Actives in Oral Care Products

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The growth of oral hygiene products is not only due to the income and educational levels of the user but also due to the realisation that tooth loss is not dependent on the age of the individual. This consumer awareness propels a person into buying a premium priced product offering therapeutic or value-added benefits.

Tooth decay and dental caries results from the continuous occurrence of plaque, a sticky film of bacteria that constantly forms in the mouth together with their decomposition products and food residues. Plaque is believed to consist of salivary proteins, modified by bacterial enzymes, polysaccharides, lipids, minerals like calcium and phosphorous, water, etc. It is typical for an individual and varies widely at different parts of the oral cavity. Plaque adheres to teeth and the areas between them and, if not removed, calcifies or mineralises to form a cement-like substance called tartar or calculus. Calculus comprises of 80% of inorganic material containing calcium, magnesium, phosphorous and other elements and the remaining 20% comprise of organic matter like, carbohydrate, protein, lipid and bacteria. Calculus hardens, staining teeth and makes them rough. It also provides a perfect place for bacteria to grow and proliferate. The bacteria present generate acidic metabolites lowering the mouth pH to 5.5, which causes an attack on the dental enamel. Such repeated attack breaks down the tooth enamel exposing the sensitive part of the tooth leading to rapid onset of dental caries. The formation of calculus also irritates the gums. Gums become red, swollen, or tender, and may bleed on brushing causing gingivitis to eventually culminate in periodontal diseases.

Ultrastructural studies shows that many types of microbes are responsible and become associated with periodontal tissues. The microbes present in the interface exert a great importance in the destructive actions that are associated in periodontitis. Periodontal disease is caused by specific micro-organisms not regularly found in a healthy mouth and for which the oral cavity is not a primary habitat. Those organisms that are indigenous or belong to the resident flora do not normally cause oral disease. Only those organisms that are extraneous under circumstances of reduced host resistance or due to overgrowth, cause disease and in such a situation, anti-infective therapy becomes necessary.

Oral diseases cause tooth loss and pain, bad odour causes embarrassment in social circles, loose teeth interferes with speech and in some cases spread infection to other areas of the mouth and body. Regular and proper brushing helps prevent tartar formation, but once formed it can only be removed by a professional dentist by mechanical cleaning, either to prevent or to delay the onset of periodontal disease. Dental treatment is labour intensive and relatively expensive, causing discomfort. To prevent plaque associated diseases; plaque formed must be continuously removed. Simple brushing is only partially successful in this respect.

To control oral diseases, conventional method still involves mechanical removal of plaque and calculus. A complimentary approach nowadays used is the application of chemical agents that would alter the oral environment and prevent the growth of putative pathogens. Chemical plaque control agents are based to counter the potential deficiencies of mechanical cleaning. The first scientific report concerning the use of chemical agents dates back to more than three hundred years before. In 1683 Mr. Van Leeuwenhock A., advocated the use of vinegar as a mouth rinse as it exhibited the property of killing bacterial micro-organisms.

The most important aim of oral care is to reduce personal and social handicaps that become associated with oral diseases that an individual develops due to improper care of their dentition. Taking good and proper care of the natural dentition will not only increase the longevity, but will also improve the public status and so its function.

Decades of detailed scientific research carried out at various dental research institutes, industrial laboratories and dental colleges and hospitals has helped to understand the varied functions affecting oral health, proving the old saying that a clean tooth never aches.

Today chemical agents can be an antimicrobial or an anti-metabolic or others that are incorporated in oral care products for therapeutic benefits. Fluorides, chlorhexidine, zinc citrate, triclosan, antibiotics, enzymes, inorganic salts, etc., are used as chemical therapeutic agents in various oral care products.

Chemotherapeutic agents incorporated into oral care products with claims for being effective in protecting oral health are termed as actives. They may be anticaries agents, agents affecting oral accumulation, agents that are capable of desensitising sensitive teeth or even those that prevent oral malodour.

