THE INTERACTION OF STANNOUS FLUORIDE WITH SYNTHETIC HYDROXYAPATITE: MODELING THE ANTICARIES EFFECT

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The anti-caries mechanism of stannous fluoride has been investigated by determining its behaviour in aqueous solution and in contact with hydroxyapatite powder. Free fluoride levels in solutions of SnF_2 at total fluoride concentrations of 500 and 1000 ppm were measured using an ion-selective electrode. From the results, the value of the equilibrium constant for the process $SnF_2 \rightleftarrows SnF^+ + F^-$ was determined. Solutions were then placed in contact with synthetic hydroxyapatite powder at 5 cm^3 to 0.100 g and free fluoride determined after 1 minute, then 5 minute intervals for 1 hour. All determinations were in triplicate. Free fluoride was 38.4 (± 4.7) ppm and 57.7 (± 11.4) ppm for the nominal 500 and 1000 ppm solutions respectively. Equilibrium constants were 8.4×10^{-5} mol.dm^{-3} (± 1.0×10^{-5} mol.dm^{-3}) and 9.3×10^{-5} mol.dm-3 (± 1.8×10^{-5} mol.dm^{-3}) respectively. These were not significantly different and had a mean of 8.8×10^{-5} mol.dm^{-3} (± 1.2×10^{-5} mol.dm^{-3}). Free fluoride in solutions of SnF_2 exposed to hydroxyapatite powder increased rapidly, equilibrating within 20 minutes. Uptake of tin by hydroxyapatite was confirmed from EDAX (SEM) on the recovered hydroxyapatite. We conclude that SnF^+ is taken up by hydroxyapatite and is responsible for the anti-caries effect in vivo. Further work is required to determine the nature of this uptake, i.e. surface adsorption or incorporation into the hydroxyapatite lattice during remineralization.

INTRODUCTION

Tooth decay (dental caries) is one of the most common diseases in humans [1] and has been described as "a chronic, dietomicrobial, site-specific disease caused by a shift from protective factors favouring tooth remineralization to destructive factors leading to demineralization" [2]. The specific factors leading to destruction of the mineral phase of the tooth are the presence of oral bacteria, mainly *Streptococcus mutans* [3], and the availability of fermentable carbohydrates. This combination leads to the production of organic acids as a result of the metabolic process of the bacteria, of which the main one is lactic acid [4]. These acids dissolve the mineral component of the tooth, leading to loss of structure.

Caries is known to be inhibited by fluoride ions [1, 5]. Three mechanisms have been proposed by which fluoride ions exert their anti-caries effects:

- Combination with the tooth mineral to form the less soluble mineral fluorapatite from the naturally occurring hydroxyapatite phase [6-9];
- Promotion of remineralization processes at the surface of the hydroxyapatite phase [10-12]; and
- Reduction of the solvating ability of the saliva through forming strong hydrogen bonds with the water [13, 14].

Of these, the most important appears to be the promotion of remineralization [10-12]. This is the process whereby crystals of hydroxyapatite are induced to grow by precipitation of Ca^{2+} and PO_4^{3-} ions from saliva [15]. The mechanism is complex, involving dynamic activity mainly between the tooth and the saliva, but also involving the pellicle and the plaque [16]. Fluoride ions influence this activity by enhancing the rate of deposition of the mineral phase. In doing so, they become incorporated within the new mineral, though this is no longer considered to be their primary role [17].

Fluoride can be delivered to the tooth surface in a variety ways, including as additions to drinking water [18], as fluoridated drops applied directly to the tooth surface [19], in toothpastes and mouthrinses [20], and by release from dental restorative materials, specifically glass-ionomers, compomers and fluoridated resin composites [21]. In toothpastes, fluoride can be delivered as sodium fluoride, stannous fluoride or sodium monofluorophosphate [22, 23] and, of these, stannous fluoride has been reported to be the most effective [3, 24].

