] Furthermore, dental composite materials based on synthetic hydroxyapatite have been reported.[40,105,145,105,170]

In addition to the aforementioned medical applications, hydroxyapatite is used in oral care products due to its chemical and structural similarity to the hydroxyapatite ("bioapatite") found in dentin and enamel.[44] In contrast to many synthetic agents in oral care, many of which are regulated with respect to permitted concentrations, hydroxyapatite possesses biomimetic properties and is non-toxic. If accidentally swallowed, hydroxyapatite is dissolved in the gastric acid (pH 1–2) to release physiological ions (see equation [I]). Small particles of hydroxyapatite are believed to be naturally present in the oral cavity as a result of tooth wear. This might have an effect on biofilm management.[72]

Hydroxyapatite particles have been evaluated in the field of oral care over the past few decades. The first studies were published in the 1980s.[87,95] Publications on synthetic hydroxyapatite in the field of oral care comprise mainly in vitro studies; however, some in situ and in vivo studies have been reported.[95,70,80,137,148,149] As dental erosion may lead to irreversible loss of tooth hydroxyapatite, many studies have investigated synthetic hydroxyapatite for repairing small defects in the enamel structure.[53,75,85,86,108,127,133,137,165,166,169,184,191,207] In contrast to "classical" oral care agents, such as fluoride compounds (for example, sodium fluoride, stannous fluoride, amine fluoride) about which a large number of clinical studies have been published,[11,53,81,120,126,129,159,188,192] synthetic hydroxyapatite has barely been studied for oral care. However, several studies were recently published which investigated synthetic hydroxyapatite in oral care due to its promising natural and biomimetic properties.[80,77,146,199] Synthetic hydroxyapatite is commercially available as powders with different particle sizes that are used as active ingredients in oral care products such as toothpastes, mouthwashes, and tooth desensitizers.[61,63,153] Chemically, the synthesis of hydroxyapatite is very well understood and offers many possibilities to tailor both structure and size and the composition of the product. Tailored properties for different functions are an important prerequisite for substances used in biomimetic applications.

This review assesses the current status of synthetic hydroxyapatite in biomimetic oral care, focusing on its impact on the following key oral health issues:

A. Dentin hypersensitivity
B. Caries and biofilm management
C. Erosion and enamel lesions

We begin by summarising current techniques for the synthesis and characterisation of hydroxyapatite and subsequently provide an outlook on further research.

SYNTHESIS AND CHARACTERIZATION OF HYDROXYAPATITE

In nature, hydroxyapatite occurs geologically and in hard tissues formed by living organisms (e.g. teeth and bones of vertebrates).[41] A commonly used natural source for hydroxyapatite for biomedical applications (e.g. for bone substitution) is calcined bovine bone.[186] In addition, hydroxyapatite can be formed synthetically. Note that biological and geological hydroxyapatites always contain substitutions of foreign ions, both anionic and cationic (Table 1). Therefore, a preparation by chemical synthesis is preferred for biomedical applications where it is important to achieve hydroxyapatite crystallites with tailored properties (i.e. chemical purity, crystal morphology, and crystal size). Hydroxyapatite can be synthesised from calcium and phosphate solutions under alkaline conditions.[41]

Synthesis of stoichiometric hydroxyapatite (Ca:P molar ratio 1.67:1):

(II) $10\ Ca^{2+} + 6\ PO_4^{3-} + 2\ OH^- \rightarrow Ca_{10}(PO_4)_6(OH)_2$

Examples include wet chemical syntheses and hydrothermal syntheses. A hydrothermal synthesis (i.e. reaction conditions of high temperature and high pressure) is commonly used to achieve hydroxyapatite crystallites with a well-defined crystal morphology and crystal size. After the reaction, the hydroxyapatite crystallites are washed several times in order to remove residual ions.[21,41,42,130] Typical analytical methods to characterise the hydroxyapatite crystallites are summarised in Table 2. To achieve a stoichiometric hydroxyapatite, the pH of the reaction solution should be above 10, because at lower pH, a considerable amount of hydrogen phosphate ions will be incorporated into the apatite lattice, leading to calcium-deficient hydroxyapatite.[22,41]

