

Qualitative and Quantitative Tests for Stannous Fluoride

By JOHN J. HEFFERREN

A series of qualitative and quantitative assay procedures are presented for stannous fluoride. These data are the result of a cooperative project of the American Dental Association with the major manufacturers and users of stannous fluoride. The physical and chemical characteristics of stannous fluoride are described. The methods selected to define stannous fluoride and other methods which might be utilized are discussed.

STANNOUS FLUORIDE is an agent which has been used topically as a simple solution, in dentifrices, and in other mixtures to reduce the incidence of dental caries (1). This monograph is part of a continuing program to provide data on those drugs and chemicals which are described in "Accepted Dental Remedies." The tests are designed to be applied to stannous fluoride as such and to capsules and aqueous solutions containing stannous fluoride. The limits set in these tests are based on normal analytical and manufacturing variation.

It should be recognized that the particular tests and methods described do not necessarily represent those used by any particular firm, but rather those which have been selected as generally applicable. It is expected that there will be capsules or solutions of stannous fluoride containing interfering substances which will require modification of these methods. The terminology of the "United States Pharmacopeia" has been used wherever possible.

DESCRIPTION

Physical Properties.—Stannous fluoride (SnF_2 ; mol. wt. 156.70) is a white, crystalline solid with a bitter, salty taste, m.p. 212–214°, b.p. 845–855°. It is freely soluble in water and practically insoluble in alcohol, ether, and chloroform. The pH of an 8% aqueous solution is about 2.3.

Identity Tests.—Transfer to a small test tube about 100 mg. of stannous fluoride and dissolve in

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10 ml. of water. Mix on a spot plate 2 drops of this solution with 2 drops of 1% silver nitrate; a brown-black precipitate forms (presence of stannous ion).

Transfer to a small test tube 2 drops of mercuric chloride T.S. (6.5 Gm./100 ml. water) and add 1 drop of the above stannous fluoride solution; a white milky precipitate forms. Further addition of stannous fluoride solution gives a brown-black precipitate (presence of stannous ion).

Transfer 1 drop of the above stannous fluoride solution to a spot plate, add 1 drop of 0.001 *M* alizarin complexan and 1 drop of 0.001 *M* cerous nitrate; a lilac-blue color forms (presence of fluoride ion).

Purity Tests.—Dry about 1 Gm. of stannous fluoride, accurately weighed, at 105° for 4 hours; the loss in weight is not more than 0.5%.

Transfer 10 Gm. of stannous fluoride, accurately weighed, to a 400-ml. plastic beaker and add 200 ml. of water. Stir with a plastic rod for 3 minutes or until no more solid dissolves. Filter the mixture through a tared Gooch crucible tightly packed with asbestos fiber. Thoroughly wash first with about 50 ml. of 1% ammonium fluoride and then with about 200 ml. of water. Dry the residue at 105° for 4 hours and weigh. The water-insoluble residue does not exceed 0.2%.

ASSAY

Stannous Ion.—Place 200 ml. of water, 100 ml. of hydrochloric acid, and a few boiling chips in a 500-ml. Erlenmeyer flask. Boil the mixture for 10 minutes; add 0.25 Gm. of stannous fluoride, accurately weighed. In an inert atmosphere such as carbon dioxide or oxygen-free nitrogen, swirl the flask to dissolve the stannous fluoride, and cool the solution to room temperature. Add 5 ml. of starch T.S. and titrate in an inert atmosphere with 0.1 *N* potassium iodate to the blue starch end point. Each milliliter of 0.1 *N* potassium iodate is equivalent to 7.835 mg. of stannous fluoride. The amount of stannous fluoride, SnF_2 , is not less than 95.0% nor more than 105.0%.

Preparation of Potassium Iodate Titrant.—Transfer about 3.6 Gm. of potassium iodate in 200 ml. of oxygen-free water containing 1 Gm. of sodium hy-

dioxide and 10 Gm. of potassium iodide to a 1000-ml. volumetric flask; dilute with oxygen-free water to the mark and mix.