The effectiveness of stannous fluoride has been attributed to the toxic effect of Sn^{2+} ions on the bacteria in the plaque [22, 23, 26-28]. Stannous ions are reported to affect the ability of cells to metabolise polysaccharides, which in turn inhibits bacterial growth, and reduces the rate of development of dental caries [29]. However, biological studies of this type have generally failed to recognise the complexity of the behaviour of SnF_2 in aqueous solution. There are several features of SnF_2 solutions that have a bearing on the effect on dental caries, and they should all be considered in this context.

First, in aqueous solution, Sn^{2+} ions are unstable with respect to oxidation to Sn(IV). The conversion of Sn(II) to Sn(IV) occurs by reaction with molecular oxygen, O_2 [30, 31] and because of the limited solubility of oxygen in water, this oxidation is fairly slow. The product is finely divided SnO_2 [32].

Second, stannous fluoride is known to form complex species in aqueous solution, rather than to dissociate simply into Sn^{2+} and F^- ions. The dominant species has been shown by a combination of ^{19}F and ^{119}Sn NMR spectroscopy and ^{119m}Sn Mőssbauer spectroscopy to be hydrated undissociated SnF_2 [33]. Stannous fluoride is a Lewis acid that mainly exists in aqueous solution as the monohydrate, $SnF_2.H_2O$, with the oxygen atom of the water molecule co-ordinated to the tin in a pyramidal geometry [33]. As well as this species, polarographic measurements have suggested the occurrence of the charged species SnF^+ and SnF_3^- [34], though there is some doubt about the latter in solutions of SnF_2 alone [33]. However, this ion has been detected in aqueous solutions of SnF_2 with other metal fluorides, such as NaF or KF [33]. In concentrated solutions of stannous fluoride, the well defined compound Sn_4OF_6 has also been shown to form to a limited extent [30].

The complexity of these solutions suggests that the interaction of stannous fluoride with hydroxyapatite is less straightforward than has been widely assumed. This topic is the subject of the current study, which has been carried out with the following objectives:

- To determine the free fluoride content as a fraction of the total fluoride present in solutions of stannous fluoride in the range conventionally delivered by oral healthcare products;
- To examine how the free fluoride level is affected over time on exposure to synthetic hydroxyapatite;
- To measure the amount of fluoride taken up by the hydroxyapatite from SnF_2 solutions;
- To determine whether tin, as well as fluoride, is taken up by hydroxyapatite under these conditions.

EXPERIMENTAL

All experiments used stannous fluoride (Reagent Grade ex Sigma Aldrich, UK). Adsorption experiments employed synthetic hydroxyapatite (also Reagent Grade ex Sigma Aldrich, UK). This brand is slightly calcium-deficient, having a Ca:P ratio of 1.45 (S.D. 0.16) [36] compared with an ideal Ca:P ratio of 1.67.

Two solutions of stannous fluoride were prepared at 1000 ppm and 500 ppm respectively. The first of these involved dissolving 1.031 g SnF_2 in 250 cm^3 in a volumetric flask. The second was prepared by dilution of the 1000 ppm solution by adding 50 cm^3 of solution by pipette to a 100 cm^3 volumetric flask and making up to full volume with water. De-ionised water was used throughout.

The free (uncomplexed) fluoride content of these two SnF_2 solutions as freshly prepared was determined with a fluoride ion selective electrode (type 309/1050/03 combination electrode, ex BDH Poole, UK). Three determinations were made per concentration, each on fresh volumes of solution. Results were used to determine the value of the equilibrium constant for the reaction:

$$SnF_2 \rightleftarrows SnF^+ + F^-$$

Following this, 0.100 g of hydroxyapatite powder was weighed out and transferred to a plastic centrifuge tube, to which 5 cm^3 stannous fluoride solution was then added. Free fluoride concentration was determined at 5 min intervals for 1 h, using the ion selective electrode. A control experiment was also performed, in which stannous fluoride solutions at 500 ppm and 1000 ppm were placed in identical plastic tubes, and the concentration measured at 30 minute intervals up to 6 hours.

