UBC Faculty of Dentistry

Presentation from

Professionalism and Community Service (PACS 410)

Toothpaste: Claims made by Manufacturers

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Toothpaste: Claims made by Manufacturers

Anti-Plaque and Tartar Build-Up

Question 1: What are the active ingredients that specifically help in reducing plaque and tartar formation? What is/are the mechanisms of action? What/where is the evidence for their effectiveness?

Therapeutic Ingredients for the Prevention/Reduction of Plaque and Tartar Formation

1) Metal Salts: Metal salts are some of the most commonly added therapeutic agents added to toothpaste. Mechanistically, they act as metabolic inhibitors by oxidation of thiol groups in cytoplasmic/membrane bound enzymes (Denver, S.P et al., 1998). The most common ones indicated as an anti-plaque agent are described below:

Zinc

- Formulated as Zinc Citrate in toothpaste, zinc has a know antimicrobial effect
- Zinc is an essential mineral and required as a cofactor in many enzymatic reactions, however in high concentrations it can inhibit bacterial growth in the mouth (Saxton CA, et.al. 1986)
- Following the use of a dentifrice containing zinc, salivary zinc concentration is elevated for several hours and can inhibit the formation of hydroxyapatite crystals to prevent calculus build-up (Gilbert, R J, 1988)
- Often used in concert with other microbial agents to have a synergistic effect

Tin

• Formulated as Stannous Fluoride, it is primarily added as an anti-caries agent. However, tin has also been shown to have antimicrobial effects

2) Anti-Bacterial Agents:

Chlorhexidine

- A proven effective antibacterial agent used in mouth rinses has been also been added to toothpastes but with limited success (Davies, 2008)
- Interacts electrostatically with phospholipids to decrease cytoplasmic membrane integrity and cause intracellular coagulation (Denver, S.P et al., 1998)

Triclosan

- One of the most commonly used ant-plaque agent (accepted by the CDA) acts as a broad spectrum antibiotic effective against both gram negative and gram positive bacilli
- Functions by inhibiting the FAB 1 enzyme required by all bacteria for fatty acid synthesis (Heath, R.J.et al, 1999)

3) Chelating agents/Calculus Inhibitors:

Pyrophosphates

- Crystal growth inhibitors that PREVENT calculus build up. Two types of soluble phosphates are used: tetra sodium pyrophosphate and disodium pyrophosphate
- Orthophosphate analogs, differing by a single element disrupt calcium phosphate crystallization in calculus (White, D.J., 1997)

Evidence for effectiveness of therapeutic agents reducing plaque/tartar buildip

- There is substantial evidence surrounding the effectiveness of Triclosan in reducing supragingival plaque. Davies et al.(2004) concluded that "unsupervised use of a dentifrice containing triclosan/copolymer significantly improved the removal of supragingival plaque and gingival health when compared with a fluoride dentifrice." A meta-analysis of six-month studies of anti-plaque agents by Gunsolley reviewed 17 studies and found triclosan to reduce supragingival plaque buildup to a statistically significant value. (Gunsolley, 2006)
- Pyrophosphate is the main agent used in preventing the formation of calculus. It was found that this agent is very effective at the concentrations found in toothpaste in preventing the buildup of supragingival calculus. (Cohen et al., 1994). Yin et al. (2004) further confirmed this finding in their review of various studies. It should be noted that pyrophosphate doesn't interfere with the re-mineralization potential of fluoride found in dentifrices (Adams, 1995). Another important point to consider is that the efficacy of pyrophosphate is greatly increased when it is used in combination with polymers as they inhibit enzymes in the oral cavity that hydrolyze pyrophosphate. (Adams, 1995)
- Pyrophosphate has also been shown to reduce the buildup of plaque by inhibiting the growth of certain species of bacteria that are commonly associated with plaque. It should be noted that this bactericidal effect of pyrophosphate was seen well below its concentrations found in commonly used dentifrices. (Grisby et al., 1994)
- The evidence surrounding Chlorhexidine is controversial. Olympio et al.(2006) found it to be effective against reducing plaque buildup but also found it to be associated with staining problems. It was also mentioned that it is ineffective against preventing calculus formation. Another important point to be considered is that "incoroporation with fluoride had no adverse effects." On the contrary Rathe et al. (2007) found that it had no beneficial effects on reducing the buildup of plaque. It should be noted, however, that there is substantial evidence supporting the beneficial effects of Chlorhexidinemouth rinsesin significantly reducing the number of anaerobic bacteria of supragingival plaque. (Feres et al., 2009 and Cianco, 1992)
- There is strong evidence suggesting that zinc citrate is effective in control of supragingival plaque formation. Sreenivasan et al. (2009) found zinc citrate to be very effective in reducing the population of anaerobic and streptococci bacteria within the oral cavity, which are commonly associated with plaque. It was also found that group that received the zinc citrate treatment had a significant reduction in the formation of biofilm. To further support this, Adams et al. (2003) found that the use of zinc citrate/ triclosan dentifrice is better than using dentifrice containing triclosan alone in reducing plaque growth.