Standardization of Potassium Iodate Titrant.—Transfer 0.25 Gm. of reagent grade tin, accurately weighed, to a 500-ml. Erlenmeyer flask, add 100 ml. of hydrochloric acid, and 2 drops of 2% antimony trichloride, and allow the mixture to stand at room temperature until all the tin has dissolved. Carefully add 180 ml. of water and 10 ml. of sulfuric acid and mix. Add a nickel coil, prepared from a coiled piece of 3 × 6-in. reagent grade nickel sheet which has been washed with petroleum ether, boiled in 1:2 hydrochloric acid for 5 minutes and rinsed with water. (The coil should be treated with acid before each use.) Add 5 Gm. of hydrogen-reduced iron powder, and wash down the sides of the flask with water. Gently boil the mixture for 20 minutes in an inert atmosphere. Maintaining the inert atmosphere, cool the mixture to room temperature, add 5 ml. of starch T.S., and titrate with the potassium iodate titrant to the blue starch end point. Each milliliter of 0.1 *N* potassium iodate is equivalent to 5.935 mg. of tin.

Soluble Tin.—Transfer 0.1 Gm. of stannous fluoride, accurately weighed, to a 500-ml. volumetric flask. Add about 300 ml. of water, vigorously shake for about 5 minutes, fill to the mark with water, and mix. Filter a portion of the mixture through a piece of hard filter paper, discarding the first 10 ml. of filtrate. Transfer 2 ml. of the filtrate to a 50-ml. volumetric flask and add 10 ml. of 30% sulfuric acid and 5 drops of thioglycolic acid. Similarly, prepare a blank and three standard tin solutions containing 2, 5, and 10 ml., respectively, of *Standard Tin Solution B*, which contains 0.04 mg. tin/ml. Dilute each of these solutions with water to a total volume of 40 ml. Add 2 ml. of 2% sodium lauryl sulfate and gently swirl to mix with a minimum of foaming. With gentle swirling, add 2 ml. of *dithiol solution*, cool to room temperature, fill to the mark with water, and mix. Spectrophotometrically determine the absorbances of the solutions containing tin in 1-cm. cells at the maximum at about 530 $m\mu$ using the reagent blank as a reference. Prepare a plot of absorbance *versus* tin concentration using the absorbances of the standard tin solutions. Determine the tin concentration in the stannous fluoride solutions using this plot. The amount of stannous fluoride is not less than 95.0% nor more than 105.0%.

Preparation of Reagent.—*Standard Tin Solution A.*—Transfer 0.2 Gm. of reagent grade tin, accurately weighed, to a 1000-ml. volumetric flask and dissolve in 250 ml. of hydrochloric acid. Cool the solution to room temperature, fill to the mark, and mix. This solution is stable for about 1 month.

Standard Tin Solution B.—Transfer 50 ml. of *Standard Tin Solution A* to a 250-ml. volumetric flask, fill to the mark with water, and mix. This solution should be freshly prepared.

Dithiol Solution.—Transfer 0.15 Gm. of dithiol to a 100-ml. beaker, add 8 drops of thioglycolic acid, and 50 ml. of 2% sodium hydroxide, and stir to dissolve the dithiol. Filter the solution if it is not clear. The dithiol solution stored in a glass-stoppered bottle in the refrigerator is stable for about 1 week. The solution should be discarded if a precipitate forms.

Soluble Fluoride.—Transfer 0.2 Gm. of stannous fluoride, accurately weighed, to a 100-ml. volumetric flask. Add about 70 ml. of water, vigorously mix for about 5 minutes, fill to the mark with water, and mix. Transfer 10 ml. of this solution to a 100-ml. volumetric flask, fill to the mark with water, and mix. Transfer 10-ml. of the last solution to a third 100-ml. volumetric flask, fill to the mark with water, and mix. Prepare a standard fluoride solution containing 10 mcg./ml. of fluoride ion using sodium fluoride reagent. Transfer 1, 2, 3, and 4 ml. of the standard fluoride solution and 5 ml. of the final stannous fluoride solution to 100-ml. volumetric flasks. Add 10 ml. of zirconium-SPADNS reagent to each of the above volumetric flasks plus a flask for the blank, fill to the mark with water, and mix. Spectrophotometrically determine the absorbances of the blank and fluoride-containing solutions in 1-cm. cells at the maximum at about 590 $m\mu$ using SPADNS reference solution as a reference. Prepare a plot of absorbance *versus* fluoride concentration using the absorbances of the sodium fluoride solutions. Determine the concentration of fluoride in the stannous fluoride solution using this plot. The amount of stannous fluoride is not less than 92.0% nor more than 108.0%.