After 1 h the hydroxyapatite was separated from the solution by filtration and allowed to dry in air. The solution was then treated with Total Ionic Solubility Acid Buffer, TISAB, (ex BDH, Poole, UK) to decomplex the remaining fluoride still left in solution and thus allow the total fluoride to be determined. This procedure was also carried out in triplicate.

The air-dried samples of hydroxyapatite were bulked and a small amount of each examined by scanning electron microscopy with X-ray analysis ((JEOL, JSM 5310LV Scanning Electron Microscope, Japan). This was done with the aim of determining semi-quantitatively whether or not there had been any uptake of tin.

RESULTS

The initial values of free fluoride in the two solutions are shown in Table 1. Means and standard deviations (in parentheses) are shown. In both cases, the amount was well below the concentration as prepared, showing that most of the fluoride is present in some form of complex.

Table 1. Initial free fluoride concentrations.

Total fluoride (as prepared)	Free fluoride, ppm (S.D.)	Free fluoride, %
500	1000	38.4 (4.7)
57.7 (11.4)	7.7	5.8

Values of the equilibrium constant for the reaction:

$$SnF_2 \rightleftarrows SnF^+ + F^-$$

were estimated as follows. For the 1000 ppm solution, the initial solution was made by dissolving 1.031 g in 250 cm^3 of water. This corresponds to 0.0264 $mol.dm^{-3}$. The free fluoride level found experimentally was 57.7 ppm, which corresponds to 1.5175×10^{-3} $mol.dm^{-3}$ of F^-. Assuming the rest to be SnF^+ and un-dissociated SnF_2 (because the dissociation to SnF^+ and SnF_3^- occurs to a very limited extent, if at all [6]), this gives values of concentration of 1.5175×10^{-3} $mol.dm^{-3}$ and 0.02478 $mol.dm^{-3}$ for these species respectively. Substituting the values into the equation for the equilibrium constant, K_c, where $[SnF^+]$, $[F^-]$ and $[SnF_2]$ represent the concentrations of SnF^+, F^- and SnF_2 respectively, *i.e.*

$$K_c = [SnF^+]\,[F^-] / [SnF_2]$$

and taking account of the standard deviation in the measured concentration of free fluoride, an overall figure of 9.3×10^{-5} $mol.dm^{-3}$ ± 1.8×10^{-5} $mol.dm^{-3}$ is obtained. The equivalent value calculated from the measured free fluoride concentration in the nominal 500 pm solution is 8.4×10^{-5} $mol.dm^{-3}$ ± 1.0×10^{-5} $mol.dm^{-3}$. These two results are not significantly different. Averaging across all values for both concentrations gives a figure for K_c of 8.8×10^{-5} $mol.dm^{-3}$ ± 1.2×10^{-5} $mol.dm^{-3}$.

Tables 2 and 3 show how the measured free fluoride concentration changes with time when 5 cm^3 volumes of each of the solutions were exposed to 0.100 g of hydroxyapatite powder. There was no change in the measured fluoride concentration in the control, showing that these changes are due to the interaction of the solutions with the hydroxyapatite. In both cases, there was a rise in the concentration of free fluoride in the early stages of the experiment, with the rapid establishment of a plateau region. This occurred quicker for the 500 ppm fluoride solution, but was clearly established within 20 minutes in both cases.

The values of free and total fluoride (*i.e.* with added TISAB) are shown in Table 4. In both cases, total fluoride is lower than the initial total fluoride concentration, showing that the hydroxypatite powder has taken up fluoride.

