Topical CPP-ACP crèmes: beyond caries prevention

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Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP) is a unique naturally derived protein-based remineralizing technology which is used globally in chewing gums (such Recaldent ™) and topical crèmes (such as GC Tooth Mousse ™ and Tooth Mousse Plus ™). Phosphopeptides are derived from milk caseins are complexed with amorphous calcium phosphate, to form stable complexes which are nanoparticles of some 2 nm in diameter with a large surface area (Cross et al. 2006). CPP-ACP complexes act as biological calcium phosphate delivery vehicles, and are able to boost levels of bio-available calcium and phosphate in saliva and plaque fluid without causing indiscriminate precipitation of calcium salts. This makes this material particularly effective in the remineralization of early enamel lesions, and in the treatment of other types of enamel opacities. As such, the range of clinical applications now extends beyond altering the demin/remin balance for human enamel to treating hypoplastic enamel and other types of enamel opacities (Walsh 2012)

In many parts of the world, the use of Tooth Mousse and Tooth Mousse Plus (also known as MI Paste and MI Paste Plus in North America) has been a well established part of clinical practice for more than a decade. Underpinning these products is a large body of refereed papers and conference presentations as well as systematic reviews, the highest form of evidence in the pyramid of evidence-base practice. For example, a 2006 systematic review focused on chewing gums and lozenges enriched with CPP-ACP (Yengopal & Mickenautsch, 2006), identified over 120 journal articles, which included laboratory trials and animal studies as well as clinical trials and numerous in situ clinical studies. A 2009 meta-analysis identified more than 120 journal articles on CPP-ACP technology, which included animal model studies, in situ clinical studies, and randomized clinical trials, many of which were on the use of Tooth Mousse/MI Paste. A 2012 textbook chapter authored from our group identified that by the end of 2010, nine clinical trials of Tooth Mousse had been conducted across a range of locations around the globe which had shown regression of white spot lesions. Other studies have shown benefits in terms of caries reversal, caries prevention and altered plaque ecology in patients undergoing fixed orthodontic treatment, (He et al. 2010; Roberston et al. 2011; Akin et al. 2012; Wang et al. 2012; Uysal et al. 2012) results which are consistent with our current understanding of the various mechanisms by which Tooth Mousse affects the ionic and microbial aspects of the oral environment

The purpose of this article is to summarize the recent research effort over the past decade which underpins the current clinical applications of Tooth Mousse (TM) and its related fluoride-containing counterpart, Tooth Mousse Plus (TMP).

Bio-availability of calcium and phosphate ions

The release of ions from TM has been examined in considerable detail. TM contains 10% w/v CPP-ACP. The release of ions at oral pH was reported by Paterson et al (2008) who dissolved TM directly into deionized and then used a calcium ion-selective electrode to measure calcium ion release. The free calcium ion concentration in the solution increased with time in a saturating exponential manner, with approximately 95 % release after only 15 minutes. This rapid release means that when the crème is applied to tooth surfaces there will be a rapid increase in calcium ion concentration in the plaque fluid and saliva. Their supersaturation for calcium with respect to tooth enamel drives remineralization and prevents mineral loss.

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Comparative studies with a broad range of toothpastes, gels, liquids claimed to have remineralizing or desensitizing actions (including NovaMin ®, ClinPro ® Tooth Creme, Clin Pro 5000, and ReminPro ®) reveal that calcium contained in these products has low water solubility and poor bio-availability except for TM and TMP. The level of water soluble calcium per gram of crème in TM or TMP (321.8 ± 2.6 μmol/g) is some 14 times or greater than these other products (Cai et al. 2009; Yasuda et al. 2010). Tooth Mousse Plus also has been shown to contain the highest amount of water soluble phosphate (245.7 ± 2.7 μmol/g). The rapid release of calcium (within 1 hour) has been confirmed in studies by commercial competitors (Burwell et al. 2009).

