Application Note AN-S-375

Fluoride in sodium fluoride for pharmaceutical use

Method validation according to the U.S. Pharmacopeia

Dental care products like toothpaste often contain sodium fluoride to support tooth enamel remineralization and prevent dental cavities (caries) [1]. The WHO recommends 1000–1500 mg/L fluoride in toothpaste for adults to prevent tooth decay [2]. Manufacturers use the United States Pharmacopeia and National Formulary (USP-NF) Monograph «Sodium Fluoride» to quantify sodium fluoride and its anionic contaminants chloride and acetate in dental care products [3].

The validated USP method proposes ion chromatography (IC) with suppressed conductivity detection to carry out the fluoride assay as well as the impurity determination in a single chromatogram [3]. The demonstrated IC method uses the Metrosep A Supp 16 - 250/4.0 (L91) column and a hydroxide eluent, complying with all parameters given in the USP Monograph «Sodium Fluoride» [3]. It provides excellent separation of fluoride, acetate, and chloride, and fulfills all acceptance criteria of the Monograph. The IC method has been validated according to USP General Chapters <621> Chromatography [4] and <1225> Validation of Compendial Procedures [5].

STANDARD AND SAMPLE PREPARATION

The standard solutions and the system suitability solutions are prepared from the respective 1000 µg/mL certified standards by dilution with ultrapure water (UPW).

For the fluoride assay, the standard solution is obtained by diluting a sodium fluoride solution to 2 µg/mL. The system suitability solution contains 2 µg/mL sodium fluoride and 1 µg/mL sodium acetate. For the impurity test, the standard solution consists of 0.2 µg/mL sodium chloride in UPW. The system suitability solution for the impurity test contains 1 mg/mL sodium fluoride and 1 µg/mL sodium chloride in UPW.

Sample analyses are performed with a solution prepared from commercially available sodium fluoride salt. The sample solution is prepared by dissolving and diluting sodium fluoride salt with UPW to a nominal concentration of 2 µg/mL which corresponds to 0.9 µg/mL fluoride (for the assay). For the impurity test, samples were diluted to a nominal concentration of 1 µg/mL sodium fluoride.

No additional sample preparation is required.

EXPERIMENTAL

Samples and standard solutions were directly injected into the IC using a 919 IC Autosampler plus (Figure 1).

Figure 1. Instrumental setup including a 930 Compact IC Flex, 919 IC Autosampler plus, and an 800 Dosino for automatic regeneration of the Metrohm Suppressor Module (MSM).

Fluoride was separated from acetate and chloride using a potassium hydroxide eluent and the column Metrosep A Supp 16 with column material L91 (Table 1). The analytes were quantified by evaluating their conductivity signal after chemical suppression.

The calibration was performed using a single 2.0 µg/mL standard injected six times. The sample was analyzed in duplicate.

Table 1. Requirements for the IC method as per USP Monograph «Sodium Fluoride» [3].

Column with L91 packing	Metrosep A Supp 16 - 250/4.0
Eluent	15 mmol/L potassium hydroxide
Flow rate	1.0 mL/min
Temperature	40 °C
Injection volume	20 µL
Detection	Conductivity with suppression

RESULTS

The IC assay for fluoride content was validated according to USP Monograph «Sodium Fluoride» [3]. Suitability requirements for resolution, tailing factor, and relative standard deviation were fulfilled (Table 2).

Table 2. Suitability requirements for the assay.

Parameter (assay)	Actual	USP requirement	Status
Resolution F^-/acetate	5.9	NLT 1.5	Pass
Tailing factor	1.1	NMT 2.0	Pass
RSD fluoride (%, n=5)	0.52	NMT 0.73	Pass

The chromatographic resolution between fluoride and acetate is shown in Figure 2. The recovery of fluoride for the sample analysis (99.7%) was within the USP acceptance criteria (98–102%).

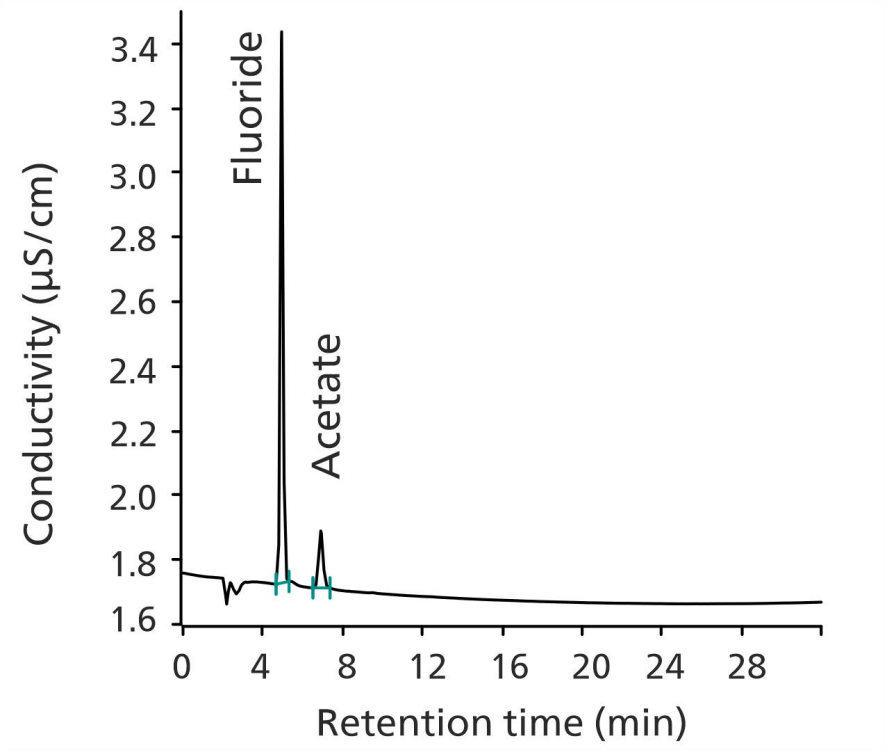

Figure 2. Chromatogram of the system suitability solution for the assay with 2.0 µg/mL sodium fluoride and 1.0 µg/mL sodium acetate.

Regarding the impurity tests for potential contamination with chloride, the IC method showed excellent compliance with the USP requirements (Table 3).

Table 3. Suitability requirements for the impurities in sodium fluoride.

Parameter (impurity)	Actual	USP requirement	Status
Resolution F^-/Cl^-	7.7	NLT 4	Pass
RSD fluoride (%, n=5)	4.2	NMT 5	Pass
S/N ratio Cl^-	>740	NLT 20	Pass

Figure 3 shows the chromatographic resolution between fluoride and chloride.

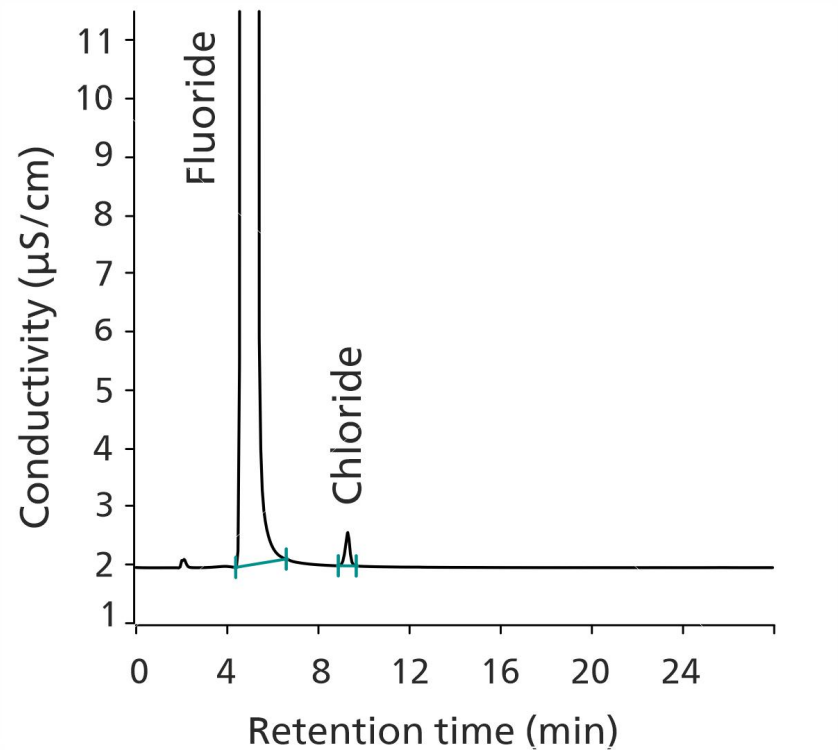

Figure 3. Chromatogram of the system suitability solution for the impurity chloride. The solution contained 1 mg/mL sodium fluoride and 1 µg/mL sodium chloride. The peaks are well resolved, and the signal-to-noise ratio for chloride was >740 (a value of more than 20 is required).

In all tested samples, the chloride content was well below the acceptance criteria of 0.012% (Table 4).

Table 4. Results of the chromatograms shown in Figures 2 and 3.

Anion	Sample ID	Result [%]	USP Limit [%]
1 Fluoride	Assay	99.7	98–102
2 Chloride	Impurity	0.0016	≤0.012

TÓM TẮT

The presented IC method is suitable to determine sodium fluoride and its impurities according to the USP Monograph «Sodium Fluoride». The method helps manufacturers of dental care products to determine fluoride content as well as impurities more easily in toothpaste.

REFERENCES

1. Yeung, C. A. A Systematic Review of the Efficacy and