Question 2: If the premise involves calcium, does this mechanism interfere with remineralization of dental enamel?

- Pyrophosphates inhibit the formation of calcium phosphate crystals from saturated solutions. Due to this inhibiting effect, Pyrophosphates widely used as anti-calculus agents. The content of pyrophosphate in dentifrices is derived from pyrophosphate salts of sodium and/or potassium. The effective agent is soluble pyrophosphate. To enhance the effects of pyrophosphates, it is typically combined with a copolymer of polyvinylmethyl ether and maleic acid anhydride (Adams, 2005).
- As dentifrice typically contains fluoride in addition to pyrophosphates, there may be
 concern whether the pyrophosphates will interfere with the re-mineralization potential of
 fluoride (Adams, 2005). As both ingredients are found combined in many dentifrice
 products, this potential concern has been extensively investigated.
- Of these investigations, Adams (1995) concluded, via a meta-analysis of 50 clinical trials since 1989, that the re-mineralizing potential of fluoride on de-mineralized enamel does not interfere with the crystal-inhibiting power of the pyrophosphates. Additionally, the pyrophosphates do not affect the anti-caries effects of fluoride. Zero (2006) also supports that the addition of pyrophosphate to a fluoride dentifrice does not interfere with the anti-caries effects of fluoride. As such, Adams (1995) and Zero (2006) support that the mechanism of action of pyrophosphates and fluorides are mutually exclusive and conclude that pyrophosphates do not interfere with re-mineralization of dental enamel whatsoever.

Question 3: How much does plaque/tartar contribute to tooth discolouration?

What is Plaque/Tartar?

- Plaque is a biofilm consisting of a variety of dead and living micro-organisms that interact with a protein layer (pellicle) that covers the enamel of teeth (Addy et al., 1995).
- This complex community flourishes in a polysaccharide rich matrix and is dependant on environmental conditions such as pH, oxygen levels, nutrients obtained from diet, as well as enzymes present in saliva.
- Frequent exposure of plaque to an acidic environment selects for acidophilic bacteria, such as Streptococcus mutants and lactobacilli, which are the primary culprits responsible for the fermentation of sucrose and decalcification of enamel which can progress to caries and inflammatory periodontal disease (Marsh P. D., 1994).
- In the absence of proper oral hygiene, plaque can calcify and form a yellowish brown crusty coat known as tartar.

Types of Tooth discolouration

Tooth discolouration can be classified as being either extinsic, intrinsic or internalized in nature.

