# THE EFFICACY OF FLUORIDE VARNISHES CONTAINING DIFFERENT CALCIUM PHOSPHATE COMPOUNDS

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**ABSTRACT: The application of fluoride varnishes is an effective method of enamel remineralization and the prevention of dental caries. Fluoride varnishes were enhanced with additional substances in order to achieve better therapeutic effects. In this review, we searched the following databases: PubMed®/MEDLINE®, Cochrane Library, EBSCO, and Embase® for original English language research papers published in 2000–2015, on fluoride varnishes enhanced with amorphous calcium phosphate (ACP), tricalcium phosphate (TCP), the functionalized form of tricalcium phosphate (fTCP), sodium calcium phosphosilicate (CSPS), sodium trimetaphosphate (TMP), and calcium glycerylphosphate (CaGP). Twelve papers fulfilled the inclusion criteria. The presence of ACP increases the fluoride ion (F) uptake in damaged enamel 2.5-fold and in healthy enamel 4-fold, compared to varnish enhanced with TCP. The effectiveness of TCP enhanced F varnishes has not been proven. Studies on TMP show its synergy with F in the remineralization of white spot lesions. CaGP and NaF varnishes with ACP protect enamel against demineralization equally well. F varnishes with ACP, TCP, and TMP effectively block demineralization and increase remineralization of dental enamel. NaF varnish enhanced with ACP is recommended by many authors for the remineralization of caries enamel lesions while varnish enhancement with TCP is recommended for the remineralization of white spot lesions caused by orthodontic treatment.**

Key words: Amorphous calcium phosphate; Calcium glycerylphosphate; Fluoride varnishes; Functionalized form of tricalcium phosphate; Sodium calcium phosphosilicate; Sodium trimetaphosphate; Tricalcium phosphate.

## INTRODUCTION

According to the WHO, dental caries is a common disease with a prevalence rate of 100% in adults and 60%–90% in children.[1] The first symptom is a white spot lesion (WSL), i.e., a macroscopically visible demineralization of dental tissue.[2] Demineralization and remineralization are dynamic processes that occur constantly inside the oral cavity affecting the development of dental caries.[3] WSLs are often observed in patients with poor oral hygiene, in patients wearing orthodontic braces, and in those who are frequent consumers of large amounts of sugar-sweetened beverages, sweets, and snacks.[4,5] Remineralization is aided by an early decision to start a cariostatic diet and the use of fluoride ion (F)-based products.[6] In an attempt to further improve the efficacy of remineralization, fluoride varnishes have been modified to include calcium and inorganic phosphate ions, e.g., amorphous calcium phosphate (ACP), tricalcium phosphate (TCP), the functionalized form of tricalcium phosphate (fTCP), calcium sodium phosphosilicate (CSPS), sodium trimetaphosphate (TMP), and calcium glycerophosphate (CaGP).

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The aim of the study was to compare the efficacy of fluoride varnishes containing different calcium phosphate compounds in the remineralization of white spot lesions.

## METHOD

A systematic review of the literature was performed, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the following databases: PubMed®/MEDLINE®, Cochrane Library, EBSCO, and Embase® for research papers on fluoride varnishes containing calcium and phosphate compounds. Our search terms were: remineralization, demineralization, white spot lesions, fluoride, fluoride varnishes, amorphous calcium phosphate (ACP), tricalcium phosphate (TCP), functionalized form of tricalcium phosphate (fTCP), calcium sodium phosphosilicate (CSPS), sodium trimetaphosphate (TMP), and calcium glycerophosphate (CaGP). We included the twelve original papers, published in English in 2000–2015, that met the search criteria.

## RESULTS

Tables 1–4 illustrate the profiles of the 12 papers presented in this review of the literature.

