Introduction – Fluoride Dentifrices
A History and Update of Fluoride Dentifrices course is a review and update of cosmetic and therapeutic dentifrices, their impact on market shares and the development of multi-benefit dentifrice technologies.
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Overview
This course is a review and update of cosmetic and therapeutic dentifrices, their impact on market shares and the development of multi-benefit dentifrice technologies. The first therapeutic dentifrice contained fluoride and entered into the US market in the mid 1950s. The public was not convinced of the importance of such a product until the American Dental Association (ADA) Seal of Acceptance was awarded to a product in the early 1960s. Both public and market pressures have resulted in a continued development of new and improved products which not only have therapeutic value but also cosmetic value. These developments have led to the use of various fluoride agents, abrasives, and additives, as well as the introduction of new technologies into dentifrices. Although some products are designed to provide single benefits, such as caries protection, other products are designed to deliver multiple benefits, such as caries and plaque reduction, or caries protection coupled with alleviation of hypersensitivity. One of the more recent benefits to be delivered from some fluoride dentifrices is protection against dental erosion, an emerging oral care issue that can be addressed with the proper therapeutic approach. There have also been 2-step dentifrice systems introduced to deliver elevated levels of efficacy (e.g., whitening, gingivitis reduction). It is clear that dentifrices have gone through an incredible evolution over the past several decades, providing many options to help patients prevent and treat oral diseases and conditions.

Learning Objectives
Upon completion of this course, the dental professional should be able to:
• Understand the history and development of modern day dentifrices.
• Discuss the changes from dentifrices that delivered only cosmetic benefits to those that focused on therapeutic benefits; and then back to products that deliver a combination of both.
• Discuss changes in ingredients and actives, and describe new technologies.
• Help dental professionals talk to their patients from a position of knowledge about the variety of fluoride dentifrices available in the current marketplace.
• Help the dental professional understand the connection between modern lifestyle (diet), new emerging issues such as dental erosion and appropriate therapies to help them guide their patients.

Glossary
abrasive – A substance, such as silica, that is used for polishing or cleaning.
acidogenic – Something that produces acid, such as cariogenic bacteria.
anti-oxidant – A chemical compound or substance that inhibits oxidation.
astringency – A taste experience, often an after-taste, that causes the mouth to pucker.
bioavailability – The degree to which a drug or substance is available to the target tissue following administration.
calculus - calcified plaque – A hard yellowish deposit on the teeth, consisting of organic secretions and food particles deposited in various salts, such as calcium carbonate; also called tartar.
caries – A bacterial infection that results in demineralization, and ultimately the destruction, of tooth minerals.
cariogenic – Contributing to the production of caries.
cation – An ion with a positive charge.
chelate – Chemical compound that can form several non-covalent bonds to a single metal ion (e.g., Ca\(^2+\)), sequestering it and preventing it from reacting with its surroundings.

covalent – In chemistry, a chemical bond formed by the sharing of one or more electrons, especially pairs of electrons, between atoms.

cyttoplasmic – The cell substance located between the cell membrane and the nucleus of the cell.

demineralization – The chemical process by which tooth minerals are removed from the dental hard tissues: enamel, dentin and cementum. This process occurs through dissolution by acids or by chelation, and the rate of demineralization will vary due to the degree of supersaturation of the immediate environment of the tooth and the presence (or absence) of fluoride.

dental erosion – Localized loss of dental hard tissue that is chemically etched away from the tooth surface by acids or chelating agents. Can be referred to as Acid Erosion or Erosive toothwear. Teeth exhibiting signs of erosion lose their surface texture (perichymata), may appear more yellow, and have an altered shape.

dentinal hypersensitivity – A short, sharp pain arising from exposed dentin in response to stimuli which cannot be ascribed to any other form of dental defect or pathology. These stimuli are typically thermal, evaporative, tactile, osmotic or chemical.

dissociation – A general process in which ionic compounds separate or split into smaller particles, ions, or radicals, usually in a reversible manner.

enzyme – Protein that catalyzes, or facilitates, biochemical reactions.

enzymatic hydrolysis – A process in digestion in which macromolecules are split from food by the enzymatic addition of water.

epidemiological – Dealing with the incidence, distribution, and control of disease in a population.

extrinsic stain – Tooth stain on the exterior surface of the tooth that can be removed through routine cleaning procedures. It is generally composed of dietary chromogenic molecules and metal ions which become bound within the salivary pellicle layer that coats exposed tooth surfaces.

fluorosis – An abnormal condition (such as mottling of the teeth) caused by an excessive intake of fluorine during the development period of the permanent teeth.

fluorohydroxyapatite – A crystal structure in tooth mineral (Ca\(_{10}\)(PO\(_4\)_6F\(_2\)) resulting from the replacement of hydroxyl ions (OH\(^-\)) in the hydroxyapatite structure with fluoride ions (F\(^-\)). Fluorohydroxyapatite (also commonly referred to as fluorapatite or fluoroapatite) is stronger and more acid resistant than hydroxyapatite.

gingivitis – Inflammation of the gums that often manifests as bleeding during brushing and flossing; mildest form of periodontal disease that is reversible.

hydrolysis – A chemical reaction of a compound with water, generally resulting in the formation of one or more new compounds.

hydroxyapatite – A crystal structure (Ca\(_{10}\)(PO\(_4\)_6(OH)\(_2\)) that forms the majority of the mineral make-up of tooth enamel and dentin.

ions – Atoms or molecules that carry either a positive or a negative electric charge in a solution. For example, sodium chloride (NaCl, common table salt) in water dissociates into Na\(^+\) and Cl\(^-\) ions.

intrinsic stain – Staining caused by the presence of pigment within the enamel or dentin. Intrinsic stain can often be mediated through bleaching procedures.

meta-analysis – A statistical technique in which the results of two or more studies are
mathematically combined in order to improve the reliability of the results. Studies chosen for inclusion in a meta-analysis must be sufficiently similar in a number of characteristics in order to accurately combine their results.