Synthesis of calcium-deficient hydroxyapatite (Ca:P molar ratio 1.5–1.67:1):

(III) $(10\text{-}x)\ Ca^{2+} + x\ (HPO_4^{2-}) + (6\text{-}x)\ PO_4^{3-} + (2\text{-}x)\ OH^- \rightarrow$
$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$; $(0 < x < 1)$

Different crystal morphologies of hydroxyapatite can be created, e.g. needle-like or spherical crystallites, and also different crystallite sizes.[46,113,210,139]

Table 1 **Examples of potential substituents within the hydroxyapatite lattice**[22,107]

$Ca_{10}(PO_4)_6(OH)_2$		
Substituent for Ca^{2+}	Substituent for PO_4^{3-}	Substituent for OH^-
Sr^{2+}, Zn^{2+}, Na^+, K^+, Cu^{2+}, Ag^+, Mg^{2+}	CO_3^{2-}, HPO_4^{2-}	CO_3^{2-}, F^-, Cl^-

Table 2 **Overview of commonly used analytical methods for the physicochemical characterization of calcium phosphates, including hydroxyapatite).**[22,24,41,48,50,103,123,130,153,154]

Analytical method	Results
X-ray powder diffraction (XRD)	Analysis of the mineral component and calculation of the lattice parameters. In the calcium phosphate family, it is possible to distinguish between hydroxyapatite and other calcium phosphate phases like brushite, $CaHPO_4 \cdot 2\,H_2O$, or monetite, $CaHPO_4$. The amount of incorporated foreign ions can be estimated by calculating the lattice parameters (Rietveld refinement). Substituting ions can cause an increase or a decrease in the lattice parameters.
Infrared (IR) spectroscopy	Analysis of the mineral component and the organic matrix.
Scanning electron microscopy (SEM)	Analysis of crystallite microstructure, morphology, particle size, and structural organization.
Energy dispersive x-ray spectroscopy (EDX)	Qualitative analysis of the elemental composition. This method gives an overview of all elements present in the sample.
Atomic absorption spectroscopy (AAS)	Quantitative analysis of calcium and other metals; calculation of the characteristic molar Ca:P ratio (1.67:1 for hydroxyapatite).
Ultraviolet (UV) spectroscopy	Quantitative analysis of phosphate (as phosphate-molybdenum blue complex); calculation of characteristic molar Ca:P ratio.
Dynamic light scattering (DLS) and laser diffraction analysis	Analysis of particle size distribution in case of dispersed particles. DLS characterises nanoparticles (including nanohydroxyapatite) whereas laser diffraction analysis is mainly used to characterise microparticles (including hydroxyapatite aggregates or agglomerates).

Moreover, hydroxyapatite can be doped with different ions to adjust the chemical composition as well as the resulting crystallite morphology and crystallinity.[162,208] Furthermore, the dissolution properties associated with hydroxyapatite may change due to the different substituents.[22] Potential substituents are summarised in Table 1.

For example, the synthesis and characterisation of a bio-inspired zinc-substituted carbonated hydroxyapatite has been previously reported for oral care. These crystallites mimic the crystallites in natural enamel.[165-167] The degree of substitution by foreign ions in the apatite lattice can vary from low substitution (such as magnesium and potassium) up to a complete substitution, e.g. resulting in stoichiometric fluoroapatite, $Ca_{10}(PO_4)_6F_2$, the mineral in shark teeth enameloid, or strontium apatite, $Sr_{10}(PO_4)_6(OH)_2$.[49,50]

Synthesis of fluoroapatite:

(IV) $10\,Ca^{2+} + 6\,PO_4^{3-} + 2\,F^- \rightarrow Ca_{10}(PO_4)_6F_2$

Synthesis of strontium apatite:

(V) $10\,Sr^{2+} + 6\,PO_4^{3-} + 2\,OH^- \rightarrow Sr_{10}(PO_4)_6(OH)_2$

It is also possible to synthesise hydroxyapatite with different particle size, ranging from the nano- to the microscale, which can be controlled by the reaction conditions.[54,62,177,185,205,210] Both particle size and crystallite structure can influence the effect of hydroxyapatite in oral care products, e.g. when an occlusion of open dentin tubuli is desired.[87,153]

