Specific Ion Electrode Determination of Fluoride in Multivitamin Preparations

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Abstract □ A simple, rapid, and specific method for direct determination of ionized fluoride in multivitamin preparations is described. Samples and fluoride standards, prepared in a high-ionic strength buffer solution (1 *M* tris–HCl buffer), are measured directly using a fluoride-specific ion-activity electrode. Total ionized fluoride in the measured sample solution is obtained from a standard fluoride calibration curve. The time required for electrode recalibration and subsequent analysis is significantly reduced by using the indicated single-point technique of standardization and determination. Precision and accuracy studies are included.

Keyphrases □ Multivitamin products—fluoride analysis □ Fluoride determination—multivitamin products □ Ion-activity electrode, specific—fluoride analysis

Previously, procedures for determining fluoride at the low concentrations found in multivitamins and other pharmaceutical preparations required prior separation followed by titrimetric or colorimetric determination of the resultant fluoride salt (1–8).

The development of a solid-state fluoride-activity electrode by Frant and Ross (9) now makes it possible to measure, directly or titrimetrically, fluoride activity or concentration in solution. The electrode, which contains a single lanthanum fluoride crystal (doped with Eu^{+2}) cemented into a plastic tube, basically functions as a highly sensitive and rapid fluoride-sensing membrane. A detailed description of the electrode and its operating principle has been previously reported (9, 10). Use of the electrode as an end point detector for potentiometric titration of fluoride ions with thorium, lanthanum, and calcium and the behavior of the electrode in alcoholic and acidic media was reported by Lingane (10, 11). The electrode has been used to determine fluoride concentration and/or activity in chromium-plating baths (12), highly acidic media (11, 13), tungsten samples (14), water samples (15), bone (16), and toothpaste (17).

In this report, the electrode was used to directly measure fluoride in multivitamin preparations. Since electrode response to fluoride activity can be influenced by total ionic strength, pH, and complex formation of fluoride with other ions such as Ca^{+2}, Fe^{+3}, and Al^{+3} in acidic solutions, optimum ionic strength and pH conditions had to be maintained. The use of a 1 *M* buffer solution (pH = 7.5) minimized ionic strength differences between sample and standard solutions, avoided other inherent problems, and resulted in a rapid, simple, and accurate method for determining fluoride in liquid and solid multivitamin preparations.[1,2]

[1] Liquid multivitamin preparations were Vi-Penta F Multivitamin Drops (herein referred to as Formulation *A*) and Vi-Penta F Infant Drops (herein referred to as Formulation *B*).

[2] Solid multivitamin preparations were Vi-Penta F Zestabs.'

EXPERIMENTAL

Reagents

Standard Fluoride Stock Solution—Exactly 2.211 g. of sodium fluoride, analytical reagent grade,[3] previously dried at least 24 hr. in an oven at 100–110° was accurately weighed, transferred to a 1-l. volumetric flask, and dissolved in about 200 ml. of demineralized water. One milliliter of 0.1 *N* NaOH (USP) was added and the solution was diluted to volume with demineralized water. This solution contained 1.0 mg. of fluoride/ml.

Working Standard Fluoride Solutions—Fluoride standard solutions, equivalent to 0.08, 0.12, 0.16, and 0.20 mg. of fluoride in 100 ml. were prepared by diluting the stock fluoride solution with tris buffer solution (TBS). These solutions were prepared fresh daily.

Tris Buffer Solution (TBS)—Five hundred milliliters of 1 *M* tris(hydroxymethyl)aminomethane, primary standard grade, was mixed with 403 ml. of 1 *M* HCl (USP) in a 1-l. volumetric flask and diluted to volume with demineralized water. The pH of this solution was 7.5 ± 0.1.

All reagent solutions were made with demineralized water to ensure minimum amounts of trace fluoride.

Apparatus

A fluoride-specific ion electrode,[4] in conjunction with a calomel reference electrode[5] (glass sleeve) was used with research digital pH meter[6] for potential measurements.