1) Extrinsic stains

- Chromogens that deposit their inherent colour within the pellicle layer or on the tooth surface (Sulieman M., 2005).
- These stains are either <u>direct or indirect</u> and can be removed with brushing or scaling.
- Direct stains are attribued to:
 - **Plaque** form molecular interactions between surface adhesins and receptors (Marsh P. D., 1994).
 - **Dietary Chromogens** polyphenolic compouds present in tea and coffee are taken up by pellicle and impart stain. This process is not clearly understood but "naked" enamel does not take up chromogens as well as pellicle proteins which suggests the pellicle acts as a "sponge"(Sulieman M., 2005).
 - **Tobacco** (smoking or chewing)
 - **Chromogenic Bacteria** *Actinomyces* species: creates a black ferric sulfide stain formed by the reaction between bacterial hydrogen sulfide and iron present in saliva (Gasparetto A., et al, 2003).
- Indirect stains are attributed to:
 - **Potassium Permangenate** (KMnO₄) mouthwash
 - Catonic Antiseptcs chlorhexidine: form brown to black discolouration. The mechanism of this interaction has sparked "a lot of interest" and much discussion and is thought to be due to the "precipitation of dietary anionic chromogens onto adsorbed cationic antiseptics or metal salts on the tooth" (Sulieman M., 2005).

2)Intrinsic stains

- Result from changes in structual composition or dentinal tissue that occur during developmental (Sulieman M., 2005).
- These stains can be iatrogenic, inherited, and due to aging or fluorosis but can not be removed brushing or scaling.
 - **Tetracyclin** pregnant women and children under the age of 12 should avoid this drug due to its chelating effects with calcium on hydroxy apatite during tooth development (Sulieman M., 2005).
 - **Amelogensis Imperfecta** disruption in mineralization or matrix formation of enamel (can be autosomal dominant or x-linked trait)

3)Internalized stains

• Extrinsic stains that are incorporated into the dentin or enamel as a result of trauma, restorations, or developmental defects.

Anti-Caries and Tooth Whitening Claims

Question 1: What are the active ingredient that causes teeth to be whiter? Do they work? How? Do toothpastes change the "colour" of tooth enamel?

Active ingredients and their mechanism

1) Abrasives

- Remove stains by mechanical means ie. scratching, chiseling, tumbling,
- Removes stains but makes teeth appear dull
- Examples are Carbonates, Phosphates, Silicas (most common) (Nathe et al., 2009)

2) Polishing agents

• Smooth out the rough surfaces created by abrasives using very fine particles; they make teeth appear shiny (O'Brien et al, 2008)

3) Chemical agents

• Lightens or eliminates surface stains through binding/releasing or oxidation/bleaching chromogens, as well as the prevention of stain formation. Examples are: Carbamide Peroxide and Hydrogen Peroxide

Do they work?

YES....

- Presence of abrasives in conventional toothpastes means that all toothpastes do have the capability to whiten by mechanical means (Claydon et al. 2004). "Whitening toothpastes" on the market have added chemical ingredients.
- Colgate Total plus Whitening vs. Crest Pro Health: both whitened teeth compared to baseline readings. **the latter is the only CDA approved whitening toothpaste**

BUT...the efficacy of the additional chemicals is unclear

- one study found that rinsing with water was more effective than rinsing with a slurry of Rembrandt whitening toothpaste! (Claydon et al. 2004)
- peroxide concentration in toothpastes is very low, and the short contact time not lead to significant changes in whiteness (Rajesh 2008)
 -a Cochrane meta-analysis on this topic is in progress

When recommending a toothpaste:

- If stain accumulation is not a problem -- recommend high polishing, low abrasion
- To control accumulating stains -- increase abrasiveness, but note that this may cause more injury to the teeth/soft tissues of the patient; therefore, follow up with proper eduction on brushing techniques (Nathe 2009).

Do toothpastes change the "colour" of tooth enamel?

No, most toothpastes readily remove extrinsic surface stains, but do not change the actual colour of the tooth enamel. (Sharif 2000).

Question 2: What are the active ingredients that specifically help in preventing caries? How do these therapeutic agents actually prevent disease? What is the

mechanism of action? How can they work when immediately washed or rinsed away? What is the evidence?

General mechanism of caries prevention by toothpaste

- The active anti-caries agent in toothpastes is one of several compounds containing fluoride ions.
- Fluoride is "incorporated into or adsorbed on the hydroxyapatite crystal" in enamel to form fluor(hydroxy)apatite, which is more acid-resistant, helping to **prevent demineralization** (Nanci, 2003; Ten Cate, 1999).
- Also, the reduction in solubility means that it "will precipitate at a higher rate when in contact with a solution containing calcium and phosphate" (i.e. saliva), which will **promote re-mineralization** (Ten Cate, 1999).
- Fluoride has been shown to have "a greater inhibiting effect on caries progression than on caries initiation" (Ten Cate, 1999).