**Table 1.** Profile of the papers on fluoride varnish enhanced with amorphous calcium phosphate (ACP) presented in the review of the literature.
($F^-$ = fluoride ion, CG = control group,
ref. no = reference number)

| Type of sample | No of samples | | Substance used in the control group | Method of evaluation | Preferable remineralizing agent | Authors (ref. no) |
|---|---|---|---|---|---|---|
| | Total | CG | | | | |
| Polyvinyl chloride plastic strips | 35 | 7 | *Duraphat*® (Colgate Oral Care, NSW, Australia; 2.26% $F^-$) | Ion chromatography | *MI Varnish* (GC, Tokyo, Japan; 2.26% $F^-$) | Cochrane et al. (10) |
| Bovine incisors | 120 | 15 | Fluoridated dentifrice *Sorriso Dentes Brancos*, 1450 ppm $F^-$ (Colgate-Palmolive) | Optical coherence tomography (OCT) | *MI Varnish* (GC, USA; 2.26% $F^-$) | Pithon et al. (11) |
| Bovine incisors | 72 | 12 | Deionized water | Ion-sensitive electrode | *Enamel Pro ACP Formula* (Premier Dental Co., Plymouth Meeting, PA) | Schemehorn et al. (12) |

**Table 2A.** Profile of the papers on fluoride varnish enhanced with tricalcium phosphate (TCP) presented in the review of the literature. ($F^{-}$ = fluoride ion, CG = control group, ref. no = reference number)

| Type of sample | No of samples | | Substance used in the control group | Method of evaluation | Preferable remineralizing agent | Authors (ref. no) |
|---|---|---|---|---|---|---|
| | Total | CG | | | | |
| Human primary incisors | 90 | 30 | No protective fluoride varnish coating | Knoop microhardness test | 5% NaF varnish with functionalized tricalcium phosphate (fTCP) | Alamoudi et al. (13) |
| Human primary incisors | 48 | 12 | Deionized water | Polarized light microscopy | No significant differences between: (i) *Duraphat® Varnish* (Colgate Oral Pharmaceuticals, New York, NY), (ii) *5% NaF z TCP Clinpro™ White Varnish* (OMNI Preventive Care, 3M ESPE Company, West Palm Beach,FL) (iii) *5% NaF z TCP* (TCP-fluoride varnish Faculty of Dentistry, Mahidol University) | Rirattana-pong et al. (15) |
| Human premolars | 40 | 10 | No protective fluoride varnish coating | (i) Scanning electron microscope (SEM) (ii) Vickers microhardness test | *Clinpro™ White Varnish* (tricalcium phosphate, 3M ESPE, Seefeld, Germany) | Ulkur et al. (8) |
| Human molars | 115 | 23 | Artificial saliva | (i) Surface micro-hardness (SMH) (ii) Surface roughness (Ra) (iii) Surface topography by scanning electron microscope (SEM) | *Clinpro™ White Varnish* (OMNI Preventive Care,3M ESPE Company, West Palm Beach,FL) | Elkassas and Arafa (16) |

**Table 2B.** Profile of the papers on fluoride varnish enhanced with tricalcium phosphate (TCP) presented in the review of the literature. ($F^-$ = fluoride ion, CG = control group, ref. no = reference number)

| Type of sample | No of samples | | Substance used in the control group | Method of evaluation | Preferable remineralizing agent | Authors (ref. no) |
|---|---|---|---|---|---|---|
| | Total | CG | | | | |
| Human incisors | 90 | 18 | Deionized water | (i) Vickers microhardness test<br>(ii) Surface topography with atomic force microscopy (AFM) | *Tooth mousse with Recaldent™* (GC, Tokyo, Japan) followed by *Clinpro™ White Varnish* (3M, Hackensack, NJ) | Memar-pour (17) |

**Table 3.** Profile of the papers on fluoride varnish enhanced with sodium trimetaphosphate (TMP) presented in the review of the literature. ($F^-$ = fluoride ion, CG = control group, ref. no = reference number)

| Type of sample | No of samples | | Substance used in the control group | Method of evaluation | Preferable remineralizing agent | Authors (ref. no) |
|---|---|---|---|---|---|---|
| | Total | CG | | | | |
| Bovine teeth | 168 | 24 | Placebo (without $F^-$ and TMP) | (i) Surface hardness recovery (%SHR)<br>(ii) Cross-sectional hardness (ΔKHN)<br>(iii) Concentrations of $CaF_2$ and F | (i) The highest SHR: 5% NaF + 5% TMP<br>(ii) The highest ΔKHN: *Duraphat®*<br>(iii) The highest concentration of CaF2: 5% NaF<br>(iv) The highest concentration of $F^-$: *Duraphat®* + 5% NaF | Manarelli et al. (21) |
| Bovine enamel discs in the oral cavity environ-ment | 12 | 4 | Placebo (without $F^-$ and TMP) | (i) Surface hardness recovery (%SHR)<br>(ii) Cross-sectional hardness (ΔKHN) | (i) % SHR: TMP>5% NaF<br>(ii) ΔKHN: 5% NaF>TMP | Manarelli et al. (22) [clinical trial] |