Assay Procedure

Sample Preparations—*Tablets*—Accurately weigh a finely ground portion of tablet mass equivalent to 0.5–0.6 mg. of fluoride and transfer to a 100-ml. volumetric flask. Add 70–80 ml. of TBS to the flask and heat on steam bath for 20–30 min. Cool the sample to room temperature and make up to volume with TBS. Transfer a portion of this solution to a 50-ml. glass-stoppered centrifuge tube and centrifuge for about 10 min. Pipet a 20-ml. aliquot of the centrifuged sample solution into a 100-ml. volumetric flask and dilute to volume with TBS.

Drops—Using a clean dry syringe, equipped with a 13-gauge blunt-edged stainless steel needle, exactly fill a volumetric flask or a graduated cylinder (10-ml. capacity or appropriate size) with sample solution equivalent to 8.0–10.0 mg. fluoride (exclude all air bubbles). Transfer the sample, without delay, to a 250-ml. volumetric flask containing about 100 ml. of TBS. Caution: since liquid multivitamin preparations are usually acidic (pH = 3), minimize contact time of the unbuffered sample solutions with glassware to prevent a loss of fluoride by reaction with the glass. Rinse the volumetric flask or graduated cylinder at least four times and add the rinse solutions to the sample solution in the 250-ml. volumetric flask. Dilute sample to volume with TBS and mix well. Pipet exactly 4 ml. of this solution into a 100-ml. volumetric flask and dilute to volume with TBS.

Potential Measurements—Transfer the solution to be measured to a 150-ml. beaker containing a polytetrafluorethylene[7]-coated stirring bar. (Although plastic lab-ware is not required, it is recommended particularly for sample containment during potential measurements.) Immerse the fluoride-specific ion and reference electrodes and measure the millivolt potential with constant stirring. Use a stirrer with an insulated top or with an asbestos pad to reduce heat transfer to solutions being stirred. Allow 1–2

[3] J. T. Baker Chemical Co., Phillipsburg, N. J.
[4] Orion, model 94-09.
[5] Sargent, model S-30084-15.
[6] Orion, model 801.
[7] Teflon.

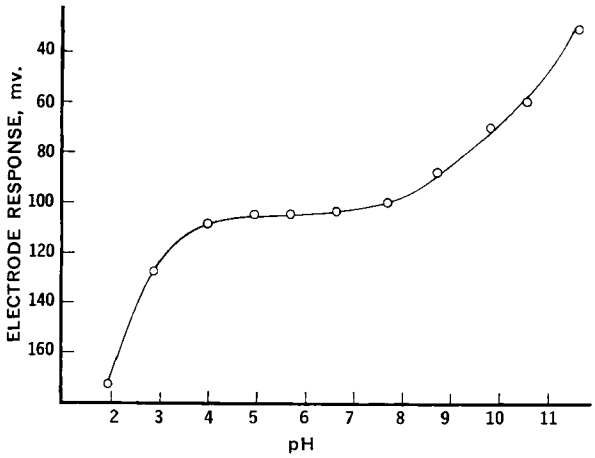

Figure 1—*Standard fluoride calibration curve.*

min. for each measurement or take a final reading when the potential has stabilized within ±0.1 mv. Measure the working standard solutions first, beginning with the lowest fluoride concentration, *i.e.*, 0.08 mg./100 ml.

Plot fluoride concentration (mg./100 ml.) *versus* millivolts for each working standard solution on semilogarithmic paper (1 cycle × 70 divisions). The fluoride concentration in the measured sample solution is determined directly from this graph.

Alternately, the potentials observed for the standard solutions can be used to obtain a least-squares line represented by the equation:

$$y = mx + b \qquad \text{(Eq. 1)}$$

where y = potential in millivolts, x = log of fluoride concentration in mg./100 ml., m = slope, b = intercept.

The potential obtained for the sample solution is substituted in Eq. 1 and the equation is solved for (x). The antilog of (x) equals the fluoride concentration of the measured sample solution.

Table I—Added Fluoride Recoveries from Sample Blanks of Multivitamin Tablets[a]

Sample	Fluoride Added, mg.	Fluoride Recovered, mg.	% Fluoride Recovered
1	0.050	0.0497	99.4
2	0.508	0.058	100.0
3	0.050	0.0487	97.4
4	0.050	0.051	102.0
5	0.050	0.0494	98.9
6	0.050	0.0485	97.0
7	0.050	0.0498	99.6
8	0.050	0.0495	99.0

[a] Sodium fluoride solution equivalent to indicated amount of added fluoride was added to multivitamin tablets containing no fluoride.