The high water solubility and bioavailability of the calcium, phosphate and fluoride in TM and TMP is due to this being a protein technology (containing casein phosphopeptides), whereas all other marketed products are inorganic in nature and lack the ability to stabilize the calcium and phosphate ions.

CPP is able to stabilize amorphous calcium fluoride phosphate (CPP-ACFP), which allows additive effects on remineralization compared with the fluoride or CPP-ACP alone (Cochrane et al. 2006; Sakaguchi et al. 2006). Moreover, CPP-ACP promotes the incorporation of fluoride into plaque and sub-surface enamel, producing effects superior to those which can be achieved using fluoride alone (Reynolds et al. 2006). Early studies showed that addition of 900 ppm fluoride to TM increased the acid resistance of the product formed when enamel lesions were remineralized, compared with using TM alone (Kariya et al. 2004). This level of fluoride was designed to provide the correct ionic ratio of components for remineralization. The inclusion of fluoride in TM to create TMP has been shown to enhance the resistance of enamel surfaces to in vitro caries formation, compared with TM or fluoride alone (Hicks 2006).

Prevention of mineral loss in caries models

Topical application of TM immediately before a cariogenic challenge has been shown to prevent demineralization of enamel during subsequent challenge, and also to reduce the pH reduction caused by S. mutans fermentation (Sato et al. 2003). This capacity to buffer acids produced by cariogenic bacteria adds to other ecological effects of TM on dental plaque. TM has benefits in preventing root surface caries as well as enamel caries, as has been shown in both laboratory caries models and clinical studies. In an in vitro caries model, both Tooth Mousse and Tooth Mousse Plus gave a reduction of lesion depth in enamel and dentine, and slowed lesion progression (Kraft et al. 2012).

The first evidence of topical application of Tooth Mousse being able to arrest and reverse root surface caries was published in 2008 (Vlacic et al. 2008), and since that time there have been many laboratory studies of root surface caries prevention, which show greater affects for Tooth Mousse and Tooth Mousse Plus compared to conventional fluoride dentifrices, a tri-calcium phosphate and fluoride containing dentifrices, fluoride rinses and fluoride varnishes (Hicks & Flaitz 2011; Hicks & Flaitz 2013; Flaitz et al. 2013; Westerman et al. 2013; Hicks & Flaitz 2014; Westerman & Flaitz 2014).

An important caries prevention application relates to hypoplastic enamel, since enamel hypoplasia is a major risk factor for severe forms of early childhood caries. Application of Tooth Mousse improves the mechanical properties of enamel affected by Molar Incisor Hypomineralisation (MIH) (Batra et al. 2011). In a recent clinical study (Baroni et al. 2012), Tooth Mousse Plus when applied to newly erupted molars with MIH gave elevated concentrations of calcium and phosphate, with ratios of calcium to carbon similar to normal enamel. The treated surface had mineral crystals with a regular shape and that were better organized, with less porosity and interprismatic spaces. Tooth Mousse Plus accelerated the maturation of the hypoplastic enamel.

Visible reversal of white spot carious lesions

Early reports of visible reversal of enamel white spot lesions (WSL) in young adult patients in Australia (dating back to 2000) (Walsh 2004; Walsh 2007) and later in Japan (from 2002) (Reynolds & Walsh, 2005) have been followed by in situ studies of laboratory-created WSL (Manton et al. 2007) and full scale randomized controlled clinical trials in patients with naturally occurring WSL (Andersson et al. 2006; Kitasako et al. 2009; Bailey et al. 2009; Yazicioglu et al. 2010). Together this body of work shows the dramatic cosmetic changes which occur in enamel as lesions undergo reversal. A particular risk group where TM is useful for causing regression of white spot lesions is patients undergoing orthodontic treatment. There are no similar studies showing visual reversal of enamel WSL for other novel remineralizing agents in the literature.

CPP-ACFP solutions have been shown to remineralize enamel subsurface lesions in vitro by depositing fluorapatite. This remineralization is accompanied by improved translucency and reduced opacity of the white spot lesions, as reversal occurs and mineral content increases (Cochrane et al. 2006).