Reagents.—*Solution A.*—Dissolve 3.16 Gm. SPADNS [4,5-dihydroxy-3(*p*-sulfophenylazo)-2,7-naphthalenedisulfonic acid, trisodium salt, Eastman No. 7309] in 550 ml. of water.

Solution B.—Transfer 0.133 Gm. of zirconium oxychloride octahydrate, $ZrOCl_2 \cdot 8H_2O$, to a 500-ml. volumetric flask and dissolve in 50 ml. of water. Add 350 ml. of hydrochloric acid, fill to the mark with water, and mix.

SPADNS Reference Solution.—Dilute 50 ml. of *Solution A* with 500 ml. of water and 35 ml. of hydrochloric acid. The SPADNS reference solution is stable.

Zirconium-SPADNS Reagent.—Mix equal volumes of *Solutions A* and *B*. The resulting solution stored in an amber bottle is stable.

DOSAGE FORMS

Capsules

Identity and Purity Tests.—Capsules of stannous fluoride respond to the identity tests in the monograph for stannous fluoride.

Assays—Stannous Ion.—The stannous ion as determined by the procedure in the monograph for stannous fluoride is not less than 90.0% nor more than 110.0% of the labeled amount.

Fluoride Ion.—The fluoride ion as determined by the procedure in the monograph for stannous fluoride is not less than 90.0% nor more than 110.0% of the labeled amount.

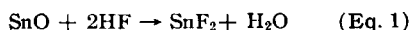
Solutions

Solutions of stannous fluoride respond to the identity tests and assay methods described in the monograph for stannous fluoride. Solutions of stannous fluoride should be prepared from oxygen-free purified water and used immediately.

DISCUSSION

Nebergall and co-workers prepared stannous fluoride in 86% yield by reacting stannous oxide

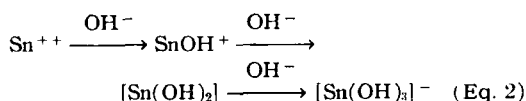
moistened with oxygen-free water with a 10% molar excess of 48% hydrofluoric acid (2). This is



an exothermic reaction from which the stannous fluoride crystallizes as the reaction mixture cools. Stannous fluoride is also prepared by reacting powdered tin with anhydrous hydrogen fluoride (3, 4).

From studies of stannous fluoride as an ingredient in solid fuels containing uranium or plutonium fluoride, Thamer and Meadows (5) found that dry stannous fluoride was unusually stable under essentially anhydrous conditions or those of low humidity. Molten stannous fluoride at 650° in an oxygen-free atmosphere in a mechanically-shaken, platinum-lined bomb did not undergo decomposition after 3 months. In the reverse reaction, tin and stannic fluoride in a similar bomb at 700° for 2 hours were substantially converted to stannous fluoride. In this work, the melting and the boiling points of stannous fluoride were reported as $213 \pm 1^\circ$ and $850 \pm 5^\circ$, respectively. During the boiling point determination in a copper still, about 3% of the distillate was oxidized to the oxyfluoride, SnOF_2 .

Stannous fluoride and the other stannous halide salts exhibit many similar physical and chemical properties (6). Stannous fluoride solutions probably contain Sn^{++} , SnF^+ , SnF_2° , SnF_3^- ; the existence of SnF_4^{--} is considered to be possible but not likely. If an excess of fluoride is present in the solution, the SnF_3^- entity is more prevalent. The stannous fluoride in aqueous solutions undergoes hydrolysis to form the sparingly soluble stannous hydroxide which gives the solution a cloudy appearance. In this hydrolysis reaction, a number of entities, as indicated by Eq. 2, can exist. The sparingly soluble stannous hydroxide, represented for simplicity as $\text{Sn}(\text{OH})_2$, may lose water to form stannous oxide. In the presence of oxygen or oxidizing agents, the stannous ion undergoes oxidation to form the stannic ion.

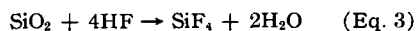


Stannous fluoride is freely soluble in water (7, 8). The solubility of stannous fluoride in solutions maintained at temperatures from 0 to 106° (the boiling point) is a straight line relationship (Fig. 1) (7). The specific gravity of a saturated solution of stannous fluoride at 25° is about 1.51; thus a saturated solution at 25° contains about 63% stannous fluoride, weight by volume (63 Gm./100 ml.).