Table II—Added Fluoride Recoveries from Multivitamin Drops in the 4.2–10.5 × 10^{-5} *M* Range[a]

Sample[b]	Fluoride Added, mg.	Fluoride Recovered, mg.	% Fluoride Recovered
A 1	3.0	3.05	101.6
A 2	4.0	3.99	99.8
A 3	5.0	4.93	98.6
A 4	6.0	5.92	98.7
A 5	7.0	6.88	98.3
B 1	3.0	3.05	101.6
B 2	4.0	3.99	99.8
B 3	5.0	4.97	99.4
B 4	6.0	5.92	98.7
B 5	7.0	6.91	98.7

[a] Aliquots of multivitamin drops without fluoride diluted with TBS after addition of sodium fluoride solution. [b] A was equivalent to Formulation *A* without fluoride and B was equivalent to Formulation *B* without fluoride.

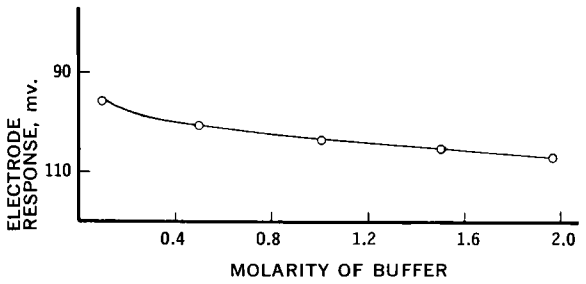

Figure 2—*Electrode response as a function of buffer molarity at constant fluoride concentration (3.16 × 10^{-5}M).*

Single-Point Standard Comparison—If the slope of the concentration curve remains fairly constant (±2 mv.), the standard curve or the corresponding slope (m) and intercept (b) values may be used as a fixed calibration for single-point reference standardization as follows.

Prepare a standard fluoride solution as previously described, equivalent to 0.12 mg. fluoride in 100 ml. With a digital pH meter or equivalent, set the dial (functional switch) in the relative millivolt position and measure the potential of this solution as previously described. Adjust the meter using the calibration control to read the exact potential (y), calculated from Eq. 1 or read directly from the fluoride-concentration curve.

For fluoride concentration in the measured sample solution, take the antilog of (x) calculated for the corresponding (y) using Eq. 1 or read fluoride concentration directly from the standard curve.

RESULTS

Linearity of Response—Electrode response to fluoride was linear throughout the working range of 4.2–10.5 × 10^{-5} *M* or 0.08–0.20 mg. F^-/100 ml. (see Fig. 1). When known amounts of fluoride (NaF) were added to sample blanks, the resulting measurements corresponded to quantitative recoveries of the added fluoride (see Tables I and II).

Effect of Buffer Solutions—The effect of buffer (TBS) concentration on millivolt readings was evaluated at 3.16 × 10^{-5} *M* fluoride. The results (see Fig. 2) indicated that at approximately 1 *M* total ionic strength, the change in millivolt readings due to change in total ionic strength was minimized. In addition, the time required to achieve constant readings in 1 *M* TBS was found to be a function of fluoride concentration, *i.e.*, the time required decreased with increased fluoride concentrations (see results listed in Table III). Although constant millivolt readings were obtained faster with stirring in 1 *M* buffer (TBS) solution, the potential difference between stirred and unstirred solutions was found to be less than ±1 mv. However, potential measurements made with constant stirring were more reproducible.

Table III—Time Required for Constant Reading as a Function of Fluoride Concentration in 1 *M* TBS Buffer[a]

F^- Concn., mg./100 ml.	1st Potential Measurement, mv.	Time (min.) Required for Constant Reading[a]	2nd Potential Measurement, mv.	Time (min.) Required for Constant Reading[a]
0.02	+125.9	14	+125.3	16
0.04	+112.3	5	+111.9	3
0.05	+107.3	1.8	+107.1	1.8
0.06	+103.4	2	+103.3	1.5
0.08	+97.0	1.8	+96.8	1.5
0.10	+91.7	1.8	+91.5	1.3
0.14	+83.4	1.7	+83.5	1
0.16	+80.1	1.5	+80.0	1
0.18	+77.4	1.5	+77.4	1
0.20	+74.6	1.3	+74.6	0.7

[a] Determined after millivolt reading was constant to ±0.1 mv.