**oxidation** – The interaction between oxygen molecules and all of the different substances they may contact.

**plaque** – An organized community of many different microorganisms that forms itself into a biofilm and is found on the surface of the tongue and all hard surfaces in the oral cavity. Dental plaque is present in all people and can vary from being comprised of totally healthy microorganisms (commensals) to being very harmful (pathogenic), predisposing the patient to dental caries or periodontal diseases. Note: Dental plaque is not food debris, nor does it contain food debris. Dental plaque can only be completely removed by mechanical means, such as toothbrushing or prophylaxis.

**phosphoenolpyruvate** – An important chemical compound in biochemistry that is directly involved in glycolysis. It is also the primary source of energy for the phosphotransferase system.

**phosphotransferase system** – A method used by bacteria for sugar uptake where the source of energy is from phosphoenolpyruvate.

**prevalence** – The percentage of a population that is affected with a particular disease at a given time.

**remineralization** – The chemical process by which tooth minerals are replaced into the dental hard tissues: enamel, dentin and cementum. This process requires an environment that includes supersaturation with calcium and phosphate ions; it is enhanced in the presence of fluoride and the proper pH.

**supersaturation** – Containing an amount of a substance greater than that required for saturation.

**systemic** – Pertaining to or affecting the body as a whole.

tartar - calcified plaque – A hard yellowish deposit on the teeth, consisting of organic secretions and food particles deposited in various salts, such as calcium carbonate; also called calculus.

**Tooth Cleaning**

Ancient chewing or cleaning sticks probably represent the forerunners of today's toothbrushes. Descriptions of their use can be found in both the gospel of Buddha and ancient Egyptian writings. The concoctions used to clean the mouth, decrease malodor and treat the gums in early writings often were more detrimental than preventive. For example, in the writings of Pliny (23-79 C.E.) several remedies are mentioned: burnt nitre (potassium nitrate) to restore whiteness; goat's milk to sweeten the breath; burnt stag's horn and ashes of various animals for strengthening the gums, etc.

Many different remedies have been proposed for improving the conditions found in the oral environment, and one may even go so far as to call these unpleasant concoctions the first dentifrices. Two basic components of oral hygiene have passed the test of time and, although modified and improved, have their roots in ancient times. These components are both the bristle toothbrush and the dentifrice used in conjunction with the brush. Primitive cleaning sticks of different types still exist today and are the brush of choice in some cultures; although the modern day brush has evolved into a skillfully designed multi-tufted product. The manual brush continues to be improved in ways that enhance both function and performance. Power brushes are also available that move the bristles in many directions. These include versions with either oscillating-rotating or sonic movements. Improved tooth cleaning, coupled with excellent safety profiles for these products, makes them important developments for efficiently delivering fluoride, as well as other key ingredients, to targeted tooth surfaces. Dentifrices have also changed dramatically from the predominantly acid concoctions of the past to more basic or neutral products. This was the result of the acceptance of Miller's acidogenic theory of caries formation which helped promote the change from acidic to basic formulations.
Caries Prevention

Early efforts to incorporate fluoride into dental preparations as well as research towards understanding the fluoride content of teeth gave conflicting results. A phenomenon called “Brown Stain”, associated with too much fluoride ingestion, was thought to be “typical caries” in a paper presented in 1904 before the German Society for Surgery. McKay and Black investigated what had been termed Colorado Brown Stain as early as 1916. They found that this stain was present in other communities and associated it with the communal water supply, although they were not certain of the cause. These and other findings led the United States Public Health Service to do extensive epidemiological surveys to study both dental caries and dental fluorosis in the late 1930s. When it was confirmed that fluoride intake from water was associated with the prevalence of dental fluorosis as well as a reduction in dental caries, many delivery systems and strategies were investigated to optimize the benefit of fluorides at the community level as well as the individual level. In 1937, a dental preparation claiming to prevent decay was not favorably looked upon by the American Dental Association’s (ADA) Council on Dental Therapeutics. The possibility of toxicity, conditions of usage and absorption questions led to the ADA’s conclusion that “The use of fluoride in dentifrices is unscientific and irrational, and therefore should not be permitted.” At that time, dental problems were considered to be a personal matter. The finding that the single greatest reason for rejecting people from the military in World War II was a result of poor oral health changed this sentiment. Very quickly, oral health became a national security issue and was recognized as a public health problem. Studies in which the water supply of cities was artificially fluoridated were done in order to determine potential effectiveness of such a measure. Fluoridation of the community water supply has been said to be an ideal public health measure. Initial studies were placed in Grand Rapids, MI in 1945, with Muskegon, MI acting as the control city. Other sister city studies were also begun around that same time. The overall results demonstrated a significant reduction in dental caries without cosmetically displeasing dental fluorosis, when the fluoride concentration in the local water supply was maintained at about 1 ppm. The mechanism of action was thought to be mainly the incorporation of fluoride into the enamel structure, thereby reducing the solubility of the enamel. Fluoridation of community water supplies has since been considered to be an ideal public health measure.