Antimicrobial activity

- Fluoride can also impact bacterial metabolism, giving it important antimicrobial effects.
- Acidophilic bacteria are able to live in acidic environments due to their alkaline cytoplasm. Fluoride makes the membrane more permeable to protons, causing the cytoplasm to become more acidic, and resulting in inhibition of their glycolytic enzymes (Marquis, 1995).
- Fluoride can act as an enzyme inhibitor, both directly, by inhibiting the glycolytic enzymes such as enolase, or indirectly by forming complexes with metals which bind ADP at reaction centres of the F-ATPases that are important in the acid-base balance of the cell (Marquis, 1995).

Distribution

- Younger enamel has better uptake of fluoride, as a result of higher enamel porosity, with "best fluoride uptake in early pre-eruption and early post-eruption" (Minah, 2010). Studies have also shown that the highest concentrations will be deposited in the outermost layer of the enamel, with much lower levels in the bulk (Brudevold et al., 1956).
- Penetration into the enamel is impeded by the binding of fluoride with calcium, and therefore "fluoride uptake is higher in decalcified areas" (Minah, 2010).

Details about Fluoride

Types available in toothpastes

- Stannous fluoride (SnF₂), sodium monofluorophosphate (MFP), sodium fluoride (NaF), and amine fluoride have been used in toothpastes. MFP and NaF are the standard types used in the US, while amine fluoride is not currently sold. SnF₂ "exhibits a shorter shelf life and may cause staining of the teeth". In contrast, MFP has covalently-bound fluoride for greater stability (with the fluoride released *in vivo* by enzymatic reactions) and better uptake by enamel crystals. (Minah, 2010)
- Hildebrandt et al. are currently conducting a systematic review regarding the addition of xylitol to toothpaste and other products for caries prevention. Their protocol states that

- "in some studies, the effectiveness of [the xylitol] treatment has been profound, rivaling that of fluoride" and that "if these results are valid, xylitol-containing oral products may be a highly significant alternative treatment" against caries.
- Trimetaphosphate (TMP) has been suggested as a toothpaste additive for the prevention of caries. While Stadler et al. (1996) found a significant difference in caries incidence with TMP-containing toothpaste, O'Mullane et al. (1997), did not find any benefit.

Concentration and efficacy

- In a systematic review, combining results from over 42,300 sixteen-year-olds, it was determined that use of fluoride toothpastes, as compared to non-fluoridated toothpastes, is associated with a decreased incidence of caries (Marinho et al., 2003).
- The different types of fluoride salts are available in different standard concentrations, however, these will all reach levels of 1000-1500 ppm F in the oral cavity (Minah, 2010). Studies have also shown that 1000 ppm F toothpaste has a significantly greater efficacy for preventing caries than a comparable 250 ppm F toothpaste (Ammari et al., 2003).

Recommended Usage for Anti-Caries Benefits

Amounts

• A pea-sized amount (0.32g) of toothpaste is recommended to prevent fluorosis (Davies et al., 2003). Thaveesangpanich et al. (2005) found that this amount led to better remineralization and prevention of demineralization in a simulation of deciduous teeth decay, as opposed to a half-pea size.

Number of acts of brushing per day

• A 3-year clinical trial found more favourable clinical and radiological scores for indviduals who brush more than once a day (O'Mullane et al., 1997) therefore brushing at least twice a day is recommended, including last thing before going to sleep at night.

Rinsing

• Ideally, toothpaste should just be spat out or rinsed with a fluoride rinse, as this allows a longer duration of fluoride in the oral cavity (Minah, 2010). O'Mullane et al. (1997) also found the amount of water with which a person rinses to be significant for caries development.