**Table 4.** Profile of the papers on fluoride varnish enhanced with calcium glycerophosphate (CaGC) presented in the review of the literature. ($F^-$ = fluoride ion, CG = control group, ref. no = reference number)

| Type of sample | No of samples | | Substance used in the control group | Method of evaluation | Preferable remineralizing agent | Authors (ref. no) |
|---|---|---|---|---|---|---|
| | Total | CG | | | | |
| Acrylic blocks and bovine enamel samples | 60 | 10 | No varnish | (i) Surface micro-hardness (%SHC)<br>(ii) Ion-sensitive electrode | (i) Varnishes containing CaGP released the greatest amount of $F^-$<br>(ii) Remineralization effect: *Duraphat*® and *Duofluorid*® (5.63% NaF/$CaF_2$; FGM, Joinville, Brazil) > CaCP varnishes | Carvalho et al. (23) |
| Human molars | 168 | Part 1: 18<br>Part 2: 60 | Part 1: No varnish<br>Part 2: No $F^-$ exposure | Part 1: Surface micro-hardness (SMH)<br>Part 2: Ion-sensitive electrode | Part 1: $F^-$ concentration: 1% CaGP was similar to the control group.<br>Part 2: $F^-$ concentration: lower than the control group. | Carvalho et al. (24) |

## AMORPHOUS CALCIUM PHOSPHATE

When amorphous calcium phosphate (ACP, $Ca_xH_y(PO_4)_z$•$nH_2O$, n = 3–4.5; 15–20% •$H_2O$) is applied onto early carious lesions,[3,4,7,8] ACP creates nanocomplexes with calcium and phosphate ions released from its reservoir, and reduces enamel sensitivity to acids and demineralization[8]. Moreover, the application of ACP improves the supply of fluoride ions to the enamel and their diffusion to the affected areas.[9,10]

*Study by Cochrane et al.[10]:* The aim of the study conducted by Cochrane et al.[10] was to compare the fluoride, calcium and inorganic phosphate ions released from five fluoride varnishes: (i) *MI Varnish* containing CPP-ACP with 2.26% (w/w) fluoride, (ii) *Clinpro™ White* with fTCP containing 2.26% (w/w) fluoride, (iii) *Enamel Pro* containing ACP and 2.26% (w/w) fluoride, (iv) *Bifluorid 5* containing 0.3% (w/w) calcium fluoride and 0.3% (w/w) sodium fluoride, and (v) *Duraphat*® containing 2.26% (w/w) fluoride (positive control). Polyvinyl chloride plastic strips were coated with one of the varnishes, rinsed with both fresh and deionized water and then subjected to chromatography. Each varnish released measurable amounts of fluoride and calcium. However, only *MI Varnish* and *Enamel Pro* released a statistically significant level of inorganic phosphate. The highest amounts of calcium and fluoride ions were released from *MI Varnish*.

*Study by Pithon et al.[1]:* The influence of fluoride varnishes containing CPP-ACP on the remineralization of caries lesions around orthodontic brackets was analyzed by Pithon et al.[11] Bovine teeth with attached orthodontic brackets were divided into eight groups: (i) brushed with a soft brush and fluoride toothpaste *Sorriso Dentes Brancos*, 1450 ppm fluoride (Colgate-Palmolive), (ii) brushed with *Sorriso Dentes Brancos* and rinsed with mouth wash *Plax Classic*, 225 ppm fluoride (Colgate-Palmolive), (iii) *Duraphat®* (22600 ppm fluoride), (iv) *Duraphat®* and brushed, (b) *Duraphat®*, brushed and rinsed with mouthwash, (vi) *MI Varnish*, (vii) *MI Varnish* and brushed, and (viii) *MI Varnish*, brushed, and rinsed with mouthwash. All samples were demineralized in a solution of artificial saliva at a temperature of 37ºC for 28 days. Evaluation of the enamel microstructure and the depth of enamel lesion by optical coherence tomography (OCT) showed that the smallest average depth of enamel lesions around the brackets was in the samples treated with MI Varnish.