Fluoride Dentifrices

With the success of water fluoridation, it was reasoned the topical application of fluoride might also result in fluoride uptake and incorporation into the teeth; and that some benefit may also be achieved with less frequent applications of higher concentrations of fluoride. Bibby initiated many early studies on both dentifrices and topical fluorides but these studies were not entirely successful. A review of these and many other dentifrice studies was published by GK Stookey in a paper presented at a conference entitled “Clinical Use of Fluorides”. There were about eight early studies using a combination of sodium fluoride with calcium abrasive systems, with none of these studies resulting in significant reductions in dental caries. The most likely explanation was the incompatibility of the abrasive system with the sodium fluoride active, since it could react with the calcium of the abrasives and form calcium fluoride. Calcium fluoride is not reactive with the enamel surface, and this lack of reactive ionic fluoride most probably resulted in the failure of these early formulations to prevent caries. In 1954, the first report of a clinically effective fluoride dentifrice was made. This dentifrice contained stannous fluoride combined with a heat-treated calcium phosphate abrasive system. This SnF$_2$–Ca$_3$P$_2$O$_7$ combination was provisionally accepted by the ADA’s Council on Dental Therapeutics with category B classification in 1960. Upon completion of additional studies showing its therapeutic effect, the dentifrice was given a category A classification in 1964. The product was marketed as Crest with Fluoristan, and it quickly became the leading toothpaste sold in the U.S. This recognition of preventive value led to continued investigations for improved formulations with different active agents and abrasive systems. The search for more effective products has been very successful,
and it continues to this day as researchers work to develop new ways to help prevent caries in addition to providing other oral care benefits.

**Mechanism of Action of Fluoride**

The development of newer dentifrice formulations has paralleled the increased understanding of the caries process and how fluoride works. The original belief of a continual dissolution of tooth surface has been replaced by the acceptance of an understanding of subsurface demineralization and the maintenance of a relatively intact surface layer (probably by remineralization). Demineralization occurs when there is an imbalance between processes of mineral gain and loss. Fluoride may interact with these processes in several ways. It is now widely accepted that fluoride has both systemic and topical modes of action, although the topical benefits are generally considered to be the dominant factor. The interaction of fluoride with the mineral component of teeth produces a fluorohydroxyapatite (FHAP or FAP) mineral, by substitution of OH\(^-\) with F\(^-\). This results in increased hydrogen bonding, a more dense crystal lattice, and an overall decrease in solubility. The incorporation of fluoride into the hydroxyapatite (HAP) lattice may occur while the tooth is forming or by ion exchange after it has erupted. A decrease in solubility increases with greater amounts of fluoride incorporation, but rarely do we exceed several thousand parts per million of fluoride in the outer enamel. Thus, only limited protection from fluoride substitution would be expected as compared to pure FAP that has 40,000 ppm fluoride. Another means of incorporating fluoride into the enamel is from topical applications and ion exchange. This surface oriented exchange could also affect the solubility of the bulk solid. The exception to limited protection may be the crystallite surface, where a thin coating of pure FAP would make the bulk solid appear to be less soluble than the degree of substitution would predict. Therefore, a limited incorporation of fluoride into the crystal lattice or on the surface may have a significant impact on solubility. The systemic “solubility reduction effect” was thought to be the only mechanism of action until studies revealed a significant topical effect on mineralization as well as a bacterial effect.

Fluoride found in solution can also affect the dissolution rate without changing the solubility of tooth mineral. As little as 0.5 mg/L in acidic solutions causes a reduction in the dissolution rate of apatite. This mechanism also involves absorption and/or ion exchange at the crystal surface. Thus, the surface may act more like FAP than HAP and have a different dissolution rate. When the enamel dissolves, it may also contribute fluoride to the surrounding solution. Under ‘sink’ conditions this would not have much of an effect, but the solutions normally bathing the teeth (i.e. saliva) are always partially saturated with respect to apatite. Extremely low fluoride levels have been shown to significantly reduce the dissolution rate of apatite. Thus, both the concentration of fluoride at the crystal surfaces and the fluoride concentration in the liquid phase during a cariogenic challenge are important.

In addition to protecting against demineralization, another way in which fluoride interacts with enamel to reduce dissolution is through remineralization. This is a process in
which partially dissolved enamel crystals act as a substrate for mineral deposition from the solution phase that enables partial repair of the damaged crystals. Therefore, remineralization helps counteract demineralization and an equilibrium then develops between the two processes. The carious lesion occurs when the demineralization process outweighs the remineralization process, and net damage occurs. One of the benefits of the demineralization/remineralization interplay is the creation of less soluble mineral in enamel. This occurs by dissolution of the more soluble calcium deficient magnesium containing carbonated apatite which makes up enamel when first formed. The remineralization process results in formation of a less soluble form of apatite. When fluoride is also present, formation of fluoroapatite (FAP) results in a mineral with an even greater level of acid resistance. The remineralization process is one controlled by the supersaturation of fluids bathing the teeth - plaque fluid or saliva. The degree of supersaturation will, in part, determine the rate of precipitation of minerals from the solution. Too high of a supersaturation will result in the rapid formation of calcium phosphate and block the surface pores of enamel. This precipitation then limits the diffusion of calcium, phosphate and fluoride into the interior of the lesion, which can result in lesion arrestment rather than lesion repair. The interior of the lesion is partially saturated with respect to HAP and can become supersaturated with respect to FAP, even if minimal levels of fluoride are present or diffuse into the lesion. The use of low concentration fluoride products, such as dentifrices on a daily basis, will help maintain this favorable saturation. Thus, remineralization of the lesion may result in the repair of the existing lesion with less soluble mineral and render this portion of the tooth less susceptible to future episodes of demineralization (Figure 2). This is probably one of the most important modes of action of fluoride.

Fluoride, at a relatively low concentration, may also interact with the oral bacteria to reduce plaque acid production. Several mechanisms have been proposed to account for this end result. One is the well-known interaction of fluoride with the enzyme enolase which could directly reduce the production of bacterial acids. There is also an indirect effect on the phosphotransferase system (PTS) pathway that decreases the amount of sugar entering the cell by limiting phosphoenolpyruvate (PEP).

