The Clinical Applications of Tooth Mousse™ and other CPP-ACP Products in Caries Prevention: Evidence-Based Recommendations

Abstract
Casein phosphor-peptides-amorphous calcium phosphate (CPP-ACP) products have been widely used in the field of preventive dentistry. CPP exerts its main effect through binding and stabilizing calcium and phosphate ions (ACP) in an amorphous, non-crystalline state where they can enter enamel and enhance remineralization. The following article presents a background on these products, in addition to the scientific rationale behind their anti-cariogenic mechanisms and a great deal of useful evidence-based clinical applications.

Key words: CPP-ACP, Tooth Mousse, Recaldent, remineralization, casein, milk.

Since its introduction in late 2002, GC Tooth Mousse has quickly become a useful topical coating for teeth with a myriad of uses. More and more applications are being suggested for Tooth Mousse and so the intent of this article was to compile the most common applications. If you already use Tooth Mousse, it’s hoped that you may find some additional applications by reading through the growing body of evidence supporting its clinical effectiveness. If you haven’t tried this amazing product, you will find lots of encouragement to sample the product.

Casein Phosphopeptides (CPP)
Casein, a bovine milk phosphor-protein is known to interact with calcium and phosphate and is a natural food component. Its technical name is casein phosphor-peptides-amorphous calcium phosphate, or CPP-ACP. It was discovered by Prof. Eric Reynolds at the school of Dental Science at the University of Melbourne in Australia. Casein phosphor-peptides (CPP) are responsible for the high bioavailability of calcium from milk and other dairy products. CPP have the ability to bind and stabilize calcium and phosphate in solution, as well as to bind to dental plaque and tooth enamel. Calcium phosphate is normally insoluble, i.e. forms a crystalline structure at neutral pH. However, the CPP keeps the calcium and phosphate in an amorphous, non-crystalline state. In this amorphous state, calcium and phosphate ions can enter the tooth enamel. The high concentration of calcium and phosphate ions in dental plaque have been extensively researched and proven to reduce the risk of enamel demineralization and promote remineralization of tooth enamel.

Casein phosphor-peptides (CPP) containing the cluster sequence [-Ser(P)-Ser(P)-Ser(P)-Glu-Glu] have a remarkable ability to stabilize calcium phosphate in solution and substantially increase the level of calcium phosphate in dental plaque.

Reynolds and coworkers, in a series of publications (reviewed in 1999), demonstrated the role of casein in the anti-cariogenic and the enamel-protective effects of milk. Calcium and phosphate bound to the protein became available under the acid conditions of the plaque and reduced demineralization. The investigators isolated casein phospho-peptides from milk that react with high concentrations of calcium and phosphate to form colloidal amorphous calcium phosphate complexes (CPP-ACP).

The CPP-ACP products contain no lactose which is the carbohydrate in milk that can cause gastrointestinal upset sometimes seen with dairy-based products. Therefore, despite its dairy origin, gastrointestinal symptoms are not seen with CPP-ACP. However, patients with a known allergy to milk protein should avoid products containing CPP-ACP because they will be allergic to the casein protein from which CPP-ACP is derived.

Background
Dairy products (milk, milk concentrates, and cheeses) have been shown to be anti-cariogenic in animal and human in situ caries models. This effect could not be attributed to a change in level of infection of Streptococcus sobrinus and so was attributed to a direct chemical effect...
Supplementation of a normal diet with milk substantially reduced the dissolution of enamel when the observed anti-cariogenic effects of cheeses (Table 1). Milk greatly reduced the dissolution of enamel when the observed anti-cariogenic effects of cheeses (Table 1). Calcium and phosphates in the milk were in large part responsible for the observed enamel-protective effects. Investigators have concluded that milk by itself was not cariogenic. Some anticariogenic characteristics of milk may be summarized in the following points:

1. Milk produced only a minimal drop in plaque pH in subjects who rinsed with milk for 30 seconds after refraining from tooth brushing for three days, the extent and duration of which was recognized as non-cariogenic.
2. Milk greatly reduced the dissolution of enamel when extracted teeth were incubated for 24 hours in either 2% milk protein solution or saliva. The result is an almost continuous exposure to acids where plaque accumulates on the teeth and a progressive dissolution of the tooth enamel under the plaque occurs.
3. Milk has been shown to be essentially “tooth friendly” (i.e. its consumption does not increase plaque acidity or conversely, lower pH) in human trials. Kashket and Yaskell in 1997, using an intraoral caries test system in human volunteers, demonstrated that enamel demineralization was reduced by approximately 50% when 3% calcium lactate was added in the preparation of cookies made with flour, shortening, and water.
4. The k-casein fractions in milk can modulate adherence of a strain of the cariogenic microorganism, Streptococcus mutans, to hydroxyapatite. Adherence of Streptococcus to enamel is an important element in the formation of dental plaque.
5. Micellar casein, a dietary component in milk, selectively modifies the microbial composition of dental plaque, reducing its cariogenic potential. The Guggenheim et al. study in 1999 was the first study that demonstrated the dietary component- micellar casein- that selectively modifies the microbial composition of dental plaque, reducing its cariogenic potential.
6. Enamel protective effects of cheese have been studied and measurements of plaque pH in humans have shown that cheese consumption does not lead to decreased pH. Instead, Rugg-Gunn et al., in 1975 found that chewing cheddar cheese after consumption of sugary food, rapidly returned the plaque pH towards neutrality. A number of investigators have proposed various mechanisms to explain the observed anti-cariogenic effects of cheeses (Table 1).

### Evidence-Based Anticariogenic Mechanism of CPP-ACP
The anti-cariogenic mechanism of CPP-ACP is achieved by the incorporation of the nano-complexes of the amorphous calcium phosphate (ACP) into plaque and onto the tooth surface. The casein phospho-peptides (CPP) have an important role as an ACP carrier localizing the highly soluble calcium phosphate phase at the tooth surface. This localization maintains high concentration gradients of calcium and phosphate ions in the subsurface enamel, thereby facilitating remineralization.

Casein phosphopeptide-calcium-phosphate complexes (CPP-CP) have been found to increase the levels of calcium and phosphates in plaque up to five folds in humans in situ caries models and short-term mouthwash studies. The proposed mechanism of their anticariogenicity is that they act as a calcium-phosphate reservoir, buffering the activities of free calcium and phosphates in the plaque fluid helping to maintain a state of supersaturation with respect to enamel minerals, thereby depressing enamel demineralization and enhancing remineralization. The binding of ACP to CPP is pH dependent; with binding decreasing as the pH falls.

Casein phosphopeptide-amorphous calcium phosphate compounds (CPP-ACP) have been demonstrated to have anticariogenic potential in laboratory, animal, and human in situ experiments.

Rose (2000a) study investigated these effects by measuring the affinity and capacity of Streptococcus mutans for CPP-ACP. The study demonstrated that CPP-ACP binds with about twice the affinity of the bacterial cells for calcium. Application of CPP-ACP to plaque may cause a transient rise in plaque fluid free calcium which may assist remineralization. Subsequently, CPP-ACP will form a source of readily available calcium to inhibit demineralization.

Rose (2000b) investigated the effects of casein phospho-peptides (CPP) in reducing demineralization and enhancing remineralization in tooth enamel by measuring the effect of CPP-ACP on calcium diffusion in plaque. Calcium diffusion was measured in streptococcal model plaques. This demonstrated that by providing a large number of possible binding sites for calcium, 0.1% CPP-ACP reduces the calcium diffusion coefficient by about 65% at pH 7 and 35% at pH 5. Hence, CPP-ACP binds well to plaque, providing a large calcium reservoir within the plaque and slowing diffusion of free calcium. This is likely to restrict mineral loss during a cariogenic episode and provide a potential source of calcium for subsequent remineralization.

CPP-ACP has been shown in animal studies to enhance the effects of fluoride. Animals receiving 0.5% CPP-ACP and 500 ppm fluoride had significantly lower caries activity than those animals receiving either CPP-ACP or fluoride alone. This is actually not surprising, since fluoride requires a good source of calcium and phosphate for remineralization of tooth enamel with the more acid-resistant fluorapatite, and CPP-ACP provides this in an amorphous, soluble form.