As the biological effect of hydroxyapatite (or, more general, calcium phosphate) strongly depends on its properties, it must be emphasised that detailed structural and chemical analyses are necessary to correlate the structure and composition of different hydroxyapatites with their effects in the oral cavity. Examples of commonly used analytical methods for the characterisation of apatite minerals include x-ray powder diffraction (XRD), scanning electron microscopy (SEM), infrared (IR) spectroscopy, and elemental analysis (Table 2).[22,49,48,50,103,124,130,154,210]

Various synthetic hydroxyapatites are commercially available as raw material for oral care products. Their properties may vary with respect to crystallite morphology, crystallinity, particle size, and substitution with foreign ions.

Table 3 Overview of publications with hydroxyapatite and hydroxyapatite-based products in the field of oral care (for details see the corresponding sections)

Oral health concerns	Publications showing the efficacy of hydroxyapatite and hydroxyapatite-based products	Critical publications concerning the efficacy of hydroxyapatite and hydroxyapatite-based products
A. Dentin hypersensitivity	Oliveira et al,[146] Wang et al,[199] Amaechi et al,[4] Farooq et al,[52] Genovesi et al,[61] Gopinath et al,[65] Vano et al,[195] Vano et al,[194] Orsini et al,[148] Browning et al,[23] Yuan et al,[209] Orsini et al,[147] Shetty et al,[174] Lee et al,[106] Hüttemann et al[87]	Arnold et al,[6] Arnold et al,[7] Hill et al[82]
B. Caries / biofilm management	Harks et al,[77] Hegazy et al,[80] Brambilla et al,[19] Hannig et al,[70] Palmieri et al,[151] Najibfard et al,[137] Itthagarun et al,[89] Huang et al,[86] Lu et al,[122] Lv et al,[127] Jeong et al,[91] Onuma et al,[147] Okashi et al,[144] Kani et al,[95] Kani et al[96]	Esteves-Oliveira et al,[51] Zhang et al,[211] Sun et al[183]
C. Erosion / enamel lesions	Min et al,[135] Bonetti et al,[16] Lelli et al,[108] Mielczarek et al,[133] Poggio et al,[157] Gjorgievska et al,[64] Sadiasa et al,[169] Swarup et al,[184] Haghgoo et al,[69] Huang et al,[85] Li et al,[110] Min et al,[136] Tschoppe et al,[191] Huang et al,[84] Poggio et al,[156] Roveri et al,[165] Ryu et al,[168] Li et al,[111] Roveri et al,[166] Yamagishi et al[207]	Esteves-Oliveira et al,[51] Kensche et al,[99] Bradna et al,[18] Aykut-Yetkiner et al,[8] Comar et al,[36] Ganss et al[60]

APPLICATIONS OF SYNTHETIC HYDROXYAPATITE IN THE FIELD OF ORAL CARE

The effect of synthetic hydroxyapatite on dentin hypersensitivity, caries, biofilm management, erosion, and enamel lesions are controversially discussed in the literature. An overview of published studies assessing synthetic hydroxyapatite in oral care is presented in Table 3.

Dentin Hypersensitivity

A symptom of dentin hypersensitivity is the pain that occurs when dentin is exposed to extrinsic stimuli, such as cold water or acidic beverages, in the oral cavity.[1,134] Possible reasons for dentin hypersensitivity are the partial loss of protective enamel as a result of erosion and pathological exposure of the tooth cervices.[134,204] There are several strategies to prevent dentin hypersensitivity in oral care, including occlusion of dentin tubuli with different particulate materials (arginine/calcium carbonate, calcium sodium phosphosilicate, strontium fluoride etc.) or nerve desensitisation with agents such as potassium salts.[9,63,87,120,128]

Due to their biocompatibility, synthetic hydroxyapatite particles seem to be ideally suited to occlude open dentin tubuli. This approach can be easily employed at home in the form of toothpastes or mouthwashes.[153]