Many recent studies have confirmed the usefulness of Tooth Mousse in reversing carious white spot lesions. In a 2011 laboratory study using naturally occurring enamel white spot lesions which had developed on third molar teeth during fixed orthodontic treatment, both Tooth Mousse and Tooth Mousse Plus gave mineral gain in the subsurface region up to 230 microns, as well as surface mineral deposition (Rodriguez et a. 2011). These results are consistent with other recent studies of reversal of white spot lesions created under laboratory conditions, in which application of Tooth Mousse or Tooth Mousse Plus increased surface microhardness and longitudinal microhardness, and caused mineral gain in the subsurface region of the lesion (Juntavee et a. 2011; Mielczarek 2012). Tooth Mousse has been shown to be more effective than fluoride varnish at treating experimental white spot enamel lesions (Kutuk et al. 2012). This extends the results of studies which compared Tooth Mousse or Tooth Mousse Plus with conventional fluoride dentifrices, and showed the superiority of the CPP-ACP products.

In a 2011 clinical trial with 80 patients who had in total 967 teeth with white spot lesions which had developed during fixed orthodontic therapy, Tooth Mousse was more effective than neutral sodium fluoride gel when applied twice daily over six months, with greater reduction in the area of white spot lesions and in the frequency of persisting white spot lesions (Akin & Bascifti 2011). Likewise, in a more recent clinical trial with 60 children exhibiting at least one white spot lesion each, subjects were randomly divided into 2 groups to receive either Tooth Mousse or a fluoride containing toothpaste for a period of 3 months. Tooth Mousse gave a useful remineralization effect on the white spot lesions (Aykut Yetkiner et al. 2013).

Treatment of cervical dentinal hypersensitivity (CDH)

One of the first clinical trials using TM to treat CDH was undertaken in Belgium in 2004. The study involved 11 private practitioners, whose patients with CDH were instructed to apply TM for 21 days, immediately after the evening brushing, leaving the material for 3 minutes, and spreading it across the mouth, and then leaving it in place during sleep. The patient cohort reported a reduction in sensitivity, particularly to stimulation with air as opposed to tactile stimuli. Daily diaries which recorded symptoms of CDH showed a progressive reduction from the first day of treatment over the following 3 weeks. Half of the treated patients reported that the general reduction in CDH symptoms was sufficiently great that they wished to repeat the treatment if symptoms of sensitivity recurred (Poitevin et al. 2004). A later randomized controlled clinical trial conducted in Brisbane showed that TM reduced sensitivity to air, osmotic, thermal and tactile stimuli, with equal effectiveness to potassium nitrate toothpaste (Walsh et al. 2006). This finding aligns with studies which show that a single application of TM can coat and partially occlude dentine tubules, and resist thermocycling (Hiller et al. 2008).

CPP-ACP inclusion in chewing gums

The inclusion of CPP-ACP in chewing gums (such as Recaldent™) is a well established caries preventive measure. Early studies of this approach used a randomized, double blind cross-over design to compare CPP-ACP containing gums with several commercial sugar-free gums. Subjects in these studies chewed the various gums for a 20 minute period 4 times per day for 14 days. By using paired enamel half slabs, precise determinations of mineral levels could be made. These studies showed that CPP-ACP gum produced 75-107% more remineralization than sugar-free gums (Manton 2005). It is well known that xylitol-based gums reduces the caries increment, but have little or no effect on approximal caries (Antonio et al. 2009). In contrast, gums containing CPP-ACP are highly effective at remineralizing WSL, and have been shown to arrest and reverse approximal lesions in a large scale clinical trial.

Aesthetic dentistry

Application of Tooth Mousse to enamel prior to in-office bleaching does not affect the colour change caused by the bleaching procedure (Lago et al. 2012a; Lago et al. 2012b). In fact, the use of Tooth Mousse prior to bleaching can be of considerable benefit since it will improve the quality of the enamel, and help prevent any reduction in surface microhardness caused by exposure to hydrogen peroxide from bleaching gels (Lago et al. 2012a).