In a human in situ enamel demineralization study, a 1.0% w/v CPP-ACP solution used twice daily, produced a 51±19% reduction in enamel mineral loss caused by frequent sugar solution exposure. The twice daily use of the 1.0% CPP-ACP solution resulted in a 144% increase in calcium level and a...
160% increase in inorganic phosphate level. These results suggested that an anticariogenic mechanism for the CPP-ACP exists, where the CPP stabilizes and localizes ACP at the tooth surface, thereby buffering plaque pH, depressing enamel demineralization and enhancing remineralization.

These results were extended by the incorporation of CPP-ACP into sugar-free chewing gum and in situ clinical studies demonstrated that the addition of 1.0% CPP-ACP to either sorbitol or xylitol-based gum resulted in an increase in enamel remineralization of 100% relative to the control gum. Shen and Reynolds in 2001, in an in situ human study showed that CPP-ACP in a sugar-free chewing gum enhanced remineralization of enamel subsurface lesions in situ by 100-150%, when compared with the control sugar-free gum not containing CPP-ACP. The results revealed a dose-related increase in enamel remineralization independent of chewing gum weight and type.

Reynolds in 2003 performed a clinical study that compared the ability of CPP-ACP with that of other forms of calcium, to be retained in supragingival plaque and remineralize enamel subsurface lesions in situ when delivered in a mouthrinse or sugar-free gum. CPP inhibited the tranformation of amorphous calcium phosphate (ACP) into the crystalline phases, such that they did not directly promote calculus formation like other plaque mineralizing solutions. The study indicated that the CPP-ACP was superior to that achieved with other forms of calcium in remineralizing enamel subsurface lesions.

A recent study by Kumar in 2008 has proved great efficiency of CPP-ACP in remineralization of initial enamel lesions and showed a higher remineralizing potential when applied as a topical coating after the use of a topical toothpaste (1100 ppm), than when used alone. Since additive effects were obtained when CPP-ACP is used in conjunction with fluoride, it can be recommended that CPP-ACP should be used as a self-applied topical coating after the teeth have been brushed with a fluoridated toothpaste by children who have a high caries risk.

**Interaction of CPP-ACP with Fluoride**

The CPP-ACP and fluoride have been shown to have additive effects in reducing caries experience. The additive anticariogenic effect of the 1.0% CPP-ACP and 500ppm fluoride in the rat caries experiments led to the investigation of the potential interaction between the CPP-ACP and fluoride. The fluoride ion had incorporated into the ACP phase that was stabilized by the CPP to produce a novel amorphous calcium fluoride phosphate phase (ACFP) at the tooth surface. The identification of this novel amorphous calcium fluoride phosphate (ACFP) phase led to the proposition that the formation of this phase is responsible for the observed additive anticariogenic effect of CPP-ACP and fluoride.

The formation of fluoroapatite, calcium and phosphate ions must be co-localized in plaque at the tooth surface with the fluoride ion for promoting enamel remineralization. Therefore the additive anti-cariogenic effect of CPP-ACP and fluoride may be attributable to the localization of ACFP at the tooth surface by the CPP, which would co-localize calcium, phosphate and fluoride. CPP may be an excellent delivery vehicle for the co-localization of calcium, phosphate, and fluoride at the tooth surface in a slow release amorphous form with superior clinical efficacy.

Mazzaoui et al. in 2003 evaluated the effect of incorporating CPP-ACP into a self-cured glass ionomer cement (GIC) in order to enhance its anticariogenic potential. Incorporation of 1.56% w/w CPP-ACP into the GIC significantly increased microtensile bond strength to dentin by 33%, increased its compressive strength by 23% and significantly enhanced the release of calcium, phosphate, and fluoride ions at neutral and acidic pH. The release of CPP-ACP and fluoride from the CPP-ACP-containing GIC as the acid erodes the cement was associated with enhanced protection of the adjacent dentin during acid challenge in vitro. It was concluded that the 1.56%-CPP-ACP-containing GIC might be a superior restorative/base with an improved anticariogenic potential. Furthermore, CPP has been shown to keep calcium, phosphate and fluoride as ions in solution, thereby enhancing the efficacy of the fluoride as a remineralizing agent.