In 1987 Hüttemann and Dönges published a clinical study of 140 patients with hypersensitive teeth who used hydroxyapatite of different particle sizes for treatment. 90% of all patients experienced relief from tooth hypersensitivity after 3 to 5 days. Importantly, the size of the hydroxyapatite particles was found to play an important role in the degree of desensitisation. A paste containing 2-µm hydroxyapatite particles was more effective than a paste containing 6-µm hydroxyapatite particles.[87] This may be due to the fact that the diameter of natural dentin tubuli is approximately 2.4–3.0 µm.[119] Obviously, smaller particles fit better into the dentin tubuli than larger particles.[63] Another more recent clinical study confirmed the efficacy of a nanohydroxyapatite-containing toothpaste in treating dentin hypersensitivity, showing similar results as a toothpaste containing calcium sodium phosphosilicate.[65] This result was confirmed by Amaechi et al,[4] who found that toothpastes containing hydroxyapatite were comparable to toothpastes containing calcium sodium phosphosilicate, both being superior to a sodium monofluorophosphate-containing toothpaste. Occlusion of dentin tubuli with hydroxyapatite was confirmed in in vitro tests conducted by Lee et al[106] and Farooq et al[52] and verified by SEM. However, another study found that the occlusion of dentin tubuli with synthetic hydroxyapatite was lost after an acid challenge.[7]

Orsini et al[148] conducted a clinical study in which the efficacy of a zinc-substituted carbonated hydroxyapatite-containing toothpaste was compared to a potassium nitrate/sodium fluoride-containing toothpaste. Both toothpastes significantly reduced dentin hypersensitivity after 4 and 8 weeks of treatment.[148] Another clinical study showed that a significant reduction of dentin hypersensitivity occurred after only 3 days of treatment with a zinc-substituted carbonated hydroxyapatite-containing toothpaste, highlighting its practical relevance.[149] Wang et al[199] reported that professional and home-care pastes containing nanohydroxyapatite were as effective as arginine/calcium carbonate-containing pastes after 1 and 3 months treatment.

In a study conducted by Shetty et al,[174] hydroxyapatite demonstrated its potential as an effective desensitizer, significantly reducing hypersensitivity symptoms after one day and after 1, 2, and 4 weeks, compared to the controls (either distilled water or no treatment) in patients with hypersensitive teeth.

In a recent study, different commercially available desensitising toothpastes were analysed, and the only toothpaste leading to immediate relief from hypersensitive teeth was a nanohydroxyapatite-containing toothpaste.[146] A desensitising prophylaxis paste with hydroxyapatite was shown to be effective in vitro[61] and a hydroxyapatite paste reduced tooth hypersensitivity after bleaching.[23] Furthermore, a combination of calcium phosphate nanoparticles loaded with chlorhexidine as desensitising and antibacterial mouthwash was also proposed.[104]

However, a detailed understanding of the basic principle behind these results is necessary to understand and improve the current treatment paradigm for dental hypersensitivity. This can be achieved by determining the structural composition of the main desensitising agents. For example, in one study, the solid components of three different commercially available desensitising toothpastes and a mouthwash were characterised using different physicochemical methods like XRD, energy dispersive x-ray spectroscopy (EDX) and SEM.[153] The solid components of these products were zinc-substituted hydroxyapatite and amorphous silica (Product A); TiO_2 (anatase) and an amorphous Na-Ca-Si-P bioglass (Product B); TiO_2 (anatase), amorphous silica and traces of a calcium-containing material (Product C). All samples contained particles with a size of 300–400 nanometers as determined by dynamic light scattering. SEM showed highly aggregated structures. Due to the small sizes of the mineral particles, all of the products were potentially able to occlude open dentin tubuli.[153]

Besides classical oral care products such as toothpastes and mouthwashes, a hydroxyapatite-containing chewing gum was found to significantly reduce dentin hypersensitivity after one and two weeks.[158]