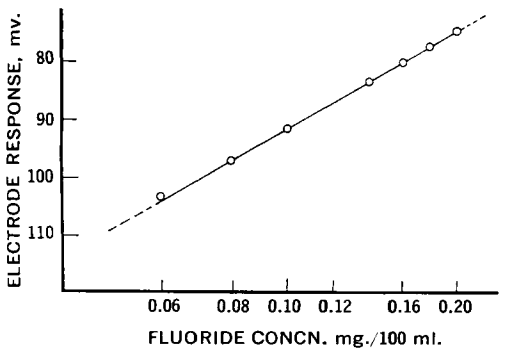

Figure 3—*Electrode response as a function of pH at constant ionic strength (1 M) and constant fluoride concentration (2.63 × 10^{-5} M).*

Electrode Selectivity—Interference from other common anions with the exception of the hydroxide ion, when its concentration exceeded that of the fluoride ion, was virtually negligible as indicated by the electrode designer (9). It was observed that a 10,000 to 1 excess of nitrate or chloride ions resulted only in a 4-mv. decrease in measured fluoride in a 10^{-5} *M* F^- solution. This suppression may be readily ascribed to increased ionic strength of the solution.

Using the Britton-Robinson buffer system (pH range 2–12) at a constant ionic strength of 1 *M* (18), electrode response as a function of pH was evaluated at a fluoride concentration of 0.05 mg. fluoride/100 ml. (2.63 × 10^{-5} *M*). Electrode response had the smallest rate of change in relation to pH at pH = 4.5 to 8 (see Fig. 3).

Sample Preparation—Fluoride in multivitamin tablet samples was solubilized using combustion, moderate heating, and ultrasonic disintegration. Since preliminary results using the combustion technique in order to minimize matrix effects indicated low results, a more complete investigation was made using the other two dissolution techniques. The average assay difference among seven sets of duplicate samples, prepared according to the procedure with heating for about 30 min. on a steam bath and with ultrasonic disintegration for a comparable period of time, was less than 0.6% (based on percent fluoride recovered). However, the samples with heating were much clearer than samples for which ultrasonic disintegration was used. A comparison between sample dissolution in buffer (TBS) and sample dissolution in 0.1 *N* sodium hydroxide, both with heating, showed that in the former case better accuracy was obtained (see Table IV).

Comparison of Analyses—Repetitive fluoride determinations of the same samples and blanks with fluoride (NaF) added, showed that the method was accurate and reproducible (see Tables V and VI). The precision was ±2.27, ±1.36, and ±1.18 relative to tablets and multivitamin drops (Formulations *A* and *B*), respectively, at the 95% confidence level.

Results obtained using the described procedure for fluoride determinations were compared with results obtained on the same set of samples, using the generally accepted combustion/colorimetric technique for tablets (19–21) and a colorimetric method for drops (22). In both cases, better precision and accuracy were obtained using the described procedure. Results for fluoride determination in various samples using this procedure are shown in Table VII.

Table IV—Determination of Sample Fluoride and Added Fluoride with Variation in Sample Dissolution

Set[a]	Added Fluoride[b] (%) TBS[d]	Added Fluoride[b] (%) TBS + NaOH[e]	Sample Fluoride[c] (%) TBS	Sample Fluoride[c] (%) TBS + NaOH
1	100.0	98.2	98.0	97.2
1	99.7	98.8	97.8	97.1
2	100.3	101.1	98.9	98.9
2	100.3	101.1	99.6	99.2
3	98.9	98.5	100.5	98.7
3	98.9	98.9	100.4	98.5
4	100.0	99.8	99.1	97.6
4	100.3	100.2	99.1	97.9
Av.	99.8	99.6	99.2	98.1
SD	0.59	1.15	0.99	0.80

[a] Duplicate fluoride determinations made on the same sample and sample blank freshly prepared each day, over a 7-day period. [b] Sodium fluoride solution equivalent to 0.5 mg. fluoride, was added to multivitamin tablets containing no fluoride. [c] Based on claim of 1 mg. fluoride /tablet. [d] TBS = 1 *M* tris buffer solution at pH = 7.5. [e] Samples were dissolved in 0.01 *N* NaOH and subsequently diluted with TBS.