Results of elemental analysis using the EDAX facility of the SEM are shown in Table 5. The as-received hydroxyapatite showed a Ca:P ratio of 1.37, which is within experimental of the previously reported ratio for this brand of hydroxyapatite of 1.45 (S.D. 0.16) [36]. Figure 1 shows the relevant traces for hydroxyapatite as received and Figures 2 and 3 show hydroxyapatite following exposure to 500 ppm and 1000 ppm fluoride solutions respectively. There is a distinct peak for tin in the latter two traces, yet no tin was detectable in the as-received hydroxyapatite. This shows that the hydroxyapatite took up tin as well as fluoride in these experiments.

Table 2. Change in free fluoride with time for 500 ppm solution.

Time/min	Free fluoride, ppm (S.D.)
0	38.4 (4.7)
1	70.0 (13.0)
5	110.3 (11.8)
10	117.0 (9.0)
15	118.3 (8.7)
20	125.3 (10.3)
25	120.3 (9.0)
30	122.7 (8.0)
35	122.0 (8.5)
40	122.3 (6.0)
45	123.0 (3.5)
50	122.0 (4.6)
55	122.7 (5.8)
60	123.3 (3.1)

Table 3. Change in free fluoride with time for 1000 ppm solution.

Time/min	Free fluoride, ppm (S.D.)
0	57.7 (11.4)
1	99.6 (15.4)
5	122.7 (10.1)
10	137.7 (2.9)
15	142.0 (8.2)
20	148.7 (16.5)
25	147.0 (10.1)
30	149.3 (14.3)
35	145.3 (10.1)
40	149.7 (8.5)
45	145.7 (6.7)
50	145.3 (5.8)
55	143.7 (8.0)
60	140.7 (6.7)

Table 4. Free and total fluoride concentrations after 1 h exposure to hydroxyapatite.

Fluoride concentration (ppm)	500 ppm initial value (S.D.)	1000 ppm initial value (S.D.)
Free fluoride	123.3 (3.1)	140.7 (6.7)
With 3:1 (v/v) TISAB	68.3 (5.6)	192.3 (20.2)
Equivalent total fluoride	273.2 (22.4)	769.3 (60.6)

Table 5. Elemental composition of hydroxyapatite (atomic %) before and after exposure to aqueous stannous fluoride solutions as determined by SEM EDAX.

Element	As-received HA (atomic %)	HA exposed to 500 ppm SnF_2 (atomic %)	HA exposed to 1000 ppm SnF_2 (atomic %)
Ca	21.3	23.6	20.3
P	15.5	12.7	15.1
Sn	0.0	2.1	1.0

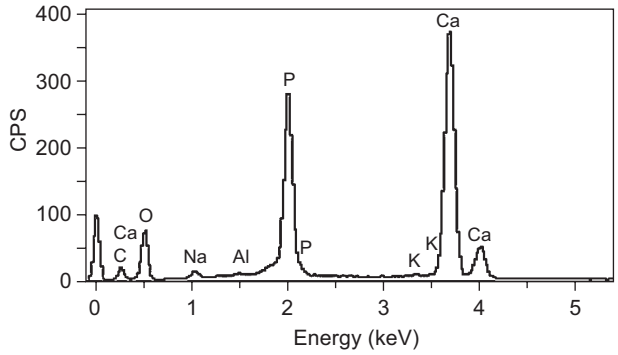

Figure 1. SEM EDAX data for as-received hydroxyapatite showing no peak for Sn.

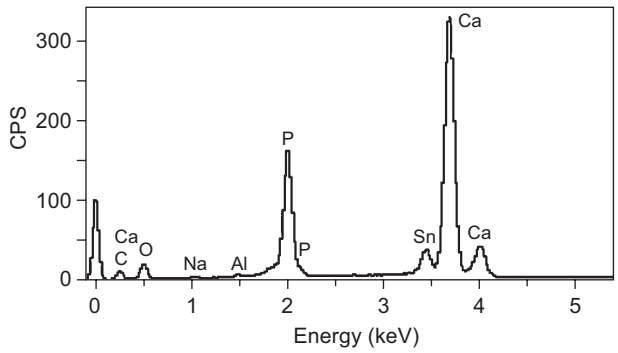

Figure 2. SEM EDAX data for hydroxyapatite exposed to SnF_2 solution (500 ppm with respect to fluoride) for 1 h showing small peak for tin at about 3.4 keV.