*Study by Schemehorn et al.[12]:* According to Schemehorn et al.,[12] ACP-enhanced fluoride varnish applied to sound and demineralized bovine enamel increased the uptake of fluoride, resulting in a significant remineralization of both the intact and the demineralized enamel. Each of three groups of samples was treated with different substances: (i) fluoride varnish containing ACP, (ii) fluoride varnish with TCP, and (iii) deionized water solution. It was found that the ACP varnish promoted significantly more fluoride deposition into or onto the sound and the demineralized enamel than the TCP containing varnish.[12] Moreover, the presence of ACP in the varnish increased the uptake of fluoride ions 2.5-fold in the damaged enamel and 4-fold in the sound enamel compared to the varnish with TCP.[12] The authors postulated that this was due to the ACP varnish containing a higher level of available calcium and phosphate ions.

## TRICALCIUM PHOSPHATE

Tricalcium phosphate (TCP, $Ca_3(PO_4)_2$) and the functionalized form of tricalcium phosphate (fTCP) are bioceramic materials. The functionalized form of tricalcium phosphate (fTCP) was developed as a means of improving the fluoride uptake of enamel. The functionalization of β-TCP with organic and/or inorganic molecules provides a barrier that prevents premature fluoride-calcium interactions and aids in mineralization.[13]

*Study by Alamoudi et al.[13]:* An *in vitro* study by Alamoudi et al.[13] demonstrated that there is a high microhardness in the surface of fTCP-treated enamel. Surface microhardness (SMH) has been used as a reliable indicator of the efficacy of fluorides, and is an effective measure of the overall impact of remineralization.[13]

*Study by Rirattanapong et al.[15]:* In contrast, Rirattanapong et al.[15] indicated that the addition of TCP does not significantly inhibit the progression of initial primary enamel lesions, compared to non-enhanced fluoride varnishes.

*Study by Ulkur et al.[8]:* A study conducted by Ulkur et al.[8] concluded that TCP varnish enhanced remineralization around brackets more effectively than ACP varnish. According to the authors TCP has a greater impact on the microhardness and smoothness of enamel than ACP varnishes and the use of Er:YAG laser irradiation. Nevertheless, both varnishes were found to be effective against demineralization around orthodontic brackets and might therefore be preferred for preventive treatments in orthodontic patients.[8]

*Study by Elkassas and Arafa[16]:* A study by Elkassas and Arafa[16] also confirmed the effectiveness of fluoride varnish containing fTCP (*Clinpro™,* 3M ESPE). fTCP varnish was compared to *Relief* (ACPF containing 1100 ppm fluoride, Discus Dental), *Tooth Mousse Plus* (CPP-ACPF, 900 ppm fluoride, GC Dental), *Varnish™ XT* (varnish based on a resin glass ionomer, 3M ESPE). The effectiveness of remineralization was determined on the basis of SMH, roughness (Ra) and surface topography by scanning electron microscope (SEM). Varnish with fTCP demonstrated the highest potential for remineralization and protection against the dissolution of enamel in acidic conditions.

*Study by Memarpour et al.[17]:* To remineralize primary teeth with early enamel lesions, Memarpour et al.[17] suggested fTCP varnish. The authors concluded that microhardness increased significantly more after fTCP treatment than after treatment with sodium fluoride varnish (5% *DuraShield*®) or 500 ppm fluoridated toothpaste. Atomic force microscopy (AFM) images showed that enamel roughness decreased most after fTCP varnish treatment, followed by CPP-ACP, fluoridated toothpaste, and fluoride varnish.[17]

## CALCIUM SODIUM PHOSPHOSILICATE

Calcium sodium phosphosilicate (CSPS) belongs to the group of compounds known as "bioactive glasses." Calcium and phosphate ions, which are released from the structure of the glass, increase the remineralization process.[18] Contact with saliva results in the immediate release of a nonorganic substance which penetrates the enamel.[19]

