ORAL AND DENTAL DELIVERY OF FLUORIDE: A REVIEW

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SUMMARY: The fluoride ion (F) is the ionic form of the element fluorine, one of the halogen group of elements, and one of the most abundant elements found in nature. F is unique in the halogen group in terms of its affinity towards mineralized tissues and is known as a seeker of mineralized tissues. A beneficial role for topical F in the treatment of dental caries is widely accepted by many dental professionals and researchers. Initially, it was thought that F was beneficial when given systemically during tooth development but later research has shown that the topical effects are more important. Various topical delivery methods for F have been developed and this review discusses the various intraoral delivery methods, the mechanisms of action, toxicity, and the limitations of this treatment.

Keywords: Drug delivery; Fluoridation; Fluoride releasing materials; Water fluoridation.

INTRODUCTION

The fluoride ion (F) has been widely used topically in the treatment of dental caries for its anticariogenic and antimicrobial properties. The antibacterial action of fluoride is due to the acidification of the bacterial cytoplasm through the formation of H^+ and F^- ions from hydrogen fluoride and the disruption the bacterial metabolism by inhibition of vital bacterial enzymes such as proton releasing adenosine triphosphatase and enolase. A more interactive role of F in the dynamic biological environment includes the formation of calcium fluoride, reduced hypersensitivity, osteoblast proliferation, and firmer bone anchorage. F has been delivered by being added to various biomaterials such as bioceramic, glasses, composite materials, and the surface coatings of dental implants. The addition of F may also improve the stability of biomaterials.[1-3]

The mechanisms suggested for the antimicrobial and remineralization roles of F for oral health include:[1,4,5]

- reduction in demineralization by inhibition of microbial growth and metabolism
- promotion of remineralization and the formation of the fluorapatite mineral phase ($Ca_{10}(PO_4)_6F_2$) which is, compared to hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), more resistant to demineralization and acid dissolution following acid production by bacteria
- enzyme inhibition such as reduction of IgA protease synthesis
- reduction in extracellular polysaccharide production which helps in decreasing bacterial adherence to dental hard tissues.

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Systemic F intake may come from various sources including water, dentifrices and professional therapies, and beverages, and may lead to toxic effects. The manifestations of F toxicity may include dental fluorosis, skeletal fluorosis, muscle fiber derangement, headache, skin rashes, neurological manifestations such as lowering of the IQ, depression, nervousness, tingling sensations in toes and fingers, gastrointestinal problems such as nausea, abdominal pain, reduced immunity, and urinary tract malfunctioning.[6-8] In order to prevent F toxicity the United States Institute of Medicine has recommended the daily intake of F for children up to 12 years of age should not exceed 0.05 to 0.07 mg/kg. To prevent the occurrence of dental fluorosis, the daily F ingestion should not exceed 0.10 mg/kg.[8-9]

F has been delivered to the oral cavity by number of methods and mediums including fluoridated milk and water[9], dental restorative materials,[10-14] F particle coated prostheses,[15,16] and various F delivery devices[5,17] (Figure 1). The main aim of this paper is to review these delivery methods, including their effectiveness and limitations.

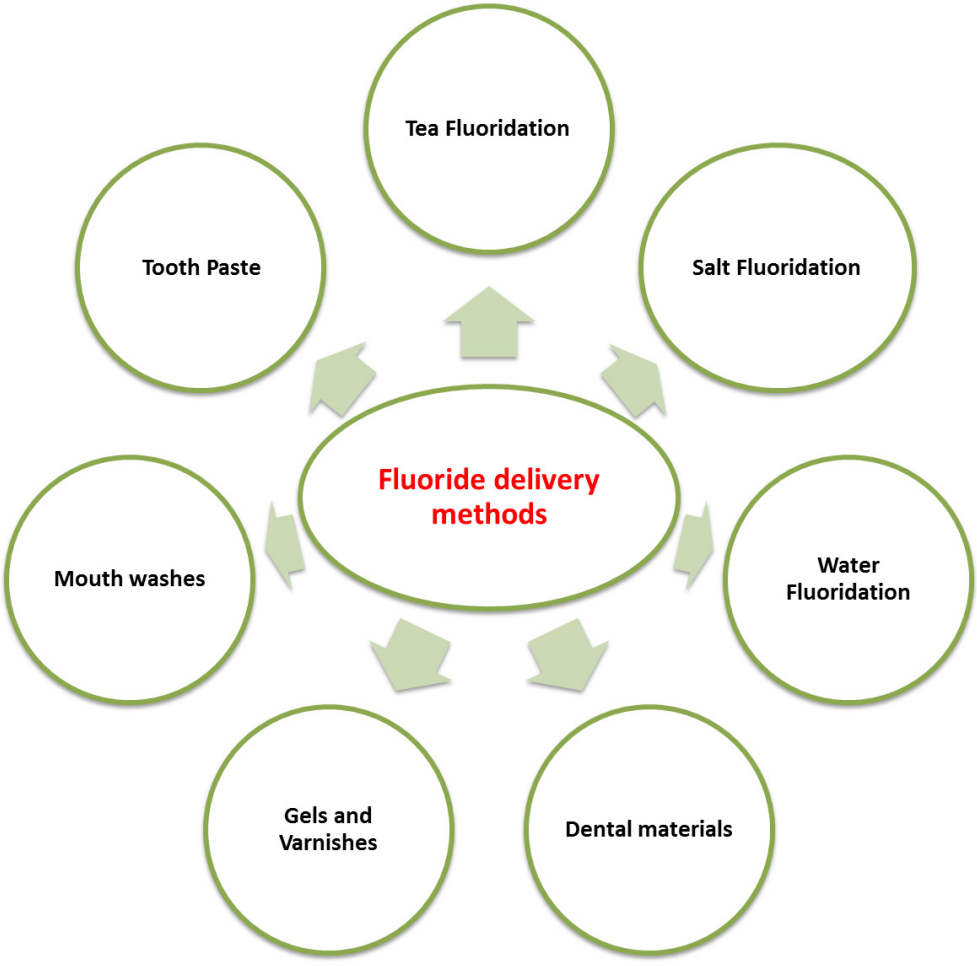

Figure 1. Commonly used fluoride delivery methods for oral tissues.

ORODENTAL FLUORIDE DELIVERY VEHICLES

Water fluoridation: Water fluoridation, in which controlled amount of F is added to the public water supply, is the most popular method of delivering fluoride systemically[6,7,9] Public water fluoridation was carried out for the first time in 1945 in United States and was recommended by the World Health Organization as the main delivery method of F for the improvement of oral health.[1] F is naturally found in the fresh water but its concentration may vary depending on the geographical location and source.[6,9,18,19] Usually, the F concentration in natural water ranges from 0.01 ppm to a maximum of 100 ppm.[20] Fluorosilicic acid and sodium fluoride are commonly used in water fluoridation. Fluoridation can deliver systemic F to a large population without any need for their active participation. To minimize F toxicity, the F concentration in the drinking water has been controlled with a level of 0.8–1 ppm being recommended.[4] Recently, the U.S. Public Health Service lowered its recommendation for the optimum concentration of F in drinking water from the range of 0.7–1.2 mg/L, recommended in 1962, to a new figure of 0.7 mg/L.[21]

Although the World Health Organization set, in 1984 and reaffirmed in 1993, a guideline of 1.5 mg F/L (1.5 ppm) as a "desirable" upper limit, it also allows countries to set Country Standards, their own national standards or local guidelines.[22] The limit of 1.5 mg F/L has been seen to be unsuitable in some countries and lower Country Standards have been set of 1 mg/L in India and 0.6 mg/L in Senegal, West Africa.[23] A rider to the Indian limit is "lesser the fluoride the better, as fluoride is injurious to health."[23] Empirical evidence suggests that to protect all against central nervous system toxicity the level should not exceed 0.1 mg/L.[24]

It is now considered that any action that F has in preventing dental caries occurs predominately after the eruption of the teeth into the mouth and that it is primarily topical, for both adults and children, via inhibiting demineralization, enhancing remineralization, and inhibiting bacterial action in dental plaque.[25] Thus the systemic administration of F via water, milk, and salt is controversial.[23] Large sections of the population in developed countries are suffering from fluorosis as a result of the fluoridation of drinking water and dental products.[23] In the USA, in 1999–2004, the prevalence of dental fluorosis was 41% in adolescents aged 12–15 yr.[21] A review of fluoridation policies has been recommended.[23]

Salt fluoridation: Edible salt is a necessary component of our diet and is often used on a daily basis. Salt fluoridation is comparable to water fluoridation in its effects and has been used as an alternative to water fluoridation in certain places not having a centralized water supply or having an interrupted water supply.[26] The amount of F added to salt is 90 to 350 mg/kg. The key advantage of salt fluoridation over water fluoridation is that the consumers have a choice on whether to use it or not.[4] Salt consumption is associated with the risk of hypertension and cannot be prescribed for certain patients with systemic illness.[1]

Miswak and tea: A mouth wash prepared from *Salvadora persica* (miswak), which contains approximately 1.0 μg F/g, has been used as an antibacterial agent

to improve oral health.[27,28] Tea leaves may contain high levels of F. Brewed tea contains up to 6 ppm F. The F from tea may interact with the oral tissues and the salivary proteins present in pellicle, the thin layer of salivary glycoproteins deposited on the teeth, thus providing a prolonged topical effect. The pellicle-associated F decreases the metabolism of the plaque bacteria that convert carbohydrate into acid and also promotes the remineralization of the enamel.[20]

Milk fluoridation: The addition of F to milk has also been used for the delivery of F. In comparison with water, milk fluoridation is a less efficient method for delivery of F. The F added to milk forms insoluble complexes that make F absorption difficult.[1]

Toothpaste: Toothpaste has an important functions in maintaining oral health. It helps the consumers in the removal of plaque and debris by its detergent action. Polishing the tooth surface with toothpaste helps prevent the accumulation of microorganisms and debris. In modern life, toothpastes are used by individuals on a daily basis and hence can be a source of various therapeutic agents including F.[29] Toothpastes containing F were first available commercially in the 1970s and are the major source of F in some communities where fluoridated drinking water is not available.[1] F is added into toothpastes mostly as sodium fluoride (NaF), sodium monofluorophosphate (MFP), amine fluoride, and stannous fluoride. The other ingredients of toothpaste may also affect the availability of F in the oral cavity. This is especially true in the case of calcium containing abrasives due to their potential to inactivate the F. Similarly, F will react with silica to form fluorosilicates if a sufficient amount of detergent is not present.[4,30,31] The use of fluoridated toothpastes has been demonstrated to have a caries reduction efficacy 25% greater than that for non-fluoridated tooth pastes. However, the benefits and therapeutic efficacy of using fluoridated tooth pastes may be affected by multiple factors such as the concentration of F, the amount of toothpaste used, and individual variations including the duration and frequency of brushing and rinsing behavior.[31,32] The main concern with this delivery method is inappropriate handling, particularly by children. The ingestion of fluoridated toothpastes can produce serious toxic effects and appropriate adult supervision is essential for children using toothpaste. Toothpastes are available in a wide range of F concentrations (Table 1).

Mouth rinse: Mouth washes can be used in conjunction with toothpaste and are recommended for patients with a high susceptibility to dental caries. The active compound for F delivery in mouth rinses is sodium fluoride (NaF). Commonly available over the counter mouth rinses contain 0.05% NaF (equivalent to 226 ppm of F).[1] F-containing mouth rinses have the advantage of having a lower viscosity than toothpastes which allows the F to reach into difficult to access areas such as the interproximal regions, narrow pits, and fissures. F delivery through a mouth rinse is recommended for children over 6 years with active dental caries, patients undergoing fixed orthodontic treatment to reduce the chances of demineralization around orthodontic brackets, patients with decreased salivary flow, and patients with decreased manual dexterity.[4] In order to prevent its

ingestion, mouthwashes must not be prescribed for children under 6 years of age and mentally retarded patients.

Table 1. Classification of toothpastes based on the fluoride concentration (ppm or mg/kg)[31,32]

Type	Availability	Indication	Comments
Low fluoride toothpaste <500 ppm (mg/kg)	Over the counter but less marketed.	For children under 6 years of age with a low risk of caries in areas with fluoridated water.	Should be used under supervision.
Standard fluoride tooth paste 1100–1500 ppm (mg/kg)	Available over the counter.	For children of 6 years of age or older and adults. Children under 6 years of age with a high risk of caries using only a pea-sized amount of toothpaste (0.25mg) and with spitting out of the excess.	Not suitable for children.
High fluoride toothpaste >1500 ppm (mg/kg)	Prescription only.	Adult patients with a high risk of caries. For the prevention and reversal of root surface caries.	Keep out of the reach of children.

Fluoride varnishes: In addition to the conventional methods of F delivery, F varnishes have been used for the prevention and control of dental caries since the 1960s. F varnish is not a consumer product and must be applied by a qualified dental hygienist or dentist. Varnishes are topical and deliver F to the surface and subsurface carious lesions by the formation of deposits of calcium fluoride. The calcium fluoride acts as a F pool and provides F for a prolonged time.[29] F varnishes are indicated for therapeutic applications to control active caries, root surface caries, xerostomia patients, hypersensitive areas of enamel and dentine, and physically or mentally handicapped patients. The advantage of F varnish is that the application method is simple and quick, requiring no special equipment and is well tolerated by patients.[29] Although varnishes contain a high F concentration (22 mg/mL, 2.2%, or 22,000 ppm) they are considered to be very safe and effective. As a very small quantity (0.3–0.6 mL containing 6.6–13.2 mg F) is applied by trained professionals the ingested amount is generally considered to be too little to induce any toxic or unwanted effects.[31] For sodium fluoride, the lethal toxic dose for an adult man, if the patient is left untreated, has been estimated to be 2.5 to 5 g.[33] However, an outbreak of acute fluoride poisoning resulting from the overfluoridation of a public water system at Hooper Bay, Alaska, in 1992, resulted in one death in a 41-yr-old man who received an estimated dose of 17.9 mg/kg, corresponding to a dose of 1.25 g in a 70kg adult.[34] The lowest estimated dose that caused symptoms was 0.3 mg/kg, corresponding to a dose of 21 mg for a 70 kg adult.[33] The dose causing symptoms, less than 1 mg F/

kg, was similar to that reported in other studies.[34] Feltman and Kosel found that 1% of their subjects (601 pregnant women and 495 children aged up to 8 years) had side effects from 1 mg F orally daily, including eczema, atopic dermatitis, urticaria, epigastric distress, emesis, and headaches, which occurred with the use of F and disappeared with use of placebo tablets, only to recur when the fluoride tablets were unknowingly given to the patient again.[35,36]

Fluoride gel: Stannous fluoride gels (0.4% SnF_2, equivalent to 970 ppm of F). are effective in arresting root surface caries and have been incorporated into artificial saliva to reduce caries after radiation therapy in cancer patients. Stannous fluoride gel has a bad taste and may stain the teeth.[4] Alternatively, high concentration acidulated phosphate fluoride (APF) gels can be used (Table 2).

Table 2. Type of gels for fluoride delivery[4]

Type of fluoride gel	Amount of fluoride	Examples	Comments
Low concentration	1000 ppm (mg/kg)	Stannous fluoride gel	Can be used at home following professional instructions.
High concentration	9000–12300 ppm (mg/kg)	Acidulated phosphate fluoride (APF) gels, neutral NaF gel	Professional use only.

The incorporation of sodium carboxymethyl cellulose (water-soluble polymer) into aqueous acidulated phosphate fluoride (APF) gels produces a viscous solution that improves the ease of application using custom-made trays. In custom-made trays, viscous gels flow under pressure and which facilitates penetration between the teeth. A neutral pH gel (e.g., 2% w/v neutral F ion releasing gel, 9000 ppm F) can be applied for treatment of conditions such as exposed or carious dentine, hypomineralized porous enamel surfaces, and dental erosions. Sodium fluoride is chemically very stable, has an acceptable taste and is non-irritating to the gingivae. Additionally, it does not cause discoloration of tooth tissues or dental restorations. In contrast, APF or stannous fluoride gels may cause discoloration and etching of restorations.[4] APF gels therefore should not be used in patients with composite resin metal–ceramic or ceramic restorations.[37]

Restorative dental materials: A number of F releasing dental restorative materials are available for clinical applications.[12] These materials not only restore the damaged or lost tooth tissue but also act as a F reservoir. These materials release a reasonable amount of F into the oral cavity and get recharged once F becomes available from other sources such as toothpastes and mouth washes.[1]

Glass ionomer cement (GIC) is famous for its unique properties; two of the most important are the good chemical adhesion to dental hard tissues and the capability of releasing and recharging fluoride ions.[13,38-41] GIC may be the material of

choice for certain conditions such as root caries and secondary caries. GIC is comprised of fluoro-silicate glass powder that reacts to polyalkenoic acid (acid–base reaction) to set hard. There are two types of F release patterns observed with glass ionomer materials: an initial release burst followed by a period of sustained release.[37,42] The two most relevant points regarding GIC are:

(i) an irreversible process of F release that is regulated by the solubility of the precursors and diffusion into the GIC matrix

(ii) a reversible ion exchange procedure involving the glass or matrix of the cement. In this reversible ion exchange process, the glass ionomer cement can function as a reservoir of fluoride ions that can be recharged upon topical F applications.[1]

The F recharge ability depends upon various factors such as the age of the restoration, the permeability and type of material, and the concentration and frequency of F exposure. This F recharge phenomena also occurs in resin based materials but it is significantly better with GIC.[37] Similarly, cermets (metal particles modified glass ionomers) are less efficient in F release compared to the conventional GIC. This decrease in release of F may be due to the replacement of F containing glass with metal/silver particles or due to the formation of silver fluoride complexes that prevent the release of fluoride ions from the matrix.[42] The addition of nanoscale fluoroapatite nanoparticles to improve the properties of GIC has been reported.[43] More examples of F releasing dental materials, including silicate cements, compomers (poly acid modified composites), resin composites, and giomers, have been discussed previously.[3,12,44,45]

Fluoride containing delivery devices: Slow F releasing devices help in maintaining a significantly increased level of F in saliva and dental plaque.

MUCOADHESIVE TABLETS: Bio-adhesive preparations are ideal for the management of diseases of the oral cavity. These preparations have the property of adherence to tissues, such as mucosa, so that the therapeutic agents, such as F, can act for a longer time in providing caries protection.

CHITOSAN MICRO-PARTICLES: Chitosan is a copolymer of chitin produced by partial deacetylation. Micro-sized particles and a cationic charge gives it good muco-adhesive properties to facilitate intraoral retention.[5] Chitosan is capable of disrupting the bacterial cell membrane and has antibacterial properties against a wide range of pathogenic oral microbes. Chitosan anhydrous nanoparticles containing sodium fluoride have been developed. These nanoparticles have an enhanced bio-adhesion to the hydrated oral mucosal surface and can act as a reservoir for both the initial burst and the sustained release of F.[5]

ELASTOMERIC RINGS: During fixed orthodontic treatment, enamel white spot lesions are identified in up to 50% of the patients with poor oral hygiene.[17] To prevent localized enamel demineralization as a result of orthodontic treatment, different measures such as F containing tooth paste, mouth rinses, orthodontic adhesives, and cements containing F are recommended. However, these methods have either patient compliance issues or very low levels of F release.[4,17] To overcome these

problems, F releasing biocompatible non-inflammatory polyethylene co-vinyl acetate rings have been developed containing different percentages of sodium fluoride incorporated into polyethylene co-vinyl acetate polymer (PEVA). PEVA containing sodium fluoride and coated with pure polymer are used for the well-controlled and efficient release of F in the oral cavity.[17]

F has been incorporated into the polyethylene co-vinyl acetate polymer (PEVA) in variable amounts. The safest amount was observed in samples releasing up to 0.4 g of F. In order to control the initial burst effect of F release, PEVA polymer (without F) dip coatings were applied. The F release in these samples was well controlled: 6.70 µg F/ring/day (0.134 ppm) for 10 days and then a constant 1.43 µg F/ring/day (0.028 ppm) for up to 40 days.[4,17]

There are certain limitations with these *in vitro* studies. For example, the experimentation and data are based on static immersion tests and do not replicate the environment of the oral cavity. The oral cavity is a more dynamic environment with variations in the salivary flow rate, the salivary composition, and the movement of the oral musculature. Elastomeric rings are expected to be beneficial in preventing caries in patients undergoing orthodontic treatment. For example, white spot lesions representing the initiating demineralization may appear close to orthodontic brackets and fluoride ions released from elastomeric rings can be readily available to inhibit demineralization and prevent caries from developing.

POLYHYDROXY ETHYLMETHACRYLATE (PHEMA): Photo polymerized PHEMA membranes loaded with sodium fluoride and surface coated using polyhydroxybutyrate are available for the controlled release of F in artificial saliva. The amount of F release is 0.02–1 mg F/day. The amount of F released is directly related to a range of parameters including the amount of F loaded into the polymeric membrane, the pH, and the temperature of the release medium.[46]

Tooth decay (dental caries) is one of the most common conditions involving the human dentition. The progress of dental caries is a complex process involving multiple factors such as patient's oral hygiene, diet, socioeconomic status, oral microbial flora,[35] and the interaction of microbes with oral peptides.[47] *Streptococcus mutans (S. mutans)* is considered the major microorganism involved in caries progression and is sensitive to fluoride ions.[35,48] Fluoride ions released in the oral cavity may act as bacteriostatic or bactericidal therapeutic agents. However, estimating the required therapeutic dose to eradicate *(S. mutans)* may be challenging due to the complex multifactorial nature of dental caries and the dynamic oral environment. It was reported recently that adult toothpastes (1400+ ppm F) are more efficient against *(S. mutans)* than lower strength children's toothpaste (500 ppm). Pure solutions of sodium fluoride or sodium monofluorophosphate exhibited no antimicrobial activity even at a concentration of 10^4 ppm while stannous fluoride showed antibacterial activity at 10^3 or higher concentrations.[48] Hence, the antimicrobial activity is dependent not only on the F concentration but also on the source and type of F available.

CONCLUSIONS

The role of F in oral health has been studied for many decades and evidence found to support topical, but not systemic, F as being beneficial. However, it must be emphasized that tooth decay (dental caries) is not caused by F deficiency. Hence F supplementation will never reverse active or gross carious lesions. Therefore, in order to reduce dental decay in populations with a high caries risk, other measures, such as patient counselling and guidance about oral hygiene and food selection, must be taken in conjunction with the F delivery methods discussed in this review.

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