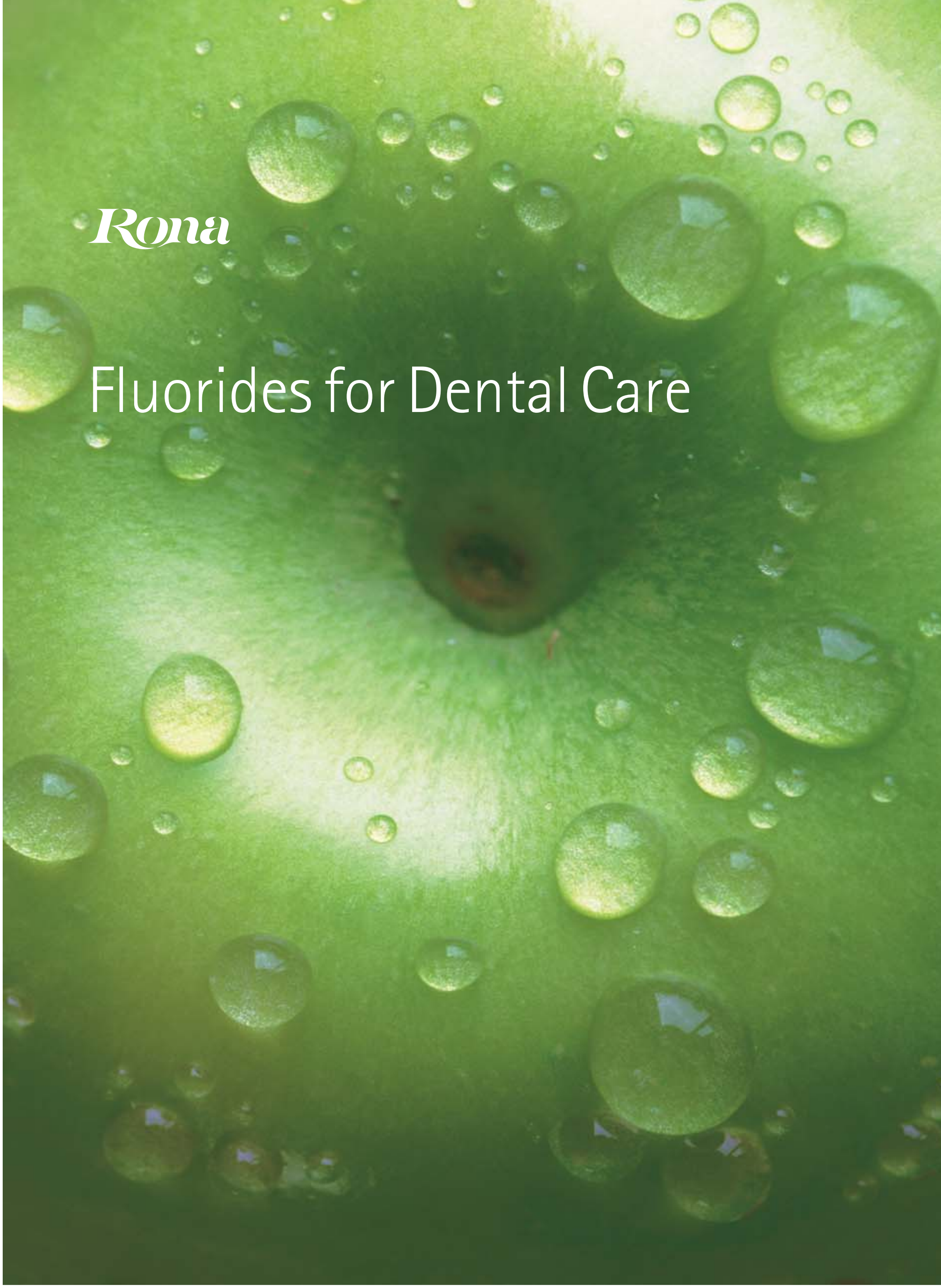


Rona

Fluorides for Dental Care

MERCK

Introduction

There are many different microorganisms, particularly bacteria, which inhabit the mouth. They attach themselves to the tooth surface where they combine with food particles primarily such as carbohydrates and proteins, to form a sticky polysaccharide (glucane, fructane) coating. This tooth coating, known as **plaque**, is the main cause of tooth decay (caries) and gum infections.