Information regarding CSPS suggests that there is a linear correlation between the exposure time of the demineralized tissue and the accumulation of ions. However, further *in situ* studies, especially comparing different treatments, are necessary to determine the efficiency of CSPS usage.[20]

## SODIUM TRIMETAPHOSPHATE

Sodium trimetaphosphate (TMP, $Na_3P_3O_9$) has a synergic effect with fluoride, which is why it supports the remineralization of white spot lesions when added to varnishes.[21]

*Studies by Manarelli et al.[21,22]:* A study conducted by Manarelli et al.[21] confirmed the efficiency of the fluoride varnish containing TMP. The authors demonstrated the highest surface hardness recovery (%SHR) and the lowest cross-sectional hardness (ΔKHN) (KHN=Knoop hardness number) in samples treated with a TMP-containing varnish. The addition of TMP significantly reduced the deposition of $CaF_2$. The highest concentration of $CaF_2$ was present in the specimens with 5% NaF. It is possible that the mechanism of action of TMP is related to its ability to retain positively charged species, which are released under cariogenic challenges to form more reactive compounds.[21]

Manarelli et al.[22] also demonstrated in another *in situ* study, the only clinical study included in this review, the effectiveness of TMP in the remineralization of artificially created enamel lesions. The participants of the study were divided into 3 groups: (i) placebo, (ii) 5% fluoride varnish, and (iii) 5% fluoride varnish with 5% TMP. An individual palatal plate with 4 bovine enamel discs was prepared for every patient. Simulated areas of demineralization were created in the discs with a solution of pH= 5.0. The bovine enamel was evaluated with the Knoop hardness test (%SHR), the hardness of the specimen cross section (ΔKHN), and the number of inbuilt fluoride ions after the experiment. The authors concluded that the addition of TMP to sodium fluoride varnish enhances the effect on enamel remineralization *in situ*. The use of a TMP-supplemented fluoride varnish leads to a higher degree of subsurface remineralization, especially at the deeper regions of the lesion. This could be regarded as the actual healing of the lesion, as opposed to a standstill of the caries process, which ultimately leaves a “scar” (inactive enamel caries).[22]

## CALCIUM GLYCERYLPHOSPHATE

According to the latest reports, fluoride varnish enhanced with calcium glycerylphosphate (CaGP) is an effective substance in the remineralization of caries lesions.

*Studies by Carvalho et al.*[23,24]*:* In a two-step research on the application of CaGP in fluoride varnishes, Carvalho et al.[23] noted its ability to release fluoride and its positive influence on enamel remineralization. The authors proved that the presence of CaGP in a fluoride varnish significantly enhanced the release of fluoride. However, the protection against enamel demineralization by the CaGP enhanced varnish showed similar results to *Duraphat*® and *Duofluorid*® varnishes.

Continuing the research, Carvalho et al.,[24] also examined the influence of CaGP on enamel erosion. The results did not confirm the conclusions from the previous work. It was found that the fluoride varnishes containing CaGP do not promote greater amounts of fluoride being bound to enamel and that fluoride bound to enamel may not be closely related to erosion prevention. Similar amounts of fluoride were found in 1% CaGP/5.63% NaF/$CaF_2$ varnish and *Duofluorid*® (5.63% NaF/$CaF_2$) while lower values were found for 5% CaGP/5.63% NaF/$CaF_2$ varnish and *Duraphat.*®[24]

## CONCLUSIONS

Fluoride varnishes with amorphous calcium phosphate, tricalcium phosphate, and sodium calcium phosphosilicate effectively inhibit demineralization and increase enamel remineralization. Patients who are at high risk for dental caries may benefit from application of these enhanced varnishes. NaF varnish enhanced with ACP is recommended by many authors for the remineralization of caries enamel lesions while varnish enhancement with TCP is recommended for the remineralization of white spot lesions caused by orthodontic treatment. It should be noted that our conclusions are based on only the limited number of studies which are currently available, especially for studies referring to varnishes with CSPS and TMP. Fluoride varnishes containing amorphous calcium phosphate, tricalcium phosphate, and sodium calcium phosphosilicate are all promising methods to inhibit the development of early caries lesions and to increase remineralization. The treatment of dental caries may be improved by the application of these enhanced varnishes, in accordance with the recommendations and indications reported in the literature.

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