In conclusion, particulate synthetic hydroxyapatite is well suited to occlude open dentin tubuli because of its solid structure as well as its chemical and structural similarity to natural hydroxyapatite. Clinical studies underline the efficacy of hydroxyapatite-containing products in the treatment of sensitive teeth. As well as chemical properties, the particle size might be important for occlusion due to the limited diameter of dentin tubuli.[63,119]

Caries and Biofilm Management

Caries prevention is still a major challenge in preventive dentistry.[100,117,153] Dental caries can be defined as "(...) the results – the signs and symptoms – of a localised chemical dissolution of the tooth surface caused by metabolic events taking place in the biofilm (dental plaque) covering the affected area".[53]

The most frequently applied prophylactic agent for caries is fluoride.[120] Fluoride-containing products, diet, improvement of oral health programmes and prophylaxis as well as other factors all contribute to the decrease in caries incidence.[20,155] Examples of fluoride compounds commonly used in oral care include sodium fluoride, amine fluoride, stannous fluoride, and sodium monofluorophosphate.[120,188] Compared with anti-caries studies of fluoride-containing products, studies about synthetic hydroxyapatite are rare. Nevertheless, finding alternative biomimetic agents or agents that enhance the effect of fluoride may be a promising approach to improve current oral therapies.[2,29,75,76,83,94,112,118,132,140,152,202,203]

Hydroxyapatite has been used in oral care products in Japan since the 1980s, and their efficacy as a caries prophylactic agent was confirmed in 1993.[120]

The first comprehensive anti-caries study of a hydroxyapatite-containing toothpaste was published by Kani et al.[95] The 3-year study included 181 schoolchildren in Japan who were assigned to either a hydroxyapatite-containing toothpaste or a control toothpaste without hydroxyapatite. It was found that the incidence of caries was significantly lower in the hydroxyapatite group than in the hydroxyapatite-free control group. The caries-reducing effect of hydroxyapatite was explained as follows:[95]

1. remineralisation of carious lesions by hydroxyapatite
2. adsorption of polysaccharides produced by *Streptococcus mutans*
3. protein adsorption
4. tooth surface abrasive properties

To the best of our knowledge, this is the only comprehensive in vivo study of a hydroxyapatite-based toothpaste in the field of caries prophylaxis. Although the study showed a clear effect of hydroxyapatite in reduction of caries incidence, one limitation of the study was that no fluoride control was employed. Therefore, future in vivo studies should compare hydroxyapatite- and fluoride-based toothpastes.

A recently published in vivo study with different mouthwashes showed the remineralisation potential of early caries lesions by a hydroxyapatite-containing mouthwash.[80]

Additionally, in situ and in vitro studies provided evidence that synthetic hydroxyapatite may aid in preventing caries. Najibfard et al[137] analysed the remineralisation ability of a nanohydroxyapatite toothpaste in situ and found similar remineralisation to a fluoride-containing toothpaste. Additionally, caries development was inhibited. Remineralisation of artificial caries lesions by nanohydroxyapatite was also further demonstrated in an in vitro study.[127] However, an in vitro study analysing mineral loss and lesion depth by transversal microradiography came to the conclusion that a hydroxyapatite-containing toothpaste was not as effective as a fluoride-containing toothpaste.[51]

Huang et al[86] analysed the potential of different concentrations of nanohydroxyapatite on remineralisation in vitro (i.e. 1, 5, 10, 15 wt% hydroxyapatite). 10 wt% nanohydroxyapatite was found to be the optimum concentration for repairing small enamel lesions.

Synergistic effects on the remineralisation of early caries lesions by the use of both nanohydroxyapatite and sodium fluoride were shown in a subsequent in vitro study. Moreover, the degree of remineralisation depended on the concentration of nanohydroxyapatite, with higher nanohydroxyapatite concentrations leading to a greater degree of remineralisation. The adhesion of nanohydroxyapatite to enamel was observed by SEM.[101] An in situ study confirmed the synergistic effects of hydroxyapatite and fluoride. A toothpaste containing both nanohydroxyapatite and sodium fluoride effectively remineralised enamel and prevented dentin demineralisation.[180]