Typical pH values of freshly prepared stannous fluoride solutions are given in Table I.

In general, the pH of a stannous fluoride solution gradually decreases on standing, and this decrease is accompanied by the formation of insoluble hydrolysis products.

Acidic fluoride solutions can etch the surface of the glass electrode, thereby reducing the electrode life. This reaction (Eq. 3) can be a problem in



solutions containing 1% or more of stannous fluoride.

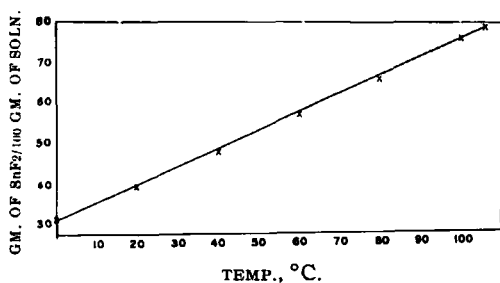


Fig. 1.—The solubility of stannous fluoride in water as a function of the temperature of the solution.

TABLE I.—pH OF FRESHLY PREPARED STANNOUS FLUORIDE SOLUTIONS

8%—2.3	2%—2.8
5%—2.5	1%—3.0
0.4%—3.2	

When the glass electrode is used to determine the pH of stannous fluoride solutions, the pH meter should be standardized with two buffer solutions. This procedure will reduce the possibility that a damaged glass electrode can be standardized at the pH of one buffer and still be inaccurate over a relatively small pH range. The sleeve-type reference electrode is preferred for measuring the pH of stannous fluoride solutions because the flow rate of electrolyte is much faster. There is a tendency for the small orifice containing the asbestos thread at the tip of the fiber-type reference electrode to become blocked. The pH of stannous fluoride solutions should be measured quickly to reduce the exposure of the electrodes to the solutions.

Stannous fluoride is somewhat more stable than stannous chloride and both are more stable in acidic solutions. The results of an early study with stannous chloride and fluoride are shown in Fig. 2. The solutions were freshly prepared and assayed immediately after the adjustment of the pH with sodium hydroxide. The assay procedure included centrifugation to remove the insoluble material,

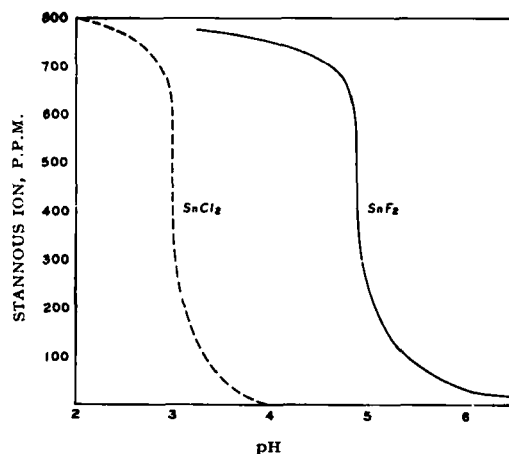


Fig. 2.—Stannous ion concentration of stannous chloride and fluoride (1000 p.p.m. Sn^{++}) solutions after adjustment of the pH of the solution with sodium hydroxide.

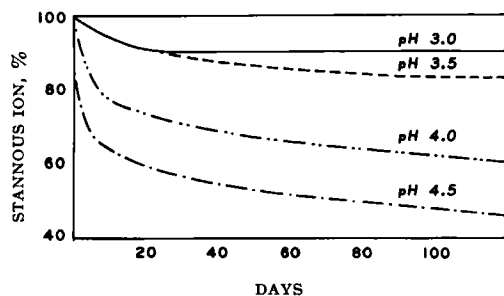


Fig. 3.—Effect of aging on stannous ion concentration in 0.4% aqueous solutions of stannous fluoride. The pH of the solutions was adjusted with sodium hydroxide.

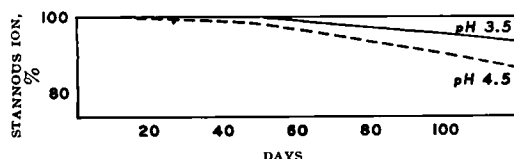


Fig. 4.—Effect of aging on stannous ion concentration of 0.4% stannous fluoride in an equal volume mixture of glycerin and water. The pH of the solutions was adjusted with sodium hydroxide.

then an iodine titration of the soluble stannous ion. In this early study, the soluble stannous ion content at the native pH of stannous chloride and fluoride was only about 85% of the theoretical value of 1000 p.p.m. This initial loss was probably because of a number of factors, including the purity of the particular samples of the stannous salts. As the pH's of the stannous chloride and fluoride solutions were raised from their native values around pH 3, the soluble stannous ion concentration dropped rapidly.