Fluorides and antimicrobials represent the largest category for which detailed studies have been conducted in various research institutions. These, when present even in low recommended levels, can selectively suppress certain micro-

organisms or inhibit bacterial proteases that are implicated in oral tissue damage, thereby improving overall oral care. All antimicrobial agents either destroy bacteria or interfere with its function that is necessary for the bacterial mass present in the oral cavity to exert its virulent behaviour.

Moreover every active therapeutic ingredient whether antimicrobial, anti-metabolic or others have its effects in alleviating problems associated in the oral cavity.

For an active therapeutic agent to be considered effective in an oral formulation, the product forms should be so designed such that the agents used are formulated to comply with some basic attributes:

* The delivery system should provide a physically, chemically and microbiologically, stable environment so that the therapeutic agent is active when used.
* The product formulated should be able to release and make the active available at the site of action in the oral cavity.
* The product formulated should encourage the end user, to use the product whether they are mouthrinses or dentifrices.
* To make the product acceptable, product properties like perceived mouth freshness, mouthfeel, flavour, and taste, stain removal, etc., should not be compromised just to include an active or therapeutic agent.
* The delivery system used should be affordable and its usage should not result in adverse reactions, such as staining of teeth and tongue, have impaired taste sensation, irritation of the oral cavity or cause mucosal desquamation or pathogenic changes in the mouth flora.
* The formulation developed and sold in the market should be in accordance to the specifications and requirements laid down by the regulatory authorities.

Thus, many factors influence the selection of the active therapeutic agent. The agent used should have a broad spectrum activity, good substantivity, i.e., be retained on the surface of the teeth and other parts of the mouth cavity. It should have either no taste or acceptable taste, and have a very low toxicity. The active should not disturb the oral microbial ecology. It should be stable, compatible with other ingredients used in an oral care product, and easy to incorporate without any loss in the therapeutic activity.

Some major therapeutic agents or actives used in oral care products are enumerated below.

Fluorides

Fluorides are used in dental creams to prevent caries. Earlier stannous fluoride and sodium fluoride were widely used in toothpaste formulations. Stannous fluoride is said to stain teeth and sodium fluoride is reported to interfere with body enzymes.

Today sodium monofluorophosphate (Na_2PO_3F) is preferred over stannous fluoride and sodium fluoride. Sodium monofluorophosphate is soluble in water upto the extent of 42%. The pH of a 2% solution is 7.2. Dilute solutions are stable, except in the presence of acids or metal ions, that may react to give insoluble fluorides. Sodium monofluorophosphate used in toothpaste should be of the approved drug grade with the minimum 12.1% fluoride, present as a complex ion and having a maximum content of free fluoride content of 1.2% essentially as sodium fluoride.

The acute and chronic toxicity values of sodium monofluorophosphate have been investigated in detail. Compared to stannous fluoride and sodium fluoride, sodium monofluorophosphate has a lower toxicity that is due to a lower availability of fluoride ion *in vivo*. Long term studies have shown that, renal injury and skeletal storage very similar to sodium fluoride are produced. Excess fluoride ingestion through oral care products can lead to dental fluorosis. Sodium monofluorophosphate is popular because of its, relatively lower toxicity; superior stability and compatibility with calcium based abrasives without causing any adverse reactions.

Sodium monofluorophosphate unlike stannous and sodium fluoride does not ionise into F^- ions that precipitates into less soluble calcium fluorapatatite in presence of calcium ions. Sodium monofluorophosphate ionises to form FPO_3^{2-} ion, the calcium salt of which is soluble and has an anti- caries effect. During the early stages in the caries process, a depletion of elements that are essential for a secure enamel takes place. A steady removal of calcium ions also occurs. This disrupts the surface of the tooth enamel and the mineral released first from the surface, and later from below, leads to the formation of a porous surface that apparently looks intact, lying over an demineralised area. This area that looks like a white spot later changes to a fully formed cavity due to continued demineralisation. It is assumed that fluoride interferes with the decaying process, at the level of the bacteria, at the surface of the tooth before and during the initial acid attack and after the acid attack with lesion formation.