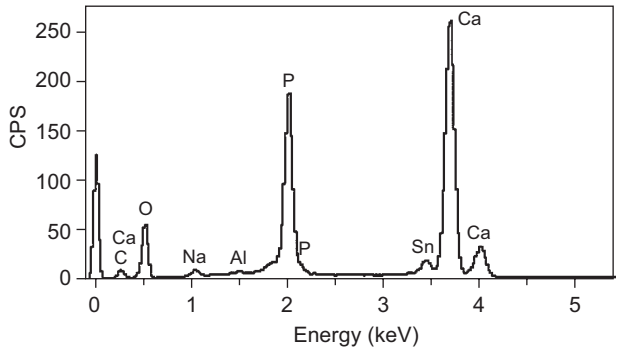

Figure 3. SEM EDAX data for hydroxyapatite exposed to SnF_2 solution (1000 ppm with respect to fluoride) for 1 h showing small peak for tin at about 3.4 keV.

DISCUSSION

The results for determination of free fluoride confirm previously published findings that solutions of stannous fluoride contain mainly complexed fluoride [33-35]. The overall conclusion from these published studies is that SnF_2 solutions do not contain free Sn^{2+} ions as such, and our results are consistent with this. A number of studies have attributed the anti-cariogenic effect of SnF_2 to the toxicity of Sn^{2+} ions [27-29], but since it seems that Sn^{2+} ions do not occur to any measurable extent in solutions of SnF_2, it seems more likely that any toxic effects are due to the various fluoro-tin species present, *i.e.* hydrated SnF_2, SnF^+ and SnF_3^-.

The determination of free fluoride in the present study allows the calculation of the equilibrium constant for the process:

$$SnF_2 \rightleftarrows SnF^+ + F^-$$

This assumes that the alternative possible equilibrium process:

$$2SnF_2 \rightleftarrows SnF^+ + SnF_3^-$$

occurs to a negligible extent, if at all, as suggested by experimental results obtained in previous studies [6]. Results for K_c at both 500 and 1000 ppm agreed within experimental error, showing that these solutions equilibrate rapidly. The values can be combined to give an overall value for K_c of 8.8×10^{-5} ($\pm1.2\times10^{-5}$) mol.dm^{-3}, a figure that shows that the equilibrium lies well to the left hand side. In other words, the majority of the stannous fluoride is present as un-dissociated hydrated SnF_2, as previously reported [33-35].

In the presence of hydroxyapatite powder, there was an increase in free fluoride concentration with time over the first 10-20 minutes, after which a new equilibrium was established. According to Le Chatelier's Principle, this means that the original equilibrium had been shifted to the right hand side, an effect that can be attributed to the removal of SnF^+ from solution by the hydroxyapatite. Such a loss of SnF^+ implies that tin is taken up by the hydroxyapatite, along with fluoride, a suggestion that was confirmed by the SEM results. Both samples of hydroxyapatite that had been exposed to SnF_2 solutions showed distinct peaks due to the presence of tin, yet these was no such peak in the as-received sample of hydroxyapatite. There appeared to be a slightly lower take-up of tin from the 1000 ppm solution than from the 500 ppm solution, but this was not considered significant, as the EDAX technique is only semi-quantitative. Of greater importance is the fact that some tin was detectable in both cases, when none was present in the original as-received sample of hydroxyapatite.