The effect of aging 0.4% aqueous solutions of stannous fluoride at different pH values is shown

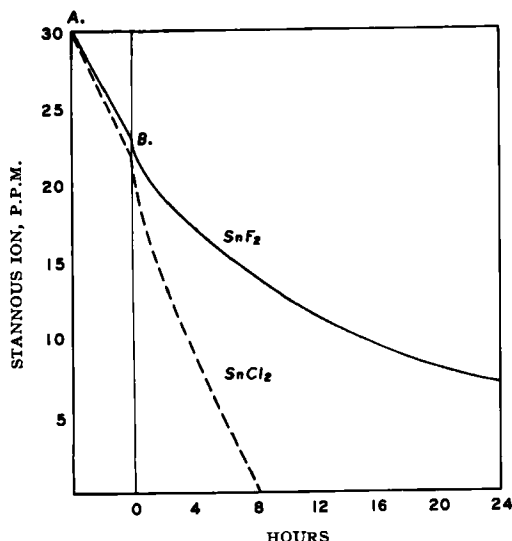


Fig. 5.—Stannous ion concentration of 0.0048% stannous chloride (30 p.p.m. Sn^{++}) and 0.004% stannous fluoride (30 p.p.m. Sn^{++}) at the time of dispensing into animal bottles and upon aging in these bottles. Key: A, initial concentration; B, concentration at time of dispensing.

in Fig. 3. The pH of these stannous fluoride solutions was adjusted with sodium hydroxide, and the solutions stored in plastic bottles under an inert atmosphere. The plastic bottles then were stored in glass containers under an inert atmosphere. Here again, the greater stability of the soluble stannous ion in solutions at the native pH of stannous fluoride was demonstrated.

The effect of adding glycerin or other highly water-soluble materials such as sugars, gums, etc., to stannous fluoride solutions is shown in Fig. 4. These stannous fluoride solutions were aged under the same conditions as those described in Fig. 3. When glycerin and these other materials are added, the activity of the free stannous ion is reduced; thus the rate of hydrolysis is reduced.

The stability data on the soluble stannous ion concentration in solutions of stannous fluoride in Figs. 3 and 4 were obtained from solutions prepared with degassed, distilled water stored in plastic containers under an inert atmosphere. With these conditions, the primary decomposition reaction is that of hydrolysis. The oxidation of the stannous ion is kept at a minimum. Stannous fluoride solutions stored without an inert atmosphere or in glass bottles decompose much more rapidly because three routes of decomposition are possible—hydrolysis, oxidation, and reaction with glass. In all such stability studies with stannous salts, it is important to centrifuge the solutions before assaying soluble stannous ion iodimetrically. The colloid-like, insoluble stannous hydroxide formed in a hydrolysis reaction is solubilized by the acidic iodimetric titration medium and thus is determined as soluble stannous ion.

As is true with most compounds, stannous fluoride is more stable in concentrated solutions. In animal experiments utilizing the drinking water as a route of administration, the exposure of very dilute solutions of stannous fluoride to the atmosphere can result in a significant loss in the soluble stannous ion. Francis (9) observed that the concentration of soluble stannous ion in mixtures containing an initial concentration of 30 p.p.m. decreased rapidly within a few hours (Fig. 5). In these experiments with rats, the solutions were prepared in the morning and transferred immediately to the usual liquid dispensing bottles of laboratory animal cages. As a result of the significant loss in soluble stannous ion concentration, it would be very easy to obtain misleading animal data. For this reason, Francis suggested that the stannous salts be administered topically rather than in the drinking water.

In all these stability studies, the concentration of soluble stannous ion was reported as a function of time, pH, or both. In these solutions, which contained essentially no foreign cations, the soluble fluoride remained relatively constant. Introduction of soluble calcium salts or calcium salts solubilized by the acidity of the solutions can significantly reduce the soluble fluoride ion concentration by the formation of calcium fluoride. The reduction in the soluble fluoride concentration reduces the overall complexing effect of the solution and therefore the stannous ions are more susceptible to hydrolysis.