Following at home or in office bleaching, the development of external stains on teeth from lifestyle factors such as cigarette smoking and consumption of beverages with tannins compromises the overall improvement to tooth shade gained by the bleaching treatment. Two recent studies show how CPP-ACP treatment of freshly bleached enamel can reduce the propensity for this surface to be stained by smoking and the consumption of tea. In a laboratory model of extrinsic tooth staining occurring after in-office bleaching, both Tooth Mousse and Tooth Mousse prevented staining of freshly bleached enamel by black tea (Imamura et al. 2012). Using a similar methodology, in a laboratory study of cigarette smoke staining of freshly bleached enamel, treatment of bleached enamel with neutral fluoride increased staining of the enamel due to cigarette smoke, while Tooth Mousse Plus did not (Publio et al. 2012).

Ecological effects on dental plaque

There is a growing awareness that daily application of CPP-ACP has substantial effects on the ecology of the oral microflora. A recent randomised trial (Pukallus et al. 2013) demonstrated that the daily application of Tooth Mousse lower the levels of mutans streptococci (MS) in infants over the first two years of their life. In this study, subjects were randomized at a mean age of 11 days old to receive once-daily Tooth Mousse (102 subjects) or no product (89 subjects) from the time of first tooth eruption. All children underwent twice daily tooth brushing using a low-dose fluoride dentifrice. At 24 months, there were fewer MS-positive children in the CPP-ACP group (26 percent) versus the comparison group (47 percent). A dose-response effect of CPP-ACP usage on MS was observed, where MS was present in eight percent of regular CPP-ACP users, 28 percent of irregular users, and 47 percent of non-users. This emphasises the point that regular daily application of Tooth Mousse alters the oral microflora, whereas less frequent application produces more limited effects.

Parallel results have been seen in studies conducted in orthodontic patients with fixed appliances. In a recent clinical trial with 60 teenage orthodontic patients who already had white spot lesions, the daily application of Tooth Mousse suppressed the counts of mutans streptococci at 3 months, an effect not seen when an ordinary fluoride dentifrice was used (Aykut Yetkiner et al. 2013).

The ecological effects of CPP-ACP are underpinned by several mechanisms. The material is bound strongly into dental plaque biofilms, with particularly strong binding seen to individual Streptococcus mutans bacterial cells. This strong binding creates a reservoir effect, leading to elevated levels of calcium and phosphate ions in the plaque fluid (Sato et al. 2011). Of the existing commercial remineralization products, only CPP-ACP based products can give high levels of water soluble calcium and phosphate in dental plaque biofilms (Sato et al. 2011). Comparing the two different CPP-ACP products, greater effects are seen for Tooth Mousse Plus (which contains 900 ppm fluoride) than for Tooth Mousse (which is fluoride free) since the greater elevation of calcium and fluoride ion concentrations in the plaque fluid inhibits fermentation and helps establish a less aciduric environment. This difference between the two products was noted in a recent clinical study with 40 subjects, in which the application of either Tooth Mousse or Tooth Mousse Plus elevated plaque pH levels for the first 48 hours, but only Tooth Mousse Plus elevated plaque pH until 96 hours (Heshmat et al. 2013).

Future applications of CPP-ACP in erosion prevention and treatment

The addition of CPP-ACP to existing foods has been shown to enhance their dental health benefits. Addition of CPP-ACP to cheese and milk at concentrations from 0.2-0.5% has been shown in laboratory studies to reduce mineral loss in enamel cased by acid exposure, and to enhance remineralization (Minami et al. 2004).

Likewise, TM has been shown to increase the hardness of enamel which has been eroded by repeated contact with acidic drinks such as colas, improving mineral uptake beyond that possible with saliva alone (Sukasaem et al. 2006; Huang & Tantbironj 2008). Topical application of TM reduces the extent of softening and mineral loss caused by subsequent exposure to erosive beverages (Kallayathi et al. 2008).