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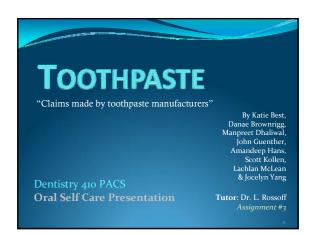
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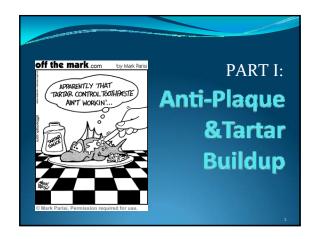
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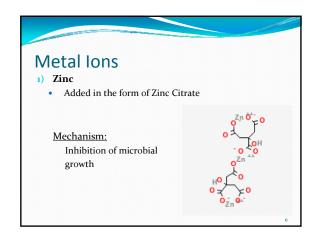












Zinc Citrate

- Very effective in killing the bacteria found in plaque.
- Sreenivasan et al. (2009) found a 24–52% reductions in anaerobic bacteria and streptococci after 14 days of

Metal Ions



- 2) Tin
 - Added in the form of Stannous Fluoride
 - Initially added as an anticaries agent in the 50's

Mechanism:

Tin acts to inhibit microbial growth

* Associated with teeth staining



Anti-Bacterial Agents

- 1) Triclosan
- Broad spectrum non-ionic antibiotic

Mechanism:

- Functions by inhibiting the FAB 1 enzyme required by all bacteria for fatty acid synthesis
- Has a short half life that is often extended through the use of patented copolymers

CI OH



Fabl-NAD Slow

Fabl-NAD Triclosan

Triclosan

- Substantial evidence regarding its effectiveness is reducing supra - gingival plaque.
- Meta-analysis of data from 16 studies by Davies et al. (2008) shows that Colgate Total, a toothpaste that contains triclosan, was effective in reducing plaque by 23%.



Anti-Bacterial Agents

- 2) Chlorhexidine
 - Very strong anti-plaque and inhibitory agent

Mechanism

- Not often in toothpastes due to inactivation by other anionic compounds
- * Associated with teeth staining
- HN NH NH NH NH NH NH NH NH NH

Chlorhexidine

- Controversial
- Olympio et al. (2006) found it to be effective in preventing plaque build-up.
- Rathe et al. (2007) showed that it had no significant reduction in plaque.
- Staining problems.
- Effective when found in mouth rinses.

Anti-Calculus

Pyrophosphates

- crystal growth inhibitors that PREVENT calculus build up
- 2 types of soluble phosphates are used: tetra sodium pyrophosphate and disodium pyrophosphate

Mechanism:

- Act as buffering/chelating agents
- Orthophosphate analogs, differing by a single element disrupt calcium phosphate crystallization in calculus



Pyrophosphate

- Effective in preventing calculus build up at concentrations normally found in toothpastes. (Yin et al., 2004).
- Also has inhibitory effect on growth of bacteria normally associated with plaque (Grisby et al., 1994).
- Efficacy is enhanced when used with a polymer that inhibits the phosphatases in the oral cavity

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Anti-Plaque & Tartar Buildup

If this premise involves calcium,
does this mechanism interfere
with re-mineralization of dental
enamel?

By Manpreet Dhaliwal

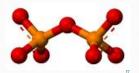
Concerns?

- There are growing concerns that anti-calculus agents may interfere with the re-mineralization process.
- Specific emphasis has been placed on pyrophosphates



Pyrophosphates

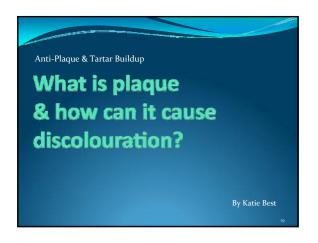
- Pyrophosphates inhibit the formation of calcium phosphate crystals from saturated solutions
- Pyrophosphates are widely used as anti-calculus agents for this reason
- The effective agent is soluble pyrophosphate

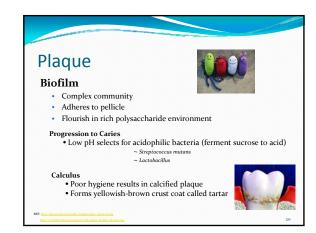


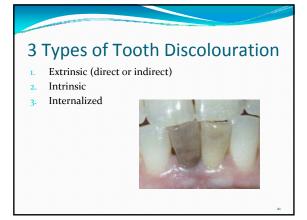
Need for concern?