It is also likely that diffusion of fluoride into the cell occurs as hydrofluoric acid (HF) which then dissociates, lowering the intercellular pH and disrupting the cell. Fluoride may affect the ability of the cell to remove excess H+ and less acid production may result from cytoplasmic acidification. The overall effect is less acid and a less acidic environment that should reduce the driving force for dissolution. If these less acidogenic conditions continue, the long-term ecology of the plaque may be altered. It is difficult to predict the long-term effects, since adaptation to the fluoride may occur. Importantly, some forms of fluoride may be better than others with respect to effects on oral bacteria. For example, stannous fluoride (SnF₂) provides antibacterial effects that are not delivered by other fluoride actives used in dentifrice formulations.

**Differences in Active Agents**

The desire to find more effective dentifrices with high compatibility between the fluoride active and different abrasive systems spurred
continued research in the development of therapeutic dentifrices. After the success achieved with SnF₂ (Figure 3a) dentifrices, sodium monofluorophosphate (SMFP, Na₂FPO₃ – Figure 3b) new dentifrices were eventually introduced with compatible abrasive systems, and the combinations demonstrated positive caries benefits in most clinical studies. The search for a more stable formulations capable of providing even greater anticaries effectiveness also led to the introduction of a sodium fluoride (NaF – Figure 3c) formulation, which eventually replaced the original stannous fluoride (SnF₂) active ingredient. This new product used the advertising phrase of “Fluoristat” and combined NaF with a silica abrasive system that proved more effective against caries than the earlier “Fluoristan” formulation. This change in active agents occurred in 1981, after silica abrasive systems were developed that were compatible with most of the active agents found in dentifrices.  

All of the fluoride actives have been shown to be successful, to some extent, in preventing dental caries when used in a regular program of oral hygiene. The highly competitive toothpaste market has been a factor in the development of more effective products as well as improving flavor and increasing worldwide usage. This has been a great benefit to public dental health, as evidenced by the decline in the prevalence of dental caries over the past several decades in most developed countries.

The predominance of NaF and Na₂FPO₃ as the active agents in most toothpastes also led to the inevitable question “Are all fluoride dentifrices the same?” This question was addressed by Stookey in 1985 after a review of over 140 articles on fluoride dentifrices. It was found that a number of dentifrices with various active ingredients (NaF, SnF₂, AmF and Na₂FPO₃) and abrasive system combinations provided significant cariostatic benefits. The major fluoride sources approved for use in the US are stannous fluoride (SnF₂), sodium fluoride (NaF) and sodium monofluorophosphate (Na₂FPO₃). During use, NaF and SnF₂ dissociate to provide the free fluoride ion and the companion cation. The Sn cation may have some interactions on its own, although the primary effects on caries are generally associated with the fluoride component. For Na₂FPO₃, the fluoride source is in a different chemical form and requires enzymatic hydrolysis to cleave the covalent bond between the phosphate molecule and fluoride. Studies of SMFP have shown it is compatible with a broader range of dentifrice abrasives, but it may differ in its mode of action from the fluoride ion. Early work suggested that Na₂FPO₃ could react with the apatite surface and reduce dissolution, and it was thought to be retained in the oral environment as the whole molecule. Later, studies by Pearce and More were unable to confirm this mechanism; and it was felt that most of the activity of this agent was due to fluoride ion present as an impurity. Unfortunately, most studies were not designed to test these active ingredients in head-to-head comparative clinical trials, since they contained different abrasives and levels of fluoride. In his review of the available data, Dr. Stookey did make several observations. He stated that SMFP formulations gave comparable results to the old SnF₂ dentifrices, and that NaF dentifrices with compatible silica abrasive systems were better in reducing caries than the original SnF₂ products. Four out of five clinical trials demonstrated numerically greater

![Figure 3a. Stannous fluoride molecule.](image)

![Figure 3b. Sodium monofluorophosphate molecule.](image)

![Figure 3c. Sodium fluoride molecule.](image)

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effectiveness for the sodium fluoride product over the monofluorophosphate dentifrices tested. Many in vitro (laboratory) studies also suggested better results for the NaF dentifrices, although some of those studies lacked the presence of enzymes thought to be necessary to break the monofluorophosphate bond and release the fluoride. Although the weight of evidence was obvious in this review, this question proved to be difficult to answer to everyone’s satisfaction. At that time, the majority of dentifrices sold in over-the-counter products contained either NaF or Na$_2$FPO$_3$.

The availability of primarily two active agents naturally resulted in the desire to directly compare these two fluoride actives. Duckworth, for example, showed significantly more fluoride was found in plaque from subjects using NaF dentifrices than those using Na$_2$FPO$_3$ dentifrices with compatible abrasive systems. To help settle the question, head-to-head clinical trials were needed to clearly distinguish between these products. An in-depth review published in Caries Research (1993) assessed results from essentially every caries clinical trial that directly compared the effectiveness of these two anticaries actives. This review concluded that NaF dentifrices perform better than Na$_2$FPO$_3$ dentifrices when using compatible abrasive systems. The mean difference in caries reduction between products is approximately 6%, as determined by meta-analysis of the available clinical studies. However, this same conclusion was not reached in a separate review that assessed the same clinical trials. Although this second review also found that a numerical difference exists that favors NaF over Na$_2$FPO$_3$, the authors of this review determined that the magnitude of the difference was not significant. A third review had the benefit of some additional large scale, head-to-head, clinical trials. Similar to the first review, this review also concluded there was a significant advantage to using NaF toothpaste when formulated with a suitable abrasive system. The new head-to-head comparisons (Marks et al. and Stephen et al.) both reported superiority for sodium fluoride over sodium monofluorophosphate dentifrice formulations. The clinical difference between the two products is likely to be due to oral clearance, uptake of fluoride into the enamel and enhanced bioavailability of fluoride in the NaF formulations. In this regard, a properly formulated NaF dentifrice has the greater potential to deliver anticaries benefits, since it will release the fluoride active into the oral environment more efficiently (ionic F release) than from an SMFP formulated dentifrice (requires enzymatic cleavage of the covalent bond to release F). Collectively, the evidence from these studies showed NaF dentifrices formulated with highly compatible silica abrasive systems gave significantly better results.