However, using synthetic hydroxyapatite in combination with soluble fluoride compounds (e.g. sodium fluoride and amine fluoride) in toothpastes may reduce the bioavailability of fluoride ions in the oral cavity.[120] This negative impact on fluoride ions was also observed in toothpastes containing calcium carbonate and calcium hydrogen phosphate dihydrate, thus emphasising the strong interaction between calcium and fluoride,[3,47] with the potential formation of the highly insoluble fluoroapatite (see above).[41]

With respect to the mode of action, synthetic hydroxyapatite could repair small enamel lesions by acting as a nucleation template to which calcium and phosphate ions from saliva can adhere.[86,120] From a chemist's point of view, an ionic interaction between synthetic hydroxyapatite and the tooth surface appears to be feasible. Other factors that may also be important are the interaction of synthetic hydroxyapatite with the dental pellicle and the influence of saliva proteins. Additionally, there might be differences in the adhesion of synthetic hydroxyapatite to enamel and dentin because of their different compositions. The adhesion of synthetic hydroxyapatite to enamel is similar to the natural remineralisation process. Dentin, however, has a lower hydroxyapatite content (70 wt%) compared to enamel (97 wt%) and calcium phosphate nanocrystals are embedded into the collagen.[55,107] Thus, attractive interaction between synthetic particulate hydroxyapatite and collagen is likely.[13,32,98,142]

However, further in situ and in vivo studies (and potentially modelling studies in silico) are still necessary to clarify the therapeutic potential and mode of action of synthetic hydroxyapatite in caries prevention.[3]

In addition to remineralisation, biofilm management is also a key component of caries prophylaxis.[29,71,90] The microbiological effectiveness of hydroxyapatite in biofilm management was analysed in several studies.[70,80,151] A zinc-substituted carbonated hydroxyapatite was found to have an inhibitory effect on the initial biofilm formation of *Streptococcus mutans*.[151] In a comprehensive in situ study, Hannig et al[70] analysed the effects of a zinc-substituted carbonate hydroxyapatite-containing mouthwash on oral biofilm management.[70] Subfractions of a suspension comprising hydroxyapatite microclusters (solid component, i.e. aggregated hydroxyapatite crystallites having a size of ca 100–300 nm)[153] and the liquid component were also analysed. Interestingly, the subfraction containing the pure zinc-substituted carbonated hydroxyapatite microclusters (without additional agents) reduced the amount of bacteria adhering to enamel. However, the liquid component (which contained a zinc salt, sorbitol and xylitol, for instance) resulted in an even stronger antimicrobial effect.[70] Thus, it can be assumed that hydroxyapatite microclusters play an important role in preventing initial bacterial colonisation without having negative impacts on the oral ecology, that is, without killing bacteria. This property supports the biomimetic approach of using synthetic hydroxyapatite as an oral care agent in biofilm management.[72,75] The specific mechanism of how hydroxyapatite microclusters minimise initial bacterial colonisation should be addressed in future studies. One possibility is the interaction between the hydroxyapatite microclusters and the bacterial surface, which could influence the adhesion of bacteria.[70,131,196]

Moreover, a future approach in oral care products could be to achieve synergetic effects in biofilm management by combining the anti-adherence properties of synthetic hydroxyapatite with antibacterial compounds such as zinc salts or xylitol.[70,79]

Additionally, hydroxyapatite can be doped with antimicrobial ions such as copper, zinc or silver.[22,35,117,173,181] In a recent study, the release kinetics of silver ions from silver-doped calcium phosphate were analysed and the antimicrobial effects on bacteria were evaluated.[161] It was found that the release of silver ions increased with time, as approximated by equation (VI).

(VI) $(\mathrm{Ca}/2\ \mathrm{Ag})_{10}(\mathrm{PO}_4)_6(\mathrm{OH})_2 \rightarrow (10\ \mathrm{Ca}^{2+}/20\ \mathrm{Ag}^{+}) + 6\ \mathrm{PO}_4^{3-} + 2\ \mathrm{OH}^{-}$

Thus, a substituted hydroxyapatite may act as a depot in the oral cavity for the constant release of antimicrobial ions for biofilm control.