- Adams (1995) conduced a meta-analysis of 50 clinical trials since 1989
 - The re-mineralizing potential of fluoride did not interfere with the crystal-inhibiting power of the pyrophosphates.
 - The pyrophosphates did not affect the anti-caries effects of the fluorides.
 - The MOA of pyrophosphates and fluorides are mutually exclusive!



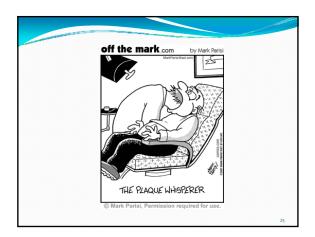


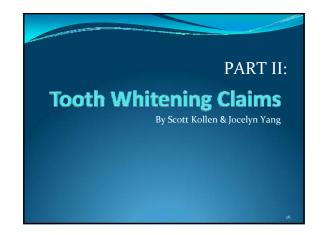


Extrinsic Stains Chromogens impart inherent colour on tooth surface or within pellicle Can be removed with brushing or scaling Direct Plaque Dietary chromogens (tea and coffee) Tobacco (smoking or chewing) Indirect KMnO₄ (mouthwash) Cationic Antiseptics (chlorhexidine)

Intrinsic Stains Change in structural composition or dentinal tissues during tooth development Can't be removed with brushing/scaling Exp's: Tetracycline Amelogenesis Imperfecta Aging Fluorosis

Internalized Stains • Extrinsic stains incorporated into dentin or enamel as a result of trauma, restorations, or developmental defects.





Active Ingredients & Mechanism 1. Abrasive Agents - remove stains by mechanical means; eg. Carbonates, phosphates, and silicas Abrasive agents may roughen teeth surface, making them look dull; therefore, manufactures add a polishing agent 2. Polishing - smoothes out rough surfaces by using very fine particles 3. Chemical – lightens or eliminate surface stains through enzymatic/chemical means a) Hydrogen Peroxide – active bleaching molecule; capable of oxidizing coloured compounds, resulting in decolourization 4. Whitening toothpastes differ from conventional toothpastes in that they contain a chemical stain remover (in addition to abrasives found in all toothpastes). Studies usually focus on the efficacy of the chemical agents

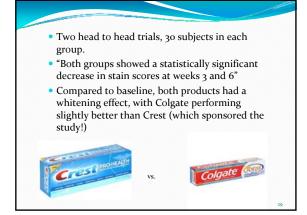
Most toothpastes work by removing extrinsic stains, and not by changing natural teeth color

•Aquafresh experimental formula slurry with NaF, silica, and PVP (a chemical whitener) performed better than water, or Rembrandt dentifrice

•PVP interfered with the binding of dietary chromogen (in this case, black tea)

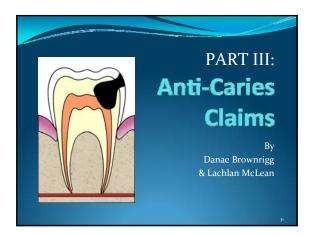
•Rembrandt's performance: cumulative effect seen over long term? Effect mostly due to mechanical action not seen with slurry?

• VS. | REMBRANDT



Do Whitening Toothpastes Work?