**Continued Development of Therapeutic Dentifrices**

The ongoing pressures of a competitive dentifrice market led to continued investigations to develop improved products, leading to changes in toothpaste formulations and packaging of products. Some examples include the development of gels vs. pastes, pumps to deliver the products, dual tube reservoirs, and the addition of many cosmetic agents as well. One of the early improvements was the development of “tartar control” toothpastes in the mid 1980s, which proved to be highly successful in the market place. A pyrophosphate or zinc additive was found to be effective in reducing the growth of tartar and not allowing it to harden into a deposit that was difficult to remove. This made cleanings easier for the hygienist during routine dental visits. Another tartar control agent made use of a co-polymer of ether and maleic acid (PVM/MA), in combination with pyrophosphate to reduce calculus formation. Not all people are troubled by excess tartar formation, but an increased public awareness of oral health has led to the addition of agents to not only clean the teeth and mouth but to improve overall oral health. Thus, manufacturers have focused on the development of “multi-benefit” formulations capable of addressing a combination of oral care needs. An example is the combination of fluoride and potassium nitrate to simultaneously control both caries and dentinal hypersensitivity. We have also seen an increase in products that combine
“cosmetic” and “therapeutic” agents into one. An example here would be the cleaning, tartar control, stain removal, or whitening ability of new formulations combined with fluoride to control caries.

Although fluoride dentifrices and improved oral health have greatly benefited the population by reducing caries incidence, surveys showed a continued high prevalence of gingivitis and gingival recession among adults. The desire to treat both caries and gingivitis, coupled with the changing patterns in oral health, led to extensive research by the Procter & Gamble laboratories and the “return” to stannous fluoride as an active ingredient. This required the development of a stabilized formulation that would provide sufficient stannous fluoride activity to provide the anti-gingivitis benefit and sufficient reserves of the active to provide a caries benefit. The stabilization system developed used sodium gluconate as a chelating agent to protect SnF₂ from hydrolysis. Stannous chloride was also included as an anti-oxidant to protect SnF₂ from oxidation and as a stannous reservoir to reduce the SnF₂ loss onto the abrasive. The broad range of beneficial aspects of stannous fluoride, such as dentin desensitization, root surface reactivity, plaque and gingivitis benefits as well as its anticaries effectiveness strongly suggested that this unique active could be the basis for many future improvements in dentifrice formulations. Thus, the active agents most readily available in the US market once again included SnF₂ as well as NaF and Na₂FPO₃. Unfortunately, the use of SnF₂ continued to be limited at the time, largely due to poor taste, astringency, and potential for minor extrinsic stain. These challenges would take another decade to overcome.

Using Dentifrices as a Delivery System

The widespread acceptance of using toothpaste for improved oral health has resulted in the use of dentifrices as an effective delivery system for both cosmetic and therapeutic agents. This is evident by the myriad of dentifrice brands and types available at the local supermarket. One of the caveats when using proven caries preventive dentifrices to deliver additional oral health benefits is that the original anticaries benefits of that product must be retained in addition to providing significant new benefits. This has meant significant testing is needed when formulating multi-benefit products to ensure that each ingredient is able to perform in the presence of the others. This is the same situation that faced NaF actives and calcium abrasives in the early dentifrices - compatibility of ingredients. In the development and marketing of new products, each manufacturer has had to test their new formulations in order to ensure the new additive or ingredient does not interfere with the existing “active” while also providing a significant new benefit. Table 1 provides a timeline of significant events in the development of cosmetic and therapeutic dentifrices. One of the more interesting developments was the addition of sodium bicarbonate dentifrices into the market. This product was introduced by Church & Dwight and included baking soda as the abrasive, which was traditionally used by previous generations as a popular tooth cleaner. The popularity of these products resulted in the production of baking soda products by all the other manufacturers as well. The dental care products from Church & Dwight had the greatest amount of baking soda (65%) compared to the Colgate and Crest products which were around 25%. Although it was commonly believed the baking soda abrasive was more aggressive, it ultimately proved to be milder than the more commonly used abrasive formulations.