Qualitative Tests.—There are many identity tests in standard chemistry texts for the stannous and fluoride ions of stannous fluoride. The two tests for stannous ion in the monograph are oxida-

tion-reduction reactions involving the oxidation of stannous to stannic ion and the reduction of silver and mercuric ions to the respective metals. By adding the stannous fluoride solution dropwise to mercuric chloride, it is possible to see the formation of the intermediate white mercurous chloride, which is then further reduced.

The reaction of fluoride with the cerium or lanthanum complex of alizarin complexan (3-aminomethylalizarin-N,N-diacetic acid) is one of the few, if not the only positive colorimetric response to fluoride ion. The alizarin complexan was prepared by Belcher and co-workers by a Mannich-type condensation of alizarin, iminoacetic acid, and formaldehyde (10). The alizarin complexan is now available from Burdick & Jackson Laboratories of Muskegon, Mich.

Polarography.—Polarography is one of the most important techniques for the detailed study of stannous fluoride alone and in combination with other agents. The hydrolysis of stannous fluoride is an example of a reaction which can be studied polarographically. The stannous ion in aqueous stannous fluoride solutions readily undergoes complex formation and partial or complete hydrolysis. Partial hydrolysis is a form of complexing in which the average number of hydroxyl groups bound per stannous ion is less than two. Polynuclear complexes involving Sn—OH—Sn bonds are frequent products of partial hydrolysis when no large excess of fluoride or other complexing anion is present.

Polarographically, freshly prepared stannous fluoride solutions (0.001 to 0.01 *M* stannous fluoride in 0.1 *M* potassium perchlorate) at or below their natural pH generally yield reversible cathodic waves at half-wave potentials of -0.45 to -0.50 volts (D.M.E. versus S.C.E.). Typical values of $i_d/Cm^{2/3}t^{1/6}$ are 3.7 to 4.4 at 25°. The presence of Sn—OH bonds and polynuclear complexes affects both the half-wave potential and the diffusion current. The polarographic behavior of any particular solution depends on the history of the stannous fluoride used—for example, its exposure to moist air, as well as the pH, ionic strength, and age of the solution. Aging of the solution or the presence of other complexing agents often leads to irreversible reduction waves.

Maxima sometimes observed in the reduction waves can usually be suppressed by addition of 0.001 to 0.01% gelatin. Complete suppression of the maxima sometimes lowers the overall diffusion current to a measurable degree.

With extremely rigorous control of manipulative variables, including careful exclusion of dissolved air from solutions, it is possible to use polarography for quantitative analysis of stannous ion in stannous fluoride solutions; however, the relatively simple iodimetric method is usually preferred. The main usefulness of polarography is in detecting and measuring changes in the nature of the soluble stannous species caused by complexing, including hydrolytic reactions.

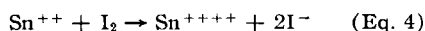
The references (11–13) do not deal specifically with polarography of stannous fluoride but do contain extensive background information about the hydrolysis of stannous fluoride, fluoride complexes of stannous ions, and polarography of tin ions under various conditions.

Amalgam-Electrode Potentiometry.—Potentiometry with a tin amalgam electrode is a technique allied to polarography that has been useful in study of tin complexes (14). From a measurement of the equilibrium potential between stannous ions in solution and tin in the amalgam, the amounts of free and complexed stannous ions can be calculated. The situation is analogous to measurement of half-wave potentials in polarography. The potentiometric method has been used to measure the stabilities of polynuclear hydroxy complexes of tin in solutions of stannous perchlorate.

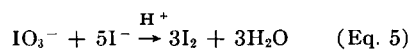
Purity Tests.—The purity test involving loss of weight on drying at 105° may be a measure of the hydrogen fluoride as well as the moisture content of the sample because hydrogen fluoride or hydrofluoric acid is used in the manufacture of stannous fluoride. The water-insoluble materials are usually the sparingly soluble hydrolysis products of stannous fluoride.

The metallic impurities in stannous fluoride can be determined spectrographically or colorimetrically (15). In the spectrographic procedure, the fluoride is usually removed by treatment with nitric acid in a platinum crucible. The usual limits placed on these materials in stannous fluoride are: iron–0.05%, nickel–0.05%, copper–0.01%, lead–0.005%, antimony–0.005%, and arsenic–0.0003%. The total of these materials should be less than 0.1%.