It is known that synthetic hydroxyapatite does not fully duplicate the composition and structure of naturally occurring hydroxyapatite [37-39]. The natural version is non-stoichiometric, with a high Ca:P ratio, and also contains between 3 and 8 % carbonate substitutions [39, 40]. These substitutions are important because they affect the chemical properties of the hydroxyapatite, decreasing the crystallinity and increasing the solubility [37-41]. However, there is sufficient similarity between synthetic and natural hydroxyapatite to enable the former to be used as a model for the latter in *in vitro* experiments.

A previous study using synthetic hydroxyapatite has shown that tin is taken up on exposure to aqueous solutions of SnF_2 [42]. The study used ^{119m}Sn Mőssbauer spectroscopy to monitor the tin and showed that both Sn(II) and Sn(IV) compounds were present on the hydroxyapatite, with Sn(II) species predominating. Peak splitting in the spectra implied that the species contained a covalent tin-fluorine bond, a result that is consistent with our proposal that SnF^+ is the main entity taken up. The precise interaction of the tin-fluoride species with the hydroxyapatite lattice is not clear, however, in particular whether it is taken up by passive diffusion or by incorporation into a new mineral phase deposited during remineralization. Further study is needed to elucidate this point.

In the present study, calculation of the fluoride loss from solution in the presence of hydroxyapatite at equilibrium shows it to have been equivalent to 226.8 ppm (±10.3 ppm) for the 500 ppm solution and 230.8 ppm (±16.5 ppm) for the 1000 ppm solution. In other words, the hydroxyapatite powder adsorbed the same amount of fluoride (to within experimental error) from both solutions. These values are equivalent to fluoride uptakes of 11.3 mg/g (±0.5 mg/g) and 11.5 mg/g (±0.8 mg/g) for 500 and 1000 ppm solutions respectively. This suggests that the hydroxyapatite has a finite number of sites at which SnF^+ can be taken up, and that both of the experimental concentrations supplied more than enough SnF^+ to occupy all of these sites.

There have been two recent *in vitro* studies that indicate the likely effect of uptake of SnF^+ on the behaviour of natural hydroxyapatite within the tooth structure. These studies have shown that tin was taken up by both enamel [43] and dentine [44], and that this uptake is associated with substantial reductions in extent of erosion of these tissues when the tooth was exposed to citric acid solution. In other words, uptake of the SnF^+ species has been found experimentally to have a distinct anti-erosion effect of its own, regardless of any possible toxic effect on oral bacteria [43, 44].

CONCLUSION

Aqueous solutions of SnF_2 have been shown by ion selective electrode measurements to contain only small proportions of free fluoride ions, with the majority of fluorine covalently bonded as either SnF^+ or un-dissociated SnF_2. This confirms previous findings in the chemical literature using a variety of techniques, including polarography and Mőssbauer spectroscopy.

Results for free fluoride concentration for nominal solutions at 500 and 1000 ppm fluoride enabled the equilibrium constant to be estimated for the reaction:

$$SnF_2 \rightleftarrows SnF^+ + F^-$$

Results were not significantly different for the two concentrations, showing that the system equilibrated rapidly, with an overall value of K_c of 8.8×10^{-5} ($\pm1.2\times10^{-5}$) mol.dm^{-3}. This shows that the majority of the stannous fluoride occurs as un-dissociated SnF_2, a conclusion which is consistent with previous findings.

Exposure of the stannous fluoride solutions to hydroxyapatite powder led to an increase in free fluoride ions in solution, showing that a tin-fluoride species was taken up by the hydroxypatite. This was confirmed using SEM EDAX, and supports previous observations using Mőssbauer spectroscopy that tin bonded covalently to fluoride is taken up in this system. Further work is necessary to elucidate the detailed mechanism of this uptake.

Various studies have shown that exposure of enamel and dentine to SnF_2 solutions increases their erosion resistance. We conclude that this relates to the ability of the mineral phase, hydroxyapatite, to take up SnF^+ ions. Stannous fluoride solutions may also be effective against dental caries as a result of the toxicity of the various tin-fluoride species that occur in solution towards cariogenic bacteria.

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