Another product innovation that helped shape the market for years came from the public’s desire for whiter teeth. Whitening agents were available in the dental office but not in the drugstore as an over-the-counter product. One of the first claims was the removal of extrinsic stains by existing tartar control agents. These formulas were optimized and tested for stain removal as well as tartar control. Intrinsic stains normally required the use of peroxides or carbamides which have the ability to bleach the teeth and increase “whiteness.” Crest Whitestrips marked the advent of consumer applied whitening agents and allowed the individual to brighten their smile at home. Dentifrice manufacturers were also aware of this public interest in a cosmetic benefit of oral health products and improved formulations for stain removal, stain...
Table 1. Timeline of Dentifrice Developments.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1890</td>
<td>Colgate in Tubes</td>
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<tr>
<td>1955</td>
<td>Crest Markets first Therapeutic Dentifrice with SnF₂</td>
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<tr>
<td>1960</td>
<td>First ADA seal for Crest</td>
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<tr>
<td>1969</td>
<td>Colgate with MFP receives ADA seal</td>
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<tr>
<td>1979</td>
<td>Aim receives ADA seal</td>
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<tr>
<td>1980</td>
<td>Crest converts to Sodium Fluoride due to formulation challenges with SnF₂</td>
</tr>
<tr>
<td>1985</td>
<td>Crest Introduces Tartar Control toothpaste</td>
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<tr>
<td>1986</td>
<td>Colgate introduces Tartar Control with NaF active</td>
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<tr>
<td>1987</td>
<td>Aim Extra Strength (1500 ppm) introduced</td>
</tr>
<tr>
<td>1993</td>
<td>Mentadent with NaF + baking soda + peroxide</td>
</tr>
<tr>
<td>1995</td>
<td>Crest Gum Care (stabilized SnF₂)</td>
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<tr>
<td>1996</td>
<td>Colgate with triclosan and co-polymer</td>
</tr>
<tr>
<td>1998</td>
<td>Arm &amp; Hammer with baking soda for cleaning and stain</td>
</tr>
<tr>
<td>1999</td>
<td>Crest receives first ADA seal for whitening dentifrice with soft silica</td>
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<tr>
<td>2001</td>
<td>Improved whitening – soft silica</td>
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<tr>
<td>2002</td>
<td>Colgate Total Plus Whitening receives ADA Seal</td>
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<tr>
<td>2002</td>
<td>Dual Action Whitening Technology with sodium hexametaphosphate introduced</td>
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<tr>
<td>2004</td>
<td>Dual Action Chamber</td>
</tr>
<tr>
<td>2006</td>
<td>Crest PRO-HEALTH, with novel technology combining stannous fluoride and sodium hexametaphosphate, receives ADA Seal</td>
</tr>
<tr>
<td>2007</td>
<td>Crest PRO-HEALTH demonstrated effective against dental erosion</td>
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<tr>
<td>2015</td>
<td>Crest PRO-HEALTH H2O2, a 2-step system with stannous fluoride dentifrice and hydrogen peroxide whitening gel, is introduced</td>
</tr>
<tr>
<td>2019</td>
<td>Colgate Total replaces triclosan with SnF₂</td>
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</tbody>
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prevention, tartar reduction, and whitening all became available in the market place. This cosmetic benefit has been a continuing focus in oral care product development since the late 1990s. The whitening effect encompasses the original cleaning function of dentifrices, such as tartar and stain removal, but may also include intrinsic stain removal agents. A dual action whitening technology based on sodium fluoride dentifrices evolved from these early efforts. As oral care products continue to evolve, we can expect to see even more interesting combinations and approaches in the future, with each iteration intended to deliver either enhanced performance or an increased number of overall oral care benefits. While some of these future products may come from unique combinations of ingredients currently in use, others may include ingredients that are completely new to oral care products. Table 2 lists various benefits and functions of ingredients that are commonly used in modern dentifrice formulations.

### Table 2. Benefits/Functions of Dentifrice Ingredients.

<table>
<thead>
<tr>
<th>Decay Reduction</th>
<th>Fluoride from NaF/SF/P/SmF&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Calculus</td>
<td>Zn Citrate/Pyrophosphate</td>
</tr>
<tr>
<td></td>
<td>Gantrex + Pyrophosphate</td>
</tr>
<tr>
<td></td>
<td>Sodium Hexametaphosphate</td>
</tr>
<tr>
<td>Anti-Plaque/Gingivitis</td>
<td>Triclosan (0.3%) + Gantrex (2%)</td>
</tr>
<tr>
<td></td>
<td>Stabilized SnF&lt;sub&gt;2&lt;/sub&gt; + Zn Citrate</td>
</tr>
<tr>
<td></td>
<td>Baking Soda + Peroxide</td>
</tr>
<tr>
<td></td>
<td>Triclosan + Pyrophosphate</td>
</tr>
<tr>
<td>Desensitizing</td>
<td>Potassium Nitrate - KNO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Strontium Chloride - SrCl&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Stannous Fluoride - SnF&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Dental Erosion</td>
<td>Stannous Fluoride - SnF&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Sodium Fluoride - NaF</td>
</tr>
<tr>
<td>Whitening</td>
<td>Sodium Hexametaphosphate</td>
</tr>
<tr>
<td>Abrasives</td>
<td>Alumina/Silica/P&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;5&lt;/sub&gt;/DCPD</td>
</tr>
<tr>
<td>Bleaches</td>
<td>Peroxide/Ca-Na Carbamide</td>
</tr>
<tr>
<td>Detergents</td>
<td>Sodium Lauryl Sulfate</td>
</tr>
<tr>
<td></td>
<td>Polyphosphates (Sodium Hexametaphosphate)</td>
</tr>
<tr>
<td>Emollients</td>
<td>Baking Soda/Glycerin Propylene Glycol</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Papain (Proteolytic)</td>
</tr>
<tr>
<td>Pigment</td>
<td>Titanium Dioxide</td>
</tr>
</tbody>
</table>

As oral care products continue to evolve, we can expect to see even more interesting combinations and approaches in the future, with each iteration intended to deliver either enhanced performance or an increased number of overall oral care benefits. While some of these future products may come from unique combinations of ingredients currently in use, others may include ingredients that are completely new to oral care products.
Several dentifrice formulations combined selected ingredients and became multi-benefit formulations. One product which had been demonstrated for almost all of the areas listed in Table 2 in a single product was Colgate Total which was introduced in the 1990’s and contained 0.3% Triclosan, 2% Gantrez, and 0.243% NaF with a silica abrasive. Extensive clinical testing was performed to receive the ADA Seal of Acceptance for protection against gingivitis, plaque, and caries. More recent versions of this product claimed efficacy with respect to caries, plaque, gingivitis, tooth whitening, calculus and oral malodor. However, in 2019, in response to global concerns related to the triclosan ingredient, the product was reformulated and now contains SnF₂, as the anticaries agent, in addition to stain mitigation technology to help reduce the potential for tooth staining. In contrast to using existing ingredients like the soft silica abrasives for whitening, Procter & Gamble developed a highly efficient stain and tartar removal formulation by using sodium hexametaphosphate (Figure 4), a calcium surface active builder (CASAB). Earlier work to ensure no loss of effectiveness in relation to caries reduction with the new hexametaphosphate (it’s not abrasive) polymer was done in vitro, in situ, and then in clinical studies. One of the difficulties in formulating products with CASAB agents is their hydrolytic stability in the aqueous phase of conventional dentifrices. The development of dual-phase packaging technology permitted the early use of polyphosphate ingredients such as sodium hexametaphosphate.

