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# Non-Fluoride Agents for Enamel Remineralization

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**Abstract:** ***In this review the potential of several candidates for remineralization of demineralized human enamel was followed within the results published through the last several decades. Remineralization of early carious lesions may be possible with a variety of currently available agents containing fluoride, bioavailable calcium and phosphate, and casein phosphopeptide in-amorphous calcium phosphate (CPP-ACP), xylitol etc. The current concept further bridges the traditional gap between prevention, non-invasive and surgical procedures which is just what dentistry needs for the current age.***

**Keywords:** remineralizing agent, CPP-ACP, fTCP, Bioactive glass, xylitol

## 1. Introduction

Dental caries is a microbial disease of the calcified tissues of the teeth, characterized by demineralization of the inorganic portion and destruction of the organic substance of the tooth, which often leads to cavitation. It is a complex and dynamic process which occurs when demineralization overpoise remineralization [1]. According to recent reports, dental caries still is the most prevalent, costly, preventable, and silent global epidemic in humankind [2]. Ninety-eight percent of the world's population will have caries across the life course (*Petersen 2008*), while 35% of all ages combined (2.4 billion individuals globally) were estimated in the Global Burden of Disease Study to have untreated cavities in permanent teeth [3]. Demineralization and remineralization are processes that normally occur in the oral cavity. Due to oral hygiene, diet variations or microbial activity the prevalence of demineralization may occur. Remineralization is facilitated by the buffering action of saliva, permitting calcium and phosphate ions to precipitate onto the tooth and form new mineral. Therefore, modulation of the demineralization-remineralization balance is the key of prophylaxis of dental caries. [4]. Until now the model of caries excavation and replacing with restorative material such as amalgam, composite, ceramics was the conventional treatment concept. The "minimally invasive" approach conjugates early diagnosis and treatment of carious lesions as soon as possible, accentuating on prevention [5]. The extensive studies on remineralization have led to the development of newer technologies that promote enamel remineralization and prevent enamel demineralization providing promising oral health assistance [6]. Remineralization of early carious lesions may be possible with a variety of currently available agents containing fluoride, bioavailable calcium and phosphate, and casein phosphopeptide inamorphous calcium phosphate (CPP-ACP), xylitol etc. The current concept further bridges the traditional gap between prevention, non-invasive and surgical procedures which is just what dentistry needs for the current age [1].

## 2. Non-fluoride Remineralizing Agents

According to *Walsh et al*., the requirements for an ideal remineralizing agent are:

- Should deliver calcium and phosphate into the subsurface
- Should not deliver any excess of calcium
- Should not favor calculus formation
- Should work at an acidic pH so as to stop demineralization during a carious attack
- Should work in xerostomic patients also, as saliva cannot effectively stop the carious process
- Should be able to boost the remineralizing properties of saliva
- The novel materials should be able to show some benefits over fluoride [7,8].

**Casein phosphopeptide–amorphous calcium phosphate**

At present, calcium-based phosphate system like CPP- ACP gives a new area to preventive dentistry. This technology was developed by *Eric Reynolds* and coworkers at the University of Melbourne. Casein phosphopeptide forms nanoclusters with amorphous calcium phosphate thus providing a pool of calcium and phosphate which can maintain the supersaturation of saliva. Since CPP–ACP can stabilize calcium and phosphate in the solution, it can also help in the buffering of plaque pH and so calcium and phosphate level in plaque is increased. Therefore calcium and phosphate concentration within the subsurface lesions is kept high which results in remineralization [9]. There is a similarity between the salivary statherin, which regulates the calcium and phosphate behavior to stabilize calcium-phosphate compounds, and CPP-ACP. Also CPP-ACP has antibacterial activity. An in vivo study shows that it binds twice the affinity of the bacterial cells for calcium up to a value of 0.16 g/g wet weight cells [10]. The binding of ACP to CPP is pH responsive, with binding decreases as the pH falls and vice versa. It stabilizes free calcium and phosphate so that unprompted precipitation of calcium phosphate does not occur which is an inherently anticalculus action [11]. CPP–ACP reduces caries activity in a dose-dependent