Tooth enamel is made up of 97 % hydroxylapatite; dentine 70 % hydroxylapatite. The bacteria in plaque (particularly Streptococcus mutans and Lactobacillus acidophilus) produce acids via the glycolysis of carbohydrates resulting in a drop in pH to below the critical limit of pH 5.5. These acids attack the tooth enamel first and then subsequently the dentine, resulting in demineralisation of the hydroxylapatite lattice.

$$Ca_5(PO_4)_3OH + H_3O^+ \Rightarrow 5\ Ca^{2+} + 3\ PO_4^{3-} + 2\ H_2O$$

The hydroxy ions in apatite are neutralised by the acids resulting in decomposition of the crystal lattice. A hole is produced, i.e. caries. As long as the plaque layer is not too thick, saliva is able to buffer the acids and remineralisation by the calcium and phosphate ions present in the saliva is possible. However, increasing thickness of the plaque layer, take-up of phosphate by the bacteria together with calcium complexation by acid residues significantly hinders remineralisation.

After three to five days the plaque layer, which up to now consisted mainly of grampositive cocci, starts to change.[7] Gram negative cocci and gram positive rods establish themselves and became stuck to each other via the tough sticky glucanes which are further produced. In the next phase, additional microorganisms establish themselves. The plaque layer becomes increasingly hardened via the enclosure of calcium and phosphate ions in the form of hydroxylapatite. **Tartar** forms onto which, thanks to its rough surface, further new plaque can easily establish themselves. [13,25,32]

Plaque bacteria which colonise on the edge of the gum are the cause of **gum infections (gingivitis)**. The triggers are released toxic metabolites (ammonia, organic acids, H_2S), bacterial enzymes and endotoxins produced via decomposition of gram negative bacteria. Lasting gum infections lead to paradontosis where upon the gums recede and there is then the threat of tooth loss. [13]

The Action of Fluorides

In addition to regular dental ceckups and reduction in consumption of sweet foods, the use of fluoride-containing dental and mouth care products and fluoride intake via drinking water, fluoride tablets and cooking salt has proned to be an effective caries prophylaxis.

Fluoridisation of the tooth enamel can be effected by the formation of fluoroapatite or by deposition of a calcium fluoride layer on to the tooth surface. [42]

Hydroxylapatite has a cage-like structure made up of calcium and phosphate ions. Hydroxy ions are located in the gaps and these can be replaced by fluoride ions.

$$Ca_5(PO_4)_3OH + F^- \Rightarrow Ca_5\ (PO_4)_3F + OH^-$$

In contrast to hydroxylapatite, fluoroapatite is acid-stable because the fluoride ions do not react with H_3O^+ ions. This type of fluoridisation is a significant component of caries prophylaxis.[2,24]

At higher fluoride doses and below pH 5 a layer of calcium fluoride can be deposited onto the tooth surface as a result of the higher concentration of free calcium ions. This layer serves as a fluoride depot for the tooth enamel underneath it. [39,45]

$$Ca_5(PO_4)_3OH + 10\ F^- \Rightarrow 5\ CaF_2 + 3(PO_4)3^- + OH^-$$

The inorganic fluorides sodium fluoride, sodium monofluorophosphate and tin fluoride and the organic fluorides olaflur, cetylamine hydrofluoride, oleylamine hydrofluoride and hexydecylamine hydrofluoride are all used for fluoridisation. Both inorganic and organic fluoride compounds demonstrate the following activity as a result of the fluoride ion:

- reduced acid solubility of dental enamel via the formation of fluoroapaptite and calcium fluoride [9,10,23,34]
- faster sugar neutralisation
- bacteriostatic action[31,30,12]
- inhibition of glycolysis and as a result acid production in the plaque via inhibition of the enzyme enolase and probably also phosphoglycerate mutase[21]
- improved remineralisation by saliva through binding calcium into the tooth enamel[35]

As a result of the cationic amine ion, the **organic fluorides** also demonstrate the following actions:

- high affinity to tooth enamel and as a result longer dwell time on the tooth ⇒ long term fluoride protection[8,39]
- reduction of the surface tension of the saliva resulting in more complete wetting including the gaps between teeth
- higher protection against caries bacteria via production of a bacteriophobic protective film[39,43]
- longer antiglycolytic action and, therefore, delayed pH drop by reduction of acid formation by bacteria[5,11,12,22,40,3,41,24]
- bactericidal action i.e. bacteria are not just inhibited they are also killed off[12,6,31,30]
- better fluoride bioavailability as it dissociates virtually completely from the organic, heteropolar compound[18]
- during glycolysis the enzymes pyruvate kinase and glyceraldehyde-3-phosphate dehydrogenase are additionally inhibited[21]
- the usage concentration for organic fluorides can be lower than inorganic fluorides because they show the same activity despite a lower concentration[5]