Continued development of the dual whitening system resulted in the use of a patented “Polyfluorite” System. The Polyfluorite System contains stabilized stannous fluoride combined with the cosmetic benefits of the sodium hexametaphosphate-CASAB (Figure 5). Thus, the CASAB is used to inhibit calculus, whiten by extrinsic stain removal, and prevent stain formation, while the stannous fluoride in the polyfluorite system fights plaque and gingivitis, provides long-lasting antibacterial action, protects against sensitivity, fights cavities, and helps freshen breath. This formulation is called Crest PRO-HEALTH™ dentifrice. Over 70 studies have been performed to support the Polyfluorite System’s ingredients benefits. A review of this technology is found in an article by Baig and He in the online Compendium journal. This technology was the first to combine proven results in caries reduction, plaque reduction, less gingivitis, less sensitivity, and decreased tartar. The ADA granted its Seal of Acceptance to this multi-benefit product in 2006. As stated by the wording of the seal, “The ADA Council on Scientific Affairs’ Acceptance of Crest PRO-HEALTH™ Toothpaste is based on its finding the product is effective in helping to prevent and reduce tooth decay, gingivitis, and plaque above the gumline, to relieve sensitivity in otherwise normal teeth, and to whiten teeth by removing surface stains, when used as directed.” In 2007, this dentifrice was clinically demonstrated to also provide a significant reduction in halitosis (breath malodor).

One of the most challenging aspects of dentifrice development is to ensure that they continue to meet the changing needs of consumers. One example of this is the increased prevalence of dental erosion that has been reported on a global basis. Most researchers believe that excessive consumption of acid-containing foods and beverages is a primary cause of this emerging issue. Excessive ingestion of acid from any source can eventually overwhelm the pellicle coating on exposed tooth surfaces, the natural protective mechanism that is designed to protect teeth against damage due to acid intake. As a result, teeth can become softened, and any abrasive action on these tooth surfaces while they are softened can result in permanent loss of the affected tooth mineral. Even the repetitive movement of the tongue over these acid-challenged surfaces...
has been noted as a potential source of abrasive activity. Dental professionals have been successful in steering consumers away from sugar laden beverages that can lead to caries. However, diet soft drinks, although better from a standpoint of caries, contain essentially all of the acid contained in their sugared counterparts. From the standpoint of erosive potential, there is little to no difference between the two varieties of beverage.

Since fluoride is well known for its ability to strengthen enamel, significant research has been done to determine whether or not fluoride is able to strengthen teeth to sufficiently protect them against erosive acid damage. Many of these studies have found that fluoride, in general, does provide some level of benefit. However, there is an increasing body of research that has demonstrated unique benefits attributable to stannous fluoride over all of the other fluoride sources used. Although all fluorides help form stronger mineral within the tooth structure after a caries challenge, under plaque, dental erosion primarily occurs on smooth surfaces of the teeth, in the absence of plaque. Thus, the type of acid challenge is much different than one that occurs during caries formation. The level of challenge and the concentration and volume of acid are generally much higher during an erosive acid challenge. Stannous fluoride is different from other fluorides in that it deposits, in addition to the caries preventative F⁻ ion, an invisible, protective barrier layer onto exposed tooth surfaces that consists of stannous (tin) precipitates. This barrier layer is highly acid resistant, and provides the tooth surface with an extra layer of protection against erosive acid challenges. The first clinical trial that demonstrated the preventive benefits of a stabilized, SnF₂ toothpaste (Crest PRO-HEALTH) against the initiation and progression of dental erosion was published in 2007. A special issue of the International Dental Journal (2014) presented a range of studies that confirmed the erosive protective benefits of stabilized stannous fluoride dentifrice. Interestingly, one study demonstrated the erosion protection potential of a stabilized SnF₂ dentifrice was...
significantly greater than that provided by some of the most popular prescription level (5000 ppm F) fluoride treatments available. More recently, several additional human in situ clinical studies have demonstrated enhanced erosion protection benefits of stabilized stannous fluoride over other formulations tested. Thus, formulations are now available that provide not only all of the major benefits generally attributable to toothpaste, but are also proven to provide a new benefit that meets the ever-changing needs of consumers (Figure 5). While it is unlikely that dental professionals will be able to get consumers to stop drinking acid-containing beverages, it is comforting to know that therapies are available to help protect these consumers against things that are difficult for them to control.

This update has shown the market forces have continued to develop new and improved products for the consumer. The therapeutic dentifrices developed have been responsible for a large portion of the caries reduction in the industrialized world. What new oral care therapies await consumers of the future is open for speculation. Most importantly, research has continued to progress, identifying opportunities to deliver enhanced levels of benefit as well as confirmation of new benefits by focusing on key mechanistic aspects of the various active ingredients. Will nanotechnology become an important component in the future? Will the use of dentifrices as a delivery system increase and expand? Will oral cancer or other systemic diseases find a delivery system from the oral environment? We only have to wait to see what new systems may come to bear in this ever-changing market place. It will be interesting to see what the future of Oral Care will include!
Course Test Preview
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1. Community water fluoridation was first introduced in Grand Rapids, MI in what year?
   A. 1872
   B. 1905
   C. 1945
   D. 1957

2. Which of the following statements is true?
   A. Caries is the result of a continuous dissolution of tooth surface resulting from dietary acid attack.
   B. Caries is a subsurface phenomenon that is the result of bacterial acid demineralization with the concurrent maintenance of a relatively intact surface layer (probably by remineralization).
   C. Caries is an irreversible process.
   D. Our understanding of the caries process has changed little over the past 50 years.