mechanism, and the subsequently formed mineral is more resistant to acid attack. In animal model, it showed that 0.1% w/v CPP–ACP produces 14% reduction on smooth surface caries and 1% w/v CPP–ACP produced a 55% reduction on smooth surfaces caries, and similarly 0.1% w/v CPP–ACP and 1% w/v CPP–ACP produced 15% and 46% reduction in fissure caries activity [12]. The properties of dental plaque might be affected of using CPP-ACP agents by providing protein and phosphate buffering of plaque fluid pH, inhibit the plaque fermentation by elevating plaque calcium ion levels, redusing the integration of *S. mutans* into dental plaque [7]. In the market there is available product which is combination of CPP-ACP with fluoride (*MI paste, Tooth Mousse plus*). The advantage of CPP-ACPF is the existence of calcium, phosphate and fluoride in one product. It's known their effect is mutually potentiated [13]. One of the most important clinical application of CPP-ACP in dentistry is treatment of white spot lesions (WSL). Other indications for clinical application are dentinal hypersensitivity, dental erosion, early childhood caries, root caries and patients with xerostomia.

**Functionalized Tricalcium Phosphate (*f*TCP)**

Functionalized tricalcium phosphate is produced by milling TCP with sodium lauryl sulfate. *f*TCP stabilizes fluoride in solution and maintains high concentration of calcium, phosphate and fluoride in white spot lesions. Inclusion of the functionalized TCP ingredient in NaF formulations has been shown to produce stronger, more acid-resistant mineral relative to fluoride alone in laboratory and clinical evaluations. *f*TCP has been shown to have remineralizing effects in both *in vitro* and *in situ* studies [14, 15, 16]. A novel 5,000 ppm fluoride dentifrice Clinpro® 5000, was recently introduced by 3M ESPE. This 1.1% NaFsilica-containing paste containing an innovative functionalized tricalcium phosphate (*f*TCP) ingredient that, when evaluated in development formulations, has been shown to boost remineralization performance relative to fluoride-only systems [17].

**Bioactive Glass (BAG)**

The discovery of bioactive glasses by Hench in 1969 pushed the boundaries of biomaterials capability and function. In an era of bio-inert materials and implantation, Hench determined the critical steps for bioactive glass ceramic interaction with the human body in order to bond. Bioglass® is a multi-component inorganic compound made of elements (silicon, calcium, sodium and phosphorous) naturally found in the body. Bioactive glass were defined as a breakthrough in remineralizing technology. NovaMin® is the brand name of a particulate bioactive glass. NovaMin® is technically described as an inorganic amorphous calcium sodium phosphosilicate (CSPS) material that was designed based on a class of materials known as bioactive glasses. It comprises $SiO_2$ (45%), $Na_2O$ (24.5%), CaO (24.5%) and $P_2O_5$ (6%). Calcium sodium phosphosilicate disintegrates and gives off sodium that gets exchanged with hydrogen cations ($H^+$ or $H_3O^+$) when it comes in contact with saliva results in the release of calcium ($Ca^{2+}$) and phosphate ($PO_4^{2-}$) ions from the particle structure [18]. The initial $Na^+$ and $H^+/H_3O^+$ ion exchange and dealkinization of the glass surface layer is quite rapid, within minutes of implantation and exposure to body fluids. The net negative charge on the surface and loss of sodium causes localized breakdown of the silica network with the resultant formation of (silanol) Si(OH) groups, which then repolymerize into a silica rich surface layer. A silica-rich surface layer forms through polycondensation of hydrated silica groups on which precipitation of ions happens which crystallizes over time to form a hydroxyl-carbonate apatite. There is a transitional increase in pH that brings about the precipitation of calcium and phosphate ions from saliva and the particles to form a calcium phosphate layer on the tooth surfaces. Ca-P complexes crystallizes to form hydroxycarbonate apatite that is chemically and structurally similar to biological apatite [19]. The combination of the residual calcium sodium phosphosilicate particles and the hydroxycarbonate apatite (HCA) layer results in the occlusion of dentinal tubules, which will relieve hypersensitivity. Although it is used extensively as a desensitizing agent reports also claim that the chemical reactions that promote apatite formation may enhance the remineralization [17].