Table V—Repetitive Fluoride Recoveries from Sample Blanks

Set[a]	% Added Fluoride Recovered[b] Sample Blank A[c]	Sample Blank B[d]	Sample Blank T[e]
1	99.1	99.1	100.0
	98.9	98.9	99.7
2	99.3	98.9	100.3
	99.4	99.1	100.3
3	99.9	99.6	98.9
	100.0	99.8	98.9
4	100.4	99.9	100.0
	99.9	99.9	100.3
Av.	99.6	99.4	99.8
SD	0.51	0.46	0.59

[a] Duplicate determination of added sample blank fluoride. [b] Sodium fluoride solution, equivalent to 8.5 mg. of fluoride was added to sample blanks A and B and 0.5 mg. fluoride was added to sample blank T. [c] Same as Formulation *A* without fluoride. [d] Same as Formulation *B* without fluoride. [e] Multivitamin tablets without fluoride.

Table VI—Repetitive Fluoride Determinations

Set[a]	% Claimed Fluoride[b] Sample A[c]	Sample B[d]	Sample T[e]
1	99.0	101.3	98.0
	99.3	101.3	97.8
2	100.1	101.7	98.9
	100.1	101.3	99.6
3	99.3	100.8	100.5
	99.4	101.3	100.4
4	98.8	100.1	99.1
	98.4	100.6	99.1
Av.	99.3	101.1	99.2
SD	0.59	0.51	0.99
Precision[f]	±1.36	±1.18	±2.27

[a] Each set represents duplicate fluoride determination on the same samples freshly prepared each time. [b] Based on claim of 0.833 mg. fluoride /ml. for multivitamin drops (Samples A and B) and claim of 1 mg. fluoride /tablet for Sample T. [c] Formulation *A* multivitamin drops. [d] Formulation *B* multivitamin drops. [e] Multivitamin tablets. [f] *ts* for 8 degrees of freedom at the 95% confidence level.

Table VII—Determination of Fluoride in Various Samples

Sample[a]	% of Claimed Fluoride[b] Multivitamin Tablets	Multivitamin Drops Formulation *A*	Formulation *B*
1	98.3	98.3	103.0
	98.5	98.7	103.0
2	95.3	99.5	102.6
	95.6	99.1	102.1
3	97.9	98.5	100.8
	97.3	98.6	100.8
4	99.7	98.7	101.2
	99.6	98.7	100.8
5	97.5	99.3	101.7
	98.0	99.4	101.3
6	99.4	101.1	100.1
	99.3	100.1	100.6

[a] Duplicate fluoride determination on each sample. [b] Based on claim of 0.833 mg. fluoride /ml. for multivitamin drops and claim of 1 mg. fluoride /tablet for multivitamin tablets.

Two different analysts, using the described procedure, obtained duplicate results within a ±2% range on the same series of samples.

DISCUSSION

Using appropriate high-ionic strength buffer conditions, a solid-state fluoride-activity electrode was used to directly measure fluoride (NaF) in multivitamin preparations without tedious sample pretreatment. This was possible because sample fluoride was completely solubilized in the buffer solution, which also maintained constant ionic strength and pH in both sample and standard. Under these conditions, exact fluoride-concentration measurements were readily made and this resulted in a simple, rapid, and accurate method.

Usually potential measurements were reproducible within ±0.1 mv., and quite stable (with equilibrium being reached in less than 60 sec. in most cases). Electrode potential tended to drift slightly over an extended period of time. Therefore, for best accuracy involving direct fluoride determinations the electrode should be recalibrated frequently. If the slope of the calibration curve has been found to remain constant (±2 mv.), the recalibration is more conveniently done by using the indicated single-point technique.

Although most of the measurements in this investigation were at the 10^{-4} *M* to 10^{-5} *M* fluoride level, this does not necessarily represent the ultimate in terms of accuracy or precision for fluoride analysis with this type of electrode. However, this does represent a practical linear working range in terms of sample size, ease of sample handling, number of sample dilutions required in relation to sample size, and instrument response or reproducibility.

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