Fluoride at optimal concentration levels exhibits several effects of caries forming bacteria. It inhibits the enolase activity of the bacteria and inhibits potassium transport system involved in the carbohydrate metabolism and effect on polysaccharide synthesis. It decreases the bacterial attachment to the surface of the tooth. It increases the uptake of cations in the affected site. The presence of fluoride directly influences bacterial plaque metabolism. It increases the resistance of the tooth enamel to attack by acids and promote remineralisation of previously demineralised enamel.

Currently the maximum level of fluorides permitted in a

fluoride dentifrice is 1000 ppm. Tooth paste specially formulated for children contains much lower fluoride level. Fluoride incorporated in a well-formulated oral care product for self-application is safe and effective. It presents a health hazard to health only when misused and is an important ingredient to fight dental caries.

Chlorhexidine

Chlorhexidine, an effective chemical antimicrobial agent, is available commercially as the gluconate salt. Chemically it is 1,1'- hexamethylene bis (5-(p- chlorophenyl) biguanide. It is cationic in nature and has a broad antimicrobial activity, effective against both gram positive and gram negative bacteria, yeast, dermatophytes, etc. It is not effective against spores and viruses. Its activity is not seriously effected by the presence of organic matter and can effectively reduce the salivary bacterial flora by 85 to 95%.

Chlorhexidine shows different effects at different concentrations; at low concentration levels, the agent is bacteriostatic, whereas at higher levels it is bactericidal. The actual level at which it manifests as bacteriostatic or bactericidal depends on the bacterial species present. Although the effect of chlorhexidine on various plaques and other oral bacteria is variable, it is effective as an antiplaque and antigingivitis agent. Microbiological studies conducted have indicated that prolonged use of chlorhexidine at an organoleptically and physiologically accepted level does not produce an adverse effect on the oral flora with overgrowth of pathogens or change the plaque bacterial susceptibility to the agent. Clinical trials of chlorhexidine indicate that the agent can have long term beneficial effect on plaque caused diseases provided it is effectively and frequently applied.

The antibacterial mode of action of chlorhexidine is thought to be as follows. The bacterial cell is characteristically negatively charged. The cationic chlorhexidine molecule that is positively charged is rapidly attracted to the negatively charged bacterial cell surface with specific, strong adsorption to the phosphate containing compounds. This changes the integrity of the bacterial cell membrane and the chlorhexidine molecule is attracted towards the inner cell membrane. Chlorhexidine binds itself to the phospholipids present in the inner membrane that increases the permeability of the inner membrane and subsequent leakage of the low-molecular weight components such as potassium ions. At this bacteriostatic stage, the effects of chlorhexidine are reversible, that is if excess chlorhexidine is removed by some neutralisers, than the bacterial cell can recover. This necessarily implies that the structural changes that are caused by the cytoplasmic membrane by low levels of chlorhexidine are minor when compared to the damage done by higher concentrations of chlorhexidine where, it behaves as a bactericidal agent. Increasing the concentrations of chlorhexidine can cause greater damage to the bacterial cell membrane directly reflected to the amount and size of the permeable species lost from the cell. As the concentration of chlorhexidine further increases, leakage of low molecular weight cytoplasmic component falls, as coagulation and precipitation of the cytoplasmic components take place by formation of phosphated complexes like adenosine triphosphate and nucleic acids, to culminate into an irreversible bactericidal stage. Specific binding sites in the cell membrane for chlorhexidine is not yet properly identified due to several different effects, that chlorhexidine cause by disrupting the cell membrane. It is suggested that there may be specific binding sites in the bactericidal membrane or may be due to different intramolecular interactions of the two molecules at the membrane, the differences in the end group substitutions between the biguanides affecting the ability to produce lipid domains in the cell membrane.

The differences of effects of chlorhexidine on the outer and inner membrane also suggest some specificity of action of chlorhexidine on the bacterial cell membrane. Chlorhexidine behaves as an anti-plaque agent due to its good substantivity. Chlorhexidine can adsorb onto the negatively charged surfaces, such as the bacterial cell wall; different sites in the oral cavity like the teeth and mucosa. Given that the plaque formation occurs on the tooth surface, the binding of chlorhexidine to the pellicle covered tooth surface is small compared to that involved in chlorhexidine-protein interactions at other oral sites.

Chlorhexidine's antibacterial effect is based on its ability to interact with, and disrupt the bacterial cell membrane. However, chlorhexidine does not distinguish between bacterial protein and other proteins found in the mature plaque. Thus to optimise the effect of chlorhexidine, this extraneous plaque protein must be first removed, professionally, ideally by a dentist. Although chlorhexidine is an antiplaque agent, that prevents plaque formation; its mode of action does not allow it to efficiently remove plaque formed already in the oral cavity. Unfortunately, chlorhexidine reacts with anionic surfactant species, reducing the activity of the agent that becomes a major factor that cannot be overlooked when used in formulating an oral care product. Thus its use is limited to mouth rinses and is not preferred for use in toothpaste and toothpowder due to its incompatibility with its many ingredients. Similarly, chlorhexidine cannot be used before, or immediately after using a toothpaste as interaction with the anionic surfactant present in these formulations will reduce the efficacy and effective delivery of chlorhexidine to the tooth surface in the active form. Toothpaste when used before using chlorhexidine, should be thoroughly rinsed away with water to prevent unwanted interaction between chlorhexidine and anionic ingredients present in toothpaste/ toothpowder. It also has an undesirable tendency to cause

discoloration or staining of teeth that can be explained with a local precipitation reaction occurring between tooth-bound chlorhexidine and chromogens found within foodstuffs & beverages. Chlorhexidine containing mouthwash is therefore not preferred for use in the early morning hours, but as the last thing at night as no food or beverages are consumed while at sleep. Another objectionable feature of chlorhexidine is its long lasting very bitter taste that has to be suitably masked while formulating a mouthrinse.

Although chlorhexidine is toxic to mammalian cells at low concentrations, it is not capable of penetrating or damaging the intact epithelium, however it is toxically acceptable at concentrations recommended for routine usage. Chlor-hexidine has undergone a large number of trials with favourable results and has a safe history of use.

Triclosan

Triclosan is a synthetic chemical that has been extensively used for more than two decades. Chemically it is 2,4,4'-trichloro-2 hydroxydiphenyl ether, an odourless or very faintly aromatic, off-white powder, with a melting point of 57°± 1°C.

This non ionic antibacterial agent is now being used by almost all major oral care product manufacturers, at 0.2% to 0.3% (w/w) of the formulation to effectively reduce gingivitis and other periodontal diseases.

Triclosan is an effective against both gram positive and gram negative organisms when formulated in oral care products like toothpaste, toothgel, toothpowder, and oral rinses. Unlike other cationic agents, triclosan does not induce staining of teeth. It is stable in normal storage conditions, easy to incorporate in oral care product formulation, and, moreover, being tasteless does not impair taste sensation. Thermal stability studies have proved that triclosan is relatively stable up to 150°C and upto 200°C, if not heated continuously for more than 2 hours. Triclosan is practically insoluble in water, moderately soluble in alkaline solutions, and readily soluble in most non polar organic solvents.

Triclosan is lipid- soluble, antibacterial substance incorporated at a level of 0.2% to 0.3% (w/w) of the formulation, dissolved in suitable solvents and added to oral care products like toothpaste, toothpowder, mouth rinses, etc., to inhibit plaque and gingivitis. It helps in not only improving, but also maintaining the high standard of oral hygiene necessary for complete oral care.

Triclosan prevents sodium lauryl sulphate induced cytotoxicity to human cells and inhibits occurrence of inflammation of the mucous membrane in the mouth that makes it a very suitable anti-microbial agent in a dentifrice. Triclosan is a broad spectrum antimicrobial agent whose activity is dependent on, the concentration and formulation of the product. Different experiments and extensive studies carried out to find the mode of action of triclosan concluded that the primary action of triclosan is directed against RNA, and protein synthesis in bacteria, and not against DNA synthesis. It is considered that the uptake of nutrient molecules by the bacterial cell wall, as well as whole bacterial cells, by diffusion might be inhabited by triclosan with the cytoplasmic membrane being the target. When exposed to low concentrations of triclosan, the bacterial cells do not die, but their growth and multiplication are inhibited although the degree may not be the same for all nutrient molecules. Experimental findings support the hypothesis that bactericidal concentrations of triclosan induce a release of cytoplasmic material from the bacterial cells, inducing a decrease in the optical density of the suspension and eventual death. Thus there is a difference between the bacteriostatic effect of triclosan that results due to the prevention of the uptake of nutrients by the cell membrane and the bactericidal effect that is caused due to the irreversible disruption and rupture of the cell membrane.

Acute toxicity studies reveal that triclosan is not an oral toxicant. The subacute and subchronic toxicity profile of triclosan has also been well documented. Studies conducted by the pathology working group, showed no evidence of carcinogenic potential at any level. Studies conducted to judge the mutagenicity of triclosan, showed negative results. In a two generation reproduction study, there were no adverse effects on the reproduction performance at any dose tested. In studies conducted to assess the development toxicity, triclosan was found to have no potential for tetratologic effect.

Triclosan is not skin sensitising and does not have photosensitising effect. Human safety studies conducted to determine the safety of triclosan in dental products showed no adverse effects. Blood chemistry and haematological measurements conducted during these studies showed no difference between control subjects and subjects using triclosan. Triclosan is not an oral toxicant and is considered safe for use in oral care products.

The antimicrobial activity of metal salts, silver, nickel, mercury, zinc, stannous and copper was recognised in the early forties. The efficacy of the salts being lower only salts such as stannous fluoride and zinc citrate showed some anti-plaque activity when used in a product. Salts when used for formulating aqueous rinses create stability problems as some salts are precipitated to biologically inactive form. This is much less observed in dentrifice as the liquid phase is made up of sorbitol or glycerol with lower water content. Zinc citrate trihydrate is a plaque inhibitor, preventing the accumulation of bacteria even though it is not primarily an antimicrobial agent. The effectiveness of zinc citrate trihydrate is considerable increased by the addition of triclosan. Clinical studies have demonstrated that when zinc citrate is combined with triclosan a superior anti-plaque system is obtained. The

effects of this combination of zinc and triclosan are complementary and synergistic. In this combination the anti-plaque and anti-gingivitis efficacy are enhanced as a result of better oral substantivity and due to the broad spectrum antimicrobial activity of both zinc and triclosan. The use of dentifrice's containing the above agents does not appear to cause any adverse population shift of dental plaque, or cause any microbial resistance. Extensive clinical studies have shown that a combination of 0.3% triclosan and 2% poly-vinylmethylether maleic acid copolymer (PVA/MA) and NaF or sodium monofluoro-phosphate in an insoluble sodium metaphosphate/silica base abrasive system dentifrice provided an effective delivery and bioavailability of triclosan at the oral site for plaque inhibition and significant reduction of gingivitis. Triclosan for use in personal hygiene and oral care products should not only be analysed for its quantitative purity, but also for the presence of impurities, at trace levels of less than 1ng/Kg or 1 part per trillion. This is specially important for polychlorinated dioxins and furans such as the 2,3,7,8, isomers commonly known as Seveso Dioxins that are un-wanted by-products during triclosan manufacture. Dioxins are highly toxic, persistent substances, with a wide range of adverse effects. Dioxans can produce a plethora of responses in animals and presumably in humans, which can lead to chloracne, carcinogenecity, reproductive and developmental effects, immunotoxicity, effects on circulating reproductive harmones, increased risk of diabetes, endometriosis and enzyme inductions. It is very important that only superior and approved quality triclosan is used in personal hygiene and oral care products.

Cetylpyridinium chloride

Cetylpyridinium chloride is one among the group of quartenary ammonium compounds, used as an effective antimicrobial agent used in oral care products. The performance of cetylpyridinium chloride has not been very much impressive concerning efficacy, safety, side effects, and taste at active concentration levels that interest modern formulators. However it has much lesser taste or staining problems when compared to chlorhexidine. Cetylpyridium chloride has relatively lower substaintivity in the oral cavity and therefore frequent use is required to provide any useful activity although oral care products containing cetylpyridium chloride do exist in the market.

Desensitising Agents

Teeth become sensitive to temperature variations when the dentine and nerve on the dentine surface stand exposed and pain is experienced when eating an ice cream or drinking hot liquids. Dentinal hypersensitivity may be due to gingival recession, surgical or periodontal treatment. Several theories have been proposed to explain this hypersensitivity. The most favoured theory proposes that the fluid movement within the dentinal tubule is responsible for the transmission of sensation. Tooth pulp and dentine sensation are characterised by pain, irrespective of the stimulus, as there is no evidence that supports the presence of specialised terminal nerve receptors for specific stimuli. Relief may be obtained by use of certain ingredients in toothpaste specially formulated for such purpose. Strontium chloride, strontium nitrate, potassium nitrate, sodium citrate, etc., are used as desensitising therapeutic agents, and are believed to block the dentinal tubes, connecting the pulp nerve endings.

Miscellaneous therapeutic agents

Enzyme systems like proteolytic, lipolytic, mutaneases, and dextranases that have the ability of disrupting the various substrates have been tried to prevent plaque build up. Plaque reducing enzymes like glucose oxidase and amyloglucoxidase have also been experimented as an active in toothpaste. However, some adverse reactions due to contaminating protease fractions have been reported in use of some enzymes. They are not prompt in action, have poor efficacy, and are difficult to formulate for long term stability in oral care products. The use of hydrogen peroxide containing mixtures has been proposed to prevent plaque and gingivitis. Use of potassium peroxidiphosphate has also been suggested. As the peroxide molecules are unstable they would liberate oxidative oxygen species *in situ* that may have anti-plaque effect. Calcium lactate, azacycloheptane-2,2-diphosphonic acid, has also been shown to possess some anti calculus activity. No detailed study of the mechanism of action of the above ingredients is available to justify their usefulness. Dentifrice containing Vitamin A palmitate, Vitamin E acetate, Vitamin C, Vitamin B6 are also being developed in various research laboratories to combat various gum diseases to improve overall oral hygiene. It is known that Vitamin A Palmitate, D-panthenol has minor wound healing properties and stimulates fibroblast proliferation that could help damaged gums. Vitamin E. Acetate could penetrate the mucous membrane and inhibit lipid peroxidation. It's anti inflammatory properties and its reaction with smoke makes it suitable for incorporation in smoker's toothpaste. Vitamin C helps in repairing the barrier function of oral epithelium and in synthesising collagen and maintains skin and mucous membrane thereby protecting one against infection.

In contemporary world, a need is felt to prevent human disease and is rated as a high social priority. In case of life threatening diseases, the introduction of preventive measures is very strong as compared to preventing plaque and periodontal disease in a healthy mouth. Nevertheless, people today have realised that it is better to be healthy than ill or dead, regardless of any severity of the disease. The need to control plaque and periodontal disease, with a desire to have an odour-free and disease-free mouth is growing. Today it is recognised that prevention of diseases by use of oral care products is proven to have benefited a large amount of people and yet has been cost effective confirming the old saying 'Prevention is better than Cure.'