In addition to remineralisation, anti-adherence and antimicrobial strategies, plaque removal is another key component of caries prophylaxis.[53,120,171] Currently, the most frequently used abrasives in toothpastes are hydrated silica and calcium carbonate.[120,171] Due to its properties as an abrasive agent,[95,120] synthetic hydroxyapatite may also provide anti-caries protection by removing bacterial biofilms.

As well as caries prophylaxis, hydroxyapatite-bases products were found to be effective in improving periodontal health in vivo.[77,80] In a recently published clinical study, hydroxyapatite-containing (zinc-substituted carbonated hydroxyapatite) and fluoride-containing toothpastes (amine fluoride/stannous fluoride) were used by patients with chronic periodontitis. In both groups, the plaque index, bleeding on probing, and the gingival index were improved. Although these toothpastes had different active ingredients, the improvements in periodontal health were comparable in both groups.[77]

In conclusion, the studies on biofilm management and remineralisation of early caries lesions by synthetic hydroxyapatite that have been published so far are promising. However, additional in situ and in vivo studies are necessary, in particular to elucidate the details regarding the mode of action of hydroxyapatite in caries prevention.

Erosion and Enamel Repair

Dental erosion can be defined as follows: "Erosion is characterised by dissolution and removal of an ultrathin layer of enamel each time it is exposed to an acidic challenge".[53]

Dissolution of tooth enamel occurs when the pH value drops below 5.5; in general, calcium phosphate is soluble in acid.[53, 200] This pH threshold is easily crossed by the consumption of acidic food and beverages (e.g. fruits, orange juice, soft drinks).[53,125] Thus, due to modern-day eating habits, dental erosion induced by acidic agents is an increasing problem.[27,115]

There is still room to improve conventional oral care products with respect to prevention and repair of erosion.[189] Several approaches to prevent erosion have been investigated.[125] For example, stannous salts and chitosan were shown to have protective properties against erosion.[28,59] In general, fluoride-containing products have anti-erosive properties.[60,99,125] Since it seems to be able to repair small enamel lesions,[64,85,108,184,191,207] the use of hydroxyapatite is a promising biomimetic approach in the field of erosion prevention.

In an 8-week in vivo study, the effects on remineralisation of enamel by hydroxyapatite- and fluoride-containing toothpastes were compared.[108] After the study, certain teeth were extracted for medical reasons (with the consent of the patients) and the tooth surfaces were thoroughly analysed by SEM, EDX, XRD, and infrared spectroscopy. SEM images and corresponding EDX outcomes showed that after application of a hydroxyapatite-containing toothpaste, a calcium phosphate-rich surface coating was achieved on enamel in vivo. The fluoride-containing toothpaste did not change the native enamel surface and no coating on enamel was observed.[108]

A recently published in situ study showed a potential accumulation of hydroxyapatite from a mouthwash in the dental pellicle, but no significant erosion protection could be observed from this accumulation.[99] Additionally, in an in vitro study, a zinc-substituted carbonated hydroxyapatite toothpaste did not prove to be more effective in preventing dentin erosion compared to other toothpastes.[8] Therefore, it is necessary to address the question of whether a biomimetic coating also protects against erosion.

In 2005, Yamagishi et al[207] published a study on the potential of hydroxyapatite in repairing enamel lesions. In this study, a hydroxyapatite-containing paste demonstrated an enamel-repairing effect that was confirmed by transmission electron microscopy and atomic force microscopy.

An in vitro study showed that the size of hydroxyapatite crystallites is correlated with its ability to repair enamel. Nano-sized hydroxyapatite crystallites were found to have a greater remineralisation potential than larger particles.[111] Additionally, scratched enamel surfaces were regenerated in vitro with a suspension of hydroxyapatite.[168] Furthermore, a toothpaste containing a zinc-substituted hydroxyapatite was less abrasive on exposed enamel compared with other toothpastes.[16]

Additionally, repair of small enamel lesions may result in a smoother surface.[165] This is an important side-effect, because bacteria adhere more strongly to a rough than a smooth surface.[73]

Interestingly, the addition of nanohydroxyapatite to sports drinks reduced their erosive potential, and hydroxyapatite-containing toothpastes effectively prevented acidic erosion by soft drinks.[135,136,156,157] Thus, there is good reason to use hydroxyapatite in repairing erosive lesions.