CPP-ACP has potential as an additive to drinks to prevent dental erosion. A key factor in such an approach is to estimate the lowest concentration of CPP-ACP which can be added to erosive drinks to eliminate the risk of erosion to enamel. Past research work on this topic has explored this issue using Powerade™, to which was added varying amounts of CPP-ACP from 0.063% up to 0.25%. Analysis of the surface characteristics of enamel slabs in the laboratory setting using stereomicroscopy, scanning electron microscopy and surface profilometry demonstrated that adding CPP-ACP at 0.25% raised the pH from 2.70 to 3.90, and lowered the titratable acidity from 1.83 to 1.36). Enamel loss from etching reduced from 3.87μm to 0.19μm, which was identical to enamel samples kept in distilled water (0.25μm). A reduction in the erosive step defect occurred at concentrations down to 0.09%. Overall, the erosive potential of Powerade™ was attenuated or eliminated completely by the addition of low concentrations of CPP-ACP (Ramalingham et al. 2002).

Both Tooth Mousse and Tooth Mousse Plus have been shown to reduce enamel surface loss in laboratory models of dental erosion using citric acid (Chapman et al. 2011). Consistent with these findings, in a recent laboratory study of the surface microhardness of human enamel, a 5 minute application of Tooth Mousse protected the enamel surface and made it resistant to subsequent acid challenges, and caused recovery of surface microhardness after acid exposure (Kargul et al. 2012). Likewise, in a laboratory study of dentine erosion, Tooth Mousse and Tooth Mousse Plus applied to dentine protected the surface when challenged with Coca Cola (pH 2.6) four times per day, and provided an additive anti-erosion effect over a regular fluoride dentifrice (Souza-Silva et a;. 2012; Mielczarek & Michalik 2013).

A particularly interesting application of TM is the management of pathological tooth wear from acid regurgitation or severe bruxism. Laboratory studies suggest that frequent application of TM reduces enamel wear under conditions simulating bruxism and acid regurgitation, probably due to its lubrication properties

(Ranjitkar et al. 2006; Ranjitkar et al. 2007; Ranjitkar et al. 2008). TM is able to reduce abrasive and acid-accelerated dentine wear (Narayana et al. 2006), supporting the use for TMP in patients with severe tooth wear from these differing causal pathways. Of direct relevance to gastric reflux is the ability of topical CPP-ACP to protect tooth structure from hydrochloric acid. A recent laboratory investigation demonstrated that both Tooth Mousse and Tooth Mousse Plus increased the hardness of enamel that had been softened by exposure to hydrochloric acid for 10 minutes, using conditions which mimicked regurgitated stomach acid. Tooth Mousse Plus restored the enamel surface microhardness within one hour to the baseline value, whereas recovery of the surface microhardness of enamel was minimal with saliva alone (Dehghan et al. 2012).

Applications in dental materials and restorative dentistry

While providing a degree of protection from dental erosion, CPP-ACP does not adversely affect adhesion or bonding to tooth structure. In fact there is evidence for the converse, which relates to how the substrate for bonding is improved. For example, application of Tooth Mousse before bonding to enamel has been shown to increase the micro-tensile bond strength of sealants bonded with either etch-and-rinse and self-etching adhesives without additional enamel acid etching (Aguiar et al. 2011). Similarly, application of Tooth Mousse to enamel was shown to improve the micro-tensile bond strength for Optibond all-in–one when used to bond composite resin restorations (Panich & Thanyakoop 2011). CPP-ACP has been included in dental materials, such as glass ionomer cements and zinc oxide non-eugenol temporary cements used in crown and bridgework, with the logic being to provide greater resistance to mineral loss at restoration margins, and reduced permeability of cut dentine beneath temporary crowns, respectively. Addition of up to 8.0% CPP-ACP into zinc oxide cements appears to be viable in terms of the compressive strength and film thickness achieved (Wong et al. 2006).

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