The chemical reactions initiated by calcium sodium phosphosilicate to promote the formation of an HCA layer for the treatment of dentinal hypersensitivity may also be useful in treating demineralized tooth structure and/or preventing further demineralization. BAG is an extensively studied biomaterial in the field of tissue engineering, bone regeneration and dentin remineralization due to the remarkable capability of forming hydroxycarbonate apatite [20]. Bioactive glass 45S5 has been experimentally incorporated into desensitizing pastes and glass-ionomer cements. It has been successfully established that materials, based on bioactive substance can promote remineralization but a limited amount of studies have quantitatively monitored the remineralization process [21, 22].

It has been reported that, when BAG comes in contact with saliva or any aqueous media, its active ingredient, calcium sodium phosphosilicate, binds to the tooth surface in order to initiate the remineralization process.

A study delivered by *Renita Soares et al*. showed an increase in surface microhardness after remineralization with BAG was observed. This could be attributed to the precipitation of a HCA layer on the surface of the enamel. Although, there was no significant difference between CPP-ACPF and BAG, BAG remineralised enamel less effectively as compared to CPP-ACPF, which was in agreement with the findings of Preethee T et al., [23, 24].

**Xylitol**

The effect of natural polyols and xylitol in particular is being dated since more than three decades ago [25, 26]. The authors concluded that xylitol inhibits the dissolution of enamel in acidic conditions by interfering the transport of the dissolved enamel from the lesion to the media e.g. lowering the diffusion coefficients of $Ca^{2+}$ and $PO_4^{3-}$ ions. *Makkinen et. al.* proposed that xylitol may influence calcium bioavailability in saliva and thus to promote remineralization of enamel subsurface lesions [27]. This mechanism can

facilitate the $Ca^{2+}$ ions in the enamel lesion leading to greater remineralisation in the deeper layers compared to the superficial layers. In combination with fluoride xylitol promotes remineralization between 14 and 15 degrees of saturation with respect to fluoroapatite (28). The synergistic effect of xylitol and NaF was reveal by the works of Tange et al. [29] and Sano et al. where it was shown that addition of xylitol to NaF containing toothpaste enhances the remineralization of early caries lesion for a 14-day treatment period compared to toothpaste containing only NaF [30]. In their study Souza et al. found that xylitol containing solution may perform better than varnishes due to the deeper penetration of solution into the teeth pores [31]. Moreover the results published by Souza et al. and Chuangmung et al. show that xylitol concentration is a key factor for successful remineralization. Xylitol solution with concentration >20% can not penetrate effectively into the deep layers of the enamel [32]. Furthermore it was shown that inclusion of 10% xylitol increases the effect of fluorinated dentifrice against both abrasion and enamel erosion by acting as an lubricant reducing the friction when toothbrushing [33]. Furthermore the potential of xylitol containing varnishes was explored by Cardoso et al [34,35]. The authors show that varnishes containing only xylitol possess a great advantage compared to the commercially fluoride containing varnishes where 20% xylitol is optimal concentration.

## 3. Conclusion

In the current review the potential of several candidates for remineralization of demineralized human enamel was followed within the results published through the last few decades. Although there is no explicit information upon their role in the tested subjects the scientific results show significant evidences for their potential. These agents can be easier and cheaper alternative of the newly created biomimetic systems for enamel remineralization whose mechanism of action differs from that of the aforementioned agents. Therefore the optimal balance between functionality and complexity of the remineralizing agent should be reconsidered in each individual thus ensuring the success in the treatment.

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