CPP-ACP has been incorporated into commercial products by (GC corporation, Tokyo, Japan) such as:
1. GC Tooth Mousse™ (water based, sugar free crème with various flavors available).
2. GC MI Paste Plus™ (with the incorporation of 900 ppm fluoride).
3. Recaldent™ Chewing Gum (xylitol and CPP-ACP).
4. Recaldent™ Lozenges.

**Clinical Applications of CPP-ACP**

The applications of CPP-ACP include:
- Used for both primary and permanent teeth. Fluoride-free regular Tooth Mousse is a safe product to use in babies’ teeth especially young children under 2 years of age with early childhood caries.
- Used for patients with special needs such as those with intellectual impairment, developmental and physical disabilities, cerebral palsy, Down syndrome and those with any medical needs - Used for patients with special needs such as those with intellectual impairment, developmental and physical disabilities, cerebral palsy, Down syndrome and those with any medical needs.
problems such as those undergoing radiation therapy.  
- Used for high caries-risk patients in an attempt to remineralize early enamel lesions, early childhood caries, stabilize carious lesions awaiting treatment and root surface caries.  
- Used in cases of molar incisor hypomineralization (MIH). This is done for remineralizing hypoplastic molars and remineralization of white spot lesions (enamel opacities and some cases of mild fluorosis).  
- Used in cases of erosion whereby it neutralizes acid challenges from internal and external acid sources.  
- Used in the prevention of tooth wear.  
- Used in patients with orthodontic appliances for the purpose of caries prevention and prevention/remineralization of white spot lesions.  
- Used to reduce dentinal sensitivity by occluding patent tubules.  
- Used as a substitute for toothpaste in those allergic to commercial toothpastes.

**Instructions for Clinicians on the Use of Tooth Mousse (TM)**

1. Explain the following product characteristics to the patients/child's parent:  
   - Tooth mousse is commercially available through dentists only.  
   - The active ingredient is derived from cow's milk, and therefore cannot be used for patients with allergies to cow's milk (milk protein allergy), but can however be used for patients complaining of lactose intolerance since no lactose is present in Tooth Mousse. Besides, patients who have an allergy to benzoates or some other components shouldn't use the product.  
   - The product has been extensively tested; very safe with minimal side effects, if any. It has been classified by the United States Food and Drug Administration as GRAS (generally recognized as safe). Any material that is swallowed is safe as it will contribute to dietary calcium. It can be used with patients of any age.  
   - The product is highly effective for re-mineralization of enamel and works well with fluoride.  
   - The product has a pleasant taste and comes with different flavors.

2. Explain benefits of TM for enamel hypoplasia, cases of erosion, caries prevention...etc.

3. Explain the proper way of using TM;  
   - It should be rubbed on tooth surfaces after brushing and no rinsing should be done after that.  
   - It should be used twice daily; after morning toothbrushing and before going to bed, avoiding eating or drinking for 30 minutes afterwards.

4. Obtain parents' consent before using the product in children:  
   - Explain the need to evaluate the product to determine the effects on your patient for long term use.  
   - Explain the need to contact the dentist if any problem arises.

5. Evaluate product use; review the patient at 1, 3, 6 and 12 months. File in case notes in patient's chart.

**Conclusions**

Based on the previous literature and the proven efficacy of CPP-ACP products through clinical and laboratory studies, it seems that we should shift our ways of caries prevention to include products such as CPP-ACP in our prevention schemes for patients through remineralization of enamel and application of minimal invasive approaches in dentistry. Recent studies support the use of fluoride in toothpastes and gels with CPP-ACP. CPP-ACP products are recommended to be used twice daily and are safe to be used in young children. Their use seems to be rewarding in the field of preventive dentistry.

**References**