3. The active ingredient in the first toothpaste approved by the ADA was ___________.
   A. sodium fluoride
   B. calcium fluoride
   C. sodium monofluorophosphate
   D. stannous fluoride

4. What concentration of fluoride in a municipal water supply is required to significantly reduce the caries incidence without causing dental fluorosis?
   A. 0.01ppm
   B. 1.0ppm
   C. 10ppm
   D. 100ppm

5. “Brown stain” was once used to describe a condition later known as ___________.
   A. Goodpasture's disease
   B. acute iron toxicity
   C. dental fluorosis
   D. chronic retro-orbital dyspnea

6. The major fluoride sources approved for use in the United States are ___________.
   A. Potassium Fluoride, Sodium Fluoride, and Magnesium Fluoride
   B. Sodium Fluoride, Sodium Monofluorophosphate and Amine Fluoride
   C. Stannous Fluoride, Sodium Fluoride and Sodium Monofluorophosphate
   D. Stannous Fluoride, Aluminum Fluoride and Lithium Fluoride

7. Which of these compounds is (are) used as anti-calculus actives in tartar control toothpastes?
   A. Aluminum silicate
   B. Titanium dioxide, silica and essential oils
   C. Cinnamaldehyde and other phenylpropanoids
   D. Pyrophosphate, Zinc and co-polymer of ether and maleic acid (PVM/MA)
8. The first Category A classification for a fluoridated dentifrice was awarded by the American Dental Association in _______.
   A. 1947  
   B. 1955  
   C. 1964  
   D. 1969  

9. In 1981, the original active ingredient in Crest toothpaste was replaced with which fluoride ingredient?
   A. Potassium fluoride  
   B. Sodium monofluorophosphate  
   C. Stannous fluoride  
   D. Sodium fluoride  

10. Public acceptance of therapeutic dentifrice occurred after the ___________.
    A. introduction of tartar control dentifrices  
    B. development of NaF products  
    C. ADA seal of acceptance was granted  
    D. introduction of MFP products  

11. Remineralization of enamel requires _________.
    A. a tufted toothbrush  
    B. supersaturation  
    C. collagen  
    D. pH < 5.0  

12. Calcium surface active builders (CASAB) are a part of the new technologies and act to ___________.
    A. reduce caries  
    B. freshen breath  
    C. control sensitivity  
    D. remove stain and whiten teeth  

13. Fluorides main influence in the oral cavity is through ___________.
    A. reducing the solubility of enamel  
    B. the formation of secondary dentin  
    C. preventing demineralization/enhancing remineralization  
    D. enhancing the cleaning potential of dentifrice  

14. Although original fluoride dentifrices greatly improved oral health by reducing caries incidence, the desire to treat both caries and gingivitis, coupled with the changing patterns in oral health, led to the development of ___________.
    A. Aluminum fluoride mouth rinses  
    B. more products using natural and herbal ingredients  
    C. Sodium fluoride and silica systems  
    D. Stabilized stannous fluoride formulations  

15. Which of the following is true?
    A. Diet soft drinks are just as erosive as their sugared counterparts.  
    B. Diet soft drinks are less erosive than their sugared counterparts.  
    C. Diet soft drinks are more erosive than their sugared counterparts.  
    D. Soft drinks have no erosive potential.
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Additional Resources
• No Additional Resources Available.
About the Authors

James S. Wefel, PhD

The staff at P&G expresses our condolences regarding the loss of Dr. Wefel on September 1, 2012. He was a major contributor to the field of cariology and prevention, leaving both a legacy of knowledge as well as mentorship to many young scientists. We will miss him.

Dr. Wefel joined The University of Iowa College of Dentistry in 1973. He was director of the Dows Institute for Dental Research, administrative director of the Office of Clinical Research, and a professor in the Department of Pediatric Dentistry. Dr. Wefel's primary teaching responsibilities included the areas of graduate cariology, undergraduate cariology and preventive therapies, and undergraduate seminars in selective courses.

Dr. Wefel's areas of research included laser and tooth interactions, early caries detection, mechanisms of action of fluoride, topical fluorides, remineralization, kinetics of calcium phosphate crystal growth, secondary caries, oral fluoride kinetics, antimicrobials, and F-releasing materials. Specific research in the Dows Institute for Dental Research included root surface caries, laser prevention of tooth demineralization, and F-releasing biomaterials and secondary caries. Activities included promotion of research from the laboratory to the clinical in the Center for Clinical Studies.

Dr. Wefel was a reviewer for The Journal of Clinical Dentistry; Journal of Dental Research; Caries Research; Calcified Tissue Research; Archives of Oral Biology; American Journal of Dentistry; Journal of Oral Pathology and Gerodontology; reserved reviewer for Oral Biology and Medicine II Study Section, National Institute of Dental and Craniofacial Research; outside reviewer for the National Science Foundation and American Fund for Dental Health; ad hoc reviewer for the Board of Scientific Counselors, NIDCR; former president of the Cariology Research Group, IADR (1990-1991); consultant for the American Dental Association Council on Scientific Affairs; recipient of the IADR Distinguished Scientists Award; member of the American Association for Dental Research; the International Association of Dental Research; the American Dental Education Association; and the European Association for Caries Research; and member of the College of Dentistry's Faculty Promotions Advisory Committee.

Robert V. Faller, BS

Robert Faller has in excess of 40 years in the Oral Care Research field. He retired from P&G after more than 31 years in Oral Care, where he focused on caries and enamel related research as P&G's chief cariologist. He is editor of Volume 17 – Monographs in Oral Science: Assessment of Oral Health – Diagnostic Techniques and Validation Criteria. He has written 3 book chapters, published 34 papers in peer-reviewed journals and has over 100 published abstracts on fluoride, caries, dental erosion, and various oral care technologies, along with 5 patents related to Oral Care and 6 Continuing Education courses. He currently resides in the UK and is a consultant to the Oral Care industry.

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