Assays.—The iodimetric determination of stannous ion is not a specific method; however, in most situations it is a convenient and generally applicable method (15). The titration depends upon the



reaction of iodine with stannous ion to form iodide and stannic ions, respectively. The two commonly used iodine titrants are an iodine solution containing potassium iodide to solubilize and reduce the volatilization of the iodine and slightly alkaline iodate solution containing potassium iodate and iodide. The iodate-iodide reagent releases iodine



when added to the acidic titration medium (Eq. 5). The iodate titrant requires an acidic titration medium; the iodine titrant does not. Although the iodate reagent is generally considered to be somewhat more stable, both reagents should be stored in amber bottles and standardized at reasonable intervals.

Because the stannous ion is easily oxidized by the oxygen in air, it is important to carry out the titration in an inert atmosphere such as carbon dioxide or oxygen-free nitrogen. Specially purified nitrogen can be purchased as such or prepared by passing the nitrogen over heated copper turnings or through Fieser's hydrosulfite solution (16). A good quality deionized or distilled water should be used in all the assays. The water used in the preparation of the reagents should be made oxygen-free by boiling and cooling under an inert atmosphere or by degassing with purified nitrogen. Polarographic measurements suggest that the degassing procedure is somewhat more efficient in removing the oxygen.

Since there are a number of variables which can affect the iodimetric determination of stannous

fluoride, it is important to standardize the titrant using conditions and reagents as similar as possible to those used in the actual titrations. The most common method of standardizing the titrant is the use of reagent grade tin (15). Another standard which may sometimes be more convenient is sodium thiosulfate. The sodium thiosulfate reagent which has been standardized against arsenic trioxide or other suitable reference standard is especially useful in standardizing very dilute titrants.

Starch is the most common indicator for iodimetric titrations. The presence of detergents in the titration medium may interfere with the colorimetric end point by absorbing the starch. With these mixtures and others containing color interfering agents, the iodimetric titration can be followed potentiometrically with a potentiometer and a set of platinum and glass electrodes or a platinum combination electrode. This particular titration is quite suitable to a number of automatic and semiautomatic titration setups. Using the potentiometric or colorimetric starch end point, it is possible to titrate with iodine titrants with a normality as low as 0.005.

Since the iodimetric procedure is basically an oxidation-reduction procedure, any agent which can act as an oxidizing or reducing agent can interfere with the titration. A more specific method for the determination of tin is reaction with dithiol to form the red tin-dithiol complex which absorbs at about 530 $m\mu$ (15, 17).

The ion exchange method for the fluoride in stannous fluoride is a nonspecific assay which is useful in routine manufacturing control. In this method, the tin ion is reacted with the acid form of strongly acidic cation exchange resin such as Dowex 50W-X8 to release hydrogen ions. The hydrofluoric acid formed by the reaction is then titrated with standard base to the phenolphthalein end point. Because of the hydrofluoric acid formed in this reaction, plastic laboratory equipment should be used for this assay. Other halide salts and many other salts can interfere with the assay by participating in the exchange reaction with the resin.

A recent review describes the many methods which are available for the determination of fluoride (18). One of the major problems in the determination of fluoride is the separation of the fluoride from other interfering ions, such as calcium, phosphate, and sulfate, which are frequently present with fluoride in biological and other materials. Although ion exchange, paper chromatography, and other methods have been used for the separation of fluoride from interfering ions, the three most important procedures have been perchloric acid distillation, pyrolytic decomposition, and perchloric acid diffusion. The carefully controlled perchloric acid distillation of the fluoro-silicon compound usually described as fluosilicic acid (H_2SiF_6) has been one of the most widely used procedures (19). This procedure has been modified for micro work by utilizing nitrogen instead of steam as a carrier gas for the distillation, thereby greatly reducing the volume of distillate required for complete recovery of the fluoride (20). Separation by pyrolysis depends upon the hydrolytic decomposition of halides at about 1000° in the presence of superheated steam (21, 22). The most recent method of separation is the diffusion of hydrogen fluoride gas formed by the reaction of the