- A review (Sharif et al. 2000) concluded that only a minority of whitening toothpaste products were effective chemical stain removers, whereas the rest failed to achieve the whitening benefits they claimed
- A meta-analysis is currently in progress, the protocols of the analysis have been outlined on the Cochrane Database





General Mechanism of Fluoride

- Shifts equilibrium of calcium and phosphate ions in solution and enamel phases
- Prevent Demineralization
 - Fluoride is "incorporated into or adsorbed on the hydroxyapatite crystal" in enamel → fluor(hydroxy)apatite (more acid-resistant) (Nanci, 2003; Ten Cate, 1999)
- Promote Remineralization
 - Fluoride increases precipitation of calcium phosphate by reducing its solubility (Ten Cate, 1999)
- Fluoride has "greater inhibiting effect on caries progression than on caries initiation" (Ten Cate, 1999)

sound

caries initiation

active lesion — arrested lesion

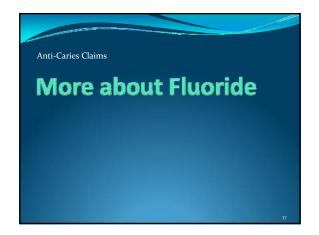
cavity caries progression

Anti-Microbial Activity

- By fluoride impacting bacterial metabolism
- Acidophilic bacteria are able to live in acidic environments due to their alkaline cytoplasm.
 - Fluoride makes the membrane more permeable to protons → more acidic cytoplasm (Marquis, 1995).
- Acts as an **enzyme inhibitor**
 - **Directly**: inhibiting glycolytic enzymes (ex: enolase)
 - **Indirectly**: complexes with metals and interferes with the acid-base balance of the bacteria (Marquis, 1995).

Distribution

- Younger enamel has better uptake of fluoride, as a result of higher enamel porosity, with "best fluoride uptake in early pre-eruption and early post-eruption" (Minah, 2010).
- Highest concentrations will be deposited in the outermost layer of the enamel, with much lower levels in the bulk (Brudevold et al., 1956).
- Penetration into the enamel is impeded by the binding of fluoride with calcium, and therefore "fluoride uptake is higher in decalcified areas" (Minah, 2010).



Types of Fluoride in Toothpaste

- Stannous fluoride (SnF₂), sodium monofluorophosphate (MFP), sodium fluoride (NaF), and amine fluoride have been used in toothpastes.
- MFP and NaF are the standard types used in the US, while amine fluoride is not currently sold.
- SnF₂ "exhibits a shorter shelf life and may cause staining of the teeth"
- MFP has covalently-bound fluoride for **greater stability** (with the fluoride released *in vivo* by enzymatic reactions) and better uptake by enamel crystals. (Minah, 2010)

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Other Anti-Caries Agents in Toothpaste

- Hildebrandt et al. are currently conducting a systematic review regarding the addition of xylitol to toothpaste and other products for caries prevention
 - "In some studies, the effectiveness ... rival[s] that of fluoride" and "may be a highly significant alternative treatment" against caries
- **Trimetaphosphate** (TMP) has been suggested as a toothpaste additive for the prevention of caries
 - Conflicting evidence about caries prevention (Stadler et al., 1996; O'Mullane et al., 1997)

Concentration & Efficacy

- Systematic review (over 42,300 sixteen-year-olds) found use of fluoride toothpastes, as compared to nonfluoridated toothpastes, is associated with a decreased incidence of caries (Marinho et al., 2003)
- The different types of fluoride salts are available in different standard concentrations, however, these will all reach levels of 1000-1500 ppm F in the oral cavity (Minah, 2010).
 - 1000 ppm F toothpaste has a significantly greater efficacy for preventing caries than 250 ppm F (Ammari et al., 2003).

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Recommended Usage

- Amount
 - A **pea-sized amount** (0.32g) of toothpaste is recommended to prevent fluorosis (Davies et al., 2003)
 - Better remineralization and prevention of demineralization in a simulation of deciduous teeth decay, as opposed to a half-pea size (Thaveesangpanich et al., 2005)
- Number of acts of brushing per day
 - A 3-year clinical trial found more favourable clinical and radiological scores for indviduals who brush more than once a day (O'Mullane et al., 1997) therefore brushing at least twice a day is recommended, including last thing before going to sleep at night

Rinsing

- Ideally, toothpaste should just be spat out or rinsed with a fluoride rinse, as this allows a longer duration of fluoride in the oral cavity (Minah, 2010)
- O'Mullane et al. (1997) also found the amount of water with which a person rinses to be significant for caries development.





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