However, in other studies, a protective layer on the enamel was not detected after the patients brushed their teeth with a hydroxyapatite-containing toothpaste,[18] and a zinc-substituted carbonated hydroxyapatite-containing toothpaste was not found to decrease mineral loss caused by erosion.[60] The mechanism of erosion repair by calcium phosphate-based products, i.e. a superficial enamel repair, was critically discussed because further erosion progression might occur.[36,127,201]

In a study by Besinis et al[13] on dentin remineralisation, silica and hydroxyapatite nanoparticles were proposed to interact with collagen from demineralised dentin, which may lead to dentin remineralisation.

Additives may improve the effects of synthetic hydroxyapatite, above and beyond what has already been established with synthetic hydroxyapatite alone. Li et al[110] reported that glutamic acid supports an oriented growth of a new hydroxyapatite layer on natural enamel. To replicate the complex enamel microstructure for regenerating native enamel is an emerging field of research, and therefore this approach could be promising in biomimetic dental care.[24,25,30,33,74,110,123,150]

In conclusion, numerous studies indicate that synthetic hydroxyapatite has the potential to repair small enamel lesions and form a biomimetic coating.[108] However, further in situ and in vivo studies are necessary to confirm, characterise, and quantify the resulting deposits on dentin, enamel, and the oral mucosa, and to demonstrate how this layer provides protection against erosion and whether this approach is clinically effective.

CONCLUSIONS AND OUTLOOK

Chemically, it is possible to synthesise many different types of hydroxyapatite.[210] Different particle sizes and crystallite morphologies of hydroxyapatite can be generated, and hydroxyapatite can also be doped with different foreign ions to tailor its chemical properties.[22] Thus, a high number of potential test compounds are available. However, they must be physicochemically characterised in detail with methods such as SEM or XRD to assess their nature and correlate this with the biological effect in the oral cavity.[153] These variants of hydroxyapatite can be used in further studies in order to analyse their effects in preventive dentistry. For example, it has been shown that the efficacy of hydroxyapatite depends on its size, for example, in the degree of enamel repair and occlusion of open dentin tubuli.[52,87,111] Similarly, the remineralisation by synthetic hydroxyapatite also appears to depend on the crystal morphology.[122]

A further promising research field is the management of biofilms with synthetic hydroxyapatite.[70,72] Due to the anti-adherence properties of synthetic hydroxyapatite, an initial bacterial colonisation can be minimised without adversely affecting the oral ecology.[70] However, further studies are needed in order to understand this mechanism.

Interestingly, hydroxyapatite and other calcium phosphates were proposed as active ingredients in the oral care of xerostomic patients.[10,78,137,152,176,182,197] Due to the fact that these individuals have a diminished saliva flow, remineralisation is significantly reduced, and the risk of caries is high.[37,66,67,138] Hydroxyapatite may therefore constitute a promising option in individuals suffering from xerostomia, as it reduces the need for calcium and phosphate ions from saliva for remineralisation.[137]

As well as prevention of key oral diseases, aesthetic improvements, such as tooth whitening, are increasingly desired properties of oral care products.[26,93] Several studies analysed the tooth-whitening effects of synthetic hydroxyapatite.[38,92,100,141] They found that synthetic hydroxyapatite in oral care products may contribute to a tooth whitening effect. However, these results need to be clinically verified and quantified.

To summarise, the clinical efficacy of synthetic hydroxyapatite in preventing dentin hypersensitivity is well documented. However, the effect on the remineralisation of early caries lesions, biofilm management, repair of small enamel defects, and erosion protection is less well documented in clinical studies. The presented studies provide insight into the possibility of using synthetic hydroxyapatite as a main or synergetic agent in oral care. Future avenues of research should include the systematic study of synthetic particulate hydroxyapatite in situ and in vivo (e.g. the adherence to dentin, enamel, and the oral mucosa for different applications), as well as the differential analysis of various hydroxyapatite structures and compositions.

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