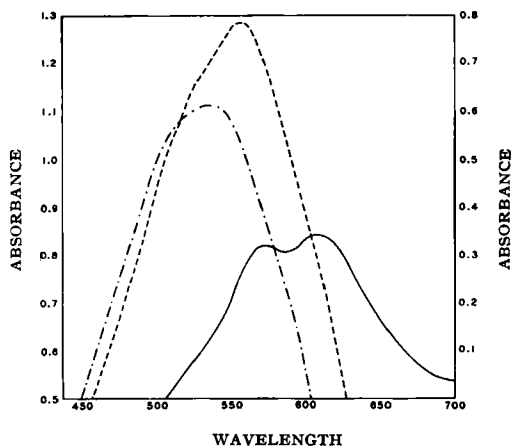


Fig. 6.—Spectra of lanthanum-alizarin complexan (reagent) and its fluoride adduct. Key: —, reagent vs. water (abs. 0.5 to 1.5); ----, reagent-fluoride vs. water (abs. 0.5 to 1.5); and —, reagent-fluoride vs. reagent (abs. 0 to 1.0).

fluoride in the sample with perchloric acid (23). From the standpoint of equipment required and overall simplicity, the diffusion method, which utilizes plastic micro Conway dishes, is the preferable method of separating the fluoride. After the fluoride has been separated from the interfering ions, a wide variety of methods can be utilized for the determination.

The reaction of fluoride with lanthanum or thorium chloranilates has been utilized for fluoride determinations (24, 25). The insoluble chloranilate salts react with fluoride to form the soluble chloranilic acid and the corresponding insoluble fluoride salt. The concentration of the solubilized chloranilic acid is then determined by the absorbance at two different wavelengths depending upon the fluoride concentration, for example, 2 to 100 p.p.m., 530 $m\mu$, 0.5 to 3 p.p.m., 330 $m\mu$. While the chloranilate methods are not sensitive to most common anions, except for phosphate, the methods utilize a two-phase system with its consequent disadvantages.

The reaction of cerium or lanthanum alizarin complexan with fluoride is one of the few positive color reactions for fluoride. Unlike most bleaching methods involving a decrease in absorption as the fluoride ion concentration increases, the reaction of the cerium or lanthanum complex with fluoride results in an increase in absorption and a shift in wavelength of the maximum. The cerium complex of alizarin complexan (3-aminomethyl-alizarin-N,N-diacetic acid) is red with an absorption maximum in water at about 495 $m\mu$ (26). The reagent reacts with fluoride to form a blue-purple color with a maximum at about 567 $m\mu$. The wavelength for the colorimetric determination is at about 610 $m\mu$. At this wavelength, the maximum difference between the absorption spectra of the fluoride-containing complex and the cerium chelate occurs. The spectra of the corresponding lanthanum compounds are illustrated in Fig. 6. The wavelength of the maximum for this method and for any colorimetric method should be determined for each instrument and with each lot of dye. The stability of this

blue fluoride complex has been increased by using acetonitrile-water (1:5) mixture as a solvent for the color reaction (27).

The colorimetric methods which depend on the bleaching of the color of metal chromophoric combinations due to the stronger complexing of the metal ion by fluoride are older and generally more widely used fluoride methods. The zirconium-alizarin red S mixture utilizes color measurement at 520–525 $m\mu$ (28). The alizarin red S reaction product with fluoride has also been titrated with thorium nitrate, which depends upon the formation of the insoluble thorium fluoride (28). Two other zirconium lakes which have a low sensitivity to foreign ions and a high sensitivity to fluoride are the zirconium-eriochrome cyanine R (29) and zirconium-SPADNS [4,5-dihydroxy-3-(*p*-sulfophenylazo)-2,7-naphthalenedisulfonic acid, trisodium salt] (30). The SPADNS reagent, which is stable indefinitely, has increased sensitivity to fluoride when the molar ratio of zirconium to SPADNS is 1 to 12 (23).

Stannous ion does not interfere with the zirconium-SPADNS color reaction. Thus, it is possible to determine the soluble fluoride in a particular sample of stannous fluoride by simply dissolving the sample in water and diluting to a fluoride concentration ordinarily used in this procedure, 1–4 mcg./ml. When there is any doubt about the composition or contaminants of the sample, it is much safer to separate the fluoride from the rest of the sample before the determination.

Commercial detergents used for cleaning laboratory ware usually contain phosphate or sulfate ions, which interfere with most fluoride methods. Thus, it is important that the rinsing subsequent to washing the laboratory ware be adequate to remove all traces of these interfering ions.

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