During the past 40 years many long term clinical studies have been carried out on humans to test the actual effectivity of the inorganic and organic fluorides. The results vary within certain limits due to the influence of factors such as age of the test subjects, treatment duration, application frequency, active ingredient concentration and base formulation of the tooth care product used which all play a role. [26,27,8,23,29,37,28]

In general the caries-inhibiting action of tooth care formulation depends on:

- time between tooth breakthrough and first application
- frequency of use (better long acting low fluoride concentrations than short acting high concentrations)
- which fluoride compound is used
- application form (paste type formulations are better than liquid ones[17], though good results were also obtained with firm liquid formulations[46,38])
- pH of the formulation (calcium fluoride accumulation better at pH 4.5-5 than at higher pH-values)
- length of time the fluoride compound spends on the tooth.

Efficacy of Organic Fluoride

Dwell Time on the Tooth

Figure 1 shows clearly the longer dwell time and hence longer availability of amine fluoride on the tooth. Whilst with sodium fluoride the average fluoride content of untreated plague, i.e. 44 ppm, is reached after only a hour, with amine fluoride the same value is reached much later i.e. after 4 hours.

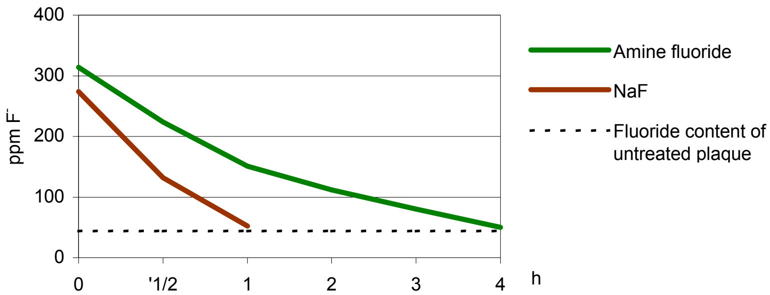


Fig. 1: *Fluoride absorption and emission from plaque after a 3 minute rinse with 10 ml of a 0.2 % sodium fluoride solution or 10 ml of a 0.09 % amine fluoride solution[16]*

Reduction of Enamel Solubility

In order to investigate the susceptibility of the teeth to caries, their resistance to the organic acids occurring in the mouth is tested. A higher fluoride content in the tooth enamel results in a proven better acid resistance.[2] As shown in fig. 2, amine fluoride reduces the enamel solubility significantly more than sodium fluoride.

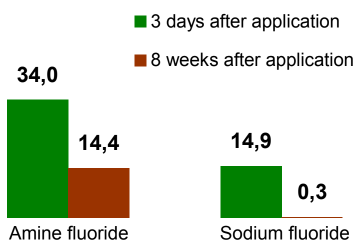


Fig. 2: *Average reduction in enamel solubility with amine fluoride and sodium fluoride solution (teeth of an app. 20 years-old volunteer)[14]*

Inhibition of Acid Production

Whilst Olaflur can cause 100 % inhibition of acid production by plaque-streptococci at a concentration low as 10^{-5} M, sodium fluoride has almost no influence on acid production at the same concentration.

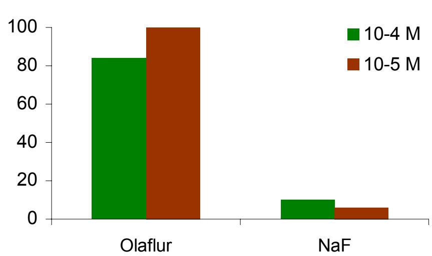


Fig. 3: *Inhibition of the acid formation from glucose caused by plaque-streptococci[3]*

Formation of a Bacteriophobic Protective Film

At a concentration of 10^{-5} M, amine fluorides cause production of a bacteriophobic protective film which is capable of completely preventing growth of plaque-streptococci. On the other hand, sodium fluoride and tin fluoride at the same concentration are unable to prevent build up of plaque (fig.4)

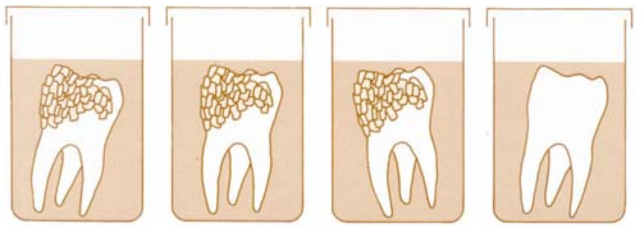


Fig. 4: *Streptococcus cultures after 24 h at 37 °C on addition of sodium, tin and amine fluoride (10^{-5} M)*

Caries Reduction

A study performed on 2008 school children demonstrated that following 3 years usage of an amine fluoride toothpaste, 21.6 % less caries per tooth, or 20.9 % per tooth surface, occurred (fig. 5).

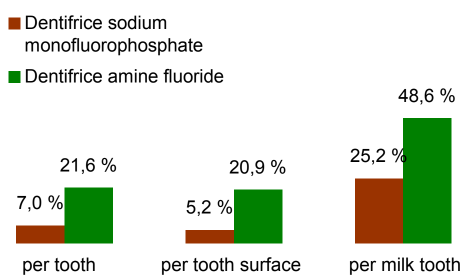


Fig. 5: *Caries reduction of a sodium monofluorophosphate and amine fluoride dentifrice (0.15 % fluorine respectively) as compared to placebo*[4]

Suggested formulations

- dental care creams, gels and lotions
- water and salt fluoridation
- tablets
- tooth picks
- dental floss
- chewing gums

Merck Fluoride Product Range

RonaCare® Olaflur - the organic fluoride

Long term protection against caries and paradontitis via formation of a fluoride depot with a long dwell time on the teeth. Suppression of plaque formation and through cleaning including of gaps between teeth.

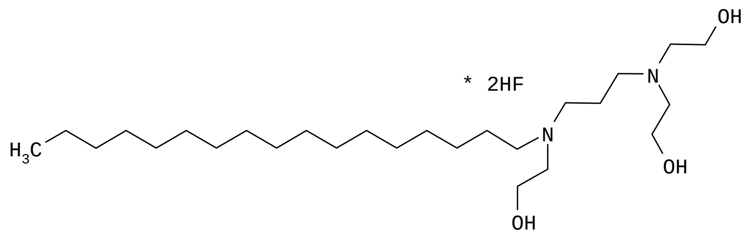
RonaCare® NaF - the inorganic fluoride

One of the most widely used fluorides in low price segment tooth care products. Protects against caries by reducing plaque formation and improving remineralisation of tooth enamel.

Technical Data

RonaCare® Olaflur

Molecular Structure



INCI Name	Propylene Glycol, Olaflur
Chemical description	Bis(hydroxyethyl)-aminopropyl-N-hydroxyethyl-octadecylamine dihydrofluoride solution in 1,2-propanediol $C_{27}H_{60}F_2N_2O_3$
Appearance	Clear, yellow to brown, viscous liquid, characteristic intrinsic odor
Solubility	Miscible in all concentrations with water, ethanol, propanol, isopropanol and glycerol.
Handling	RonaCare® Olaflur is sensitive to frost – should the product become cloudy, thicken or freeze due to cold conditions, it should be warmed up slowly to between 25 and 35 °C and homogenised briefly, after which it will be ready to use again.
Formulation guidelines	Not compatible with anionic raw materials. Amine fluoride helps to stabilize stannous fluoride in water solutions.[24] As fluorides are inactivated by reacting with calcium the use of calcium containing abrasives should be avoided. Appropriate abrasives are sodium bicarbonate, insoluble sodium metaphosphate, and hydrated silicas.[30, 31]
Use concentration	1 - 4% The max. use level is 5.90 % RonaCare® Olaflur (≅ 0.15 % fluorine) regulated by Cosmetic Directive 76/7688/EEC

RonaCare® NaF

INCI Name	Sodium Fluoride
Chemical description	NaF
Appearance	White powder
Solubility	in water about 4 % in ethanol insoluble
Formulation guidelines	As fluorides are inactivated by reacting with calcium the use of calcium containing abrasives should be avoided. Appropriate abrasives are sodium bicarbonate, insoluble sodium metaphosphate, and hydrated silicas.[19,36]
Max. use concentration	0.33 % (≅ 0.15 % fluorine) regulated by Cosmetic Directive 76/7688/EEC

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Ordering Information

Item No.	Name	Pack Sizes
130441	RonaCare® NaF	5 kg, 25 kg
111680	RonaCare® Olaflur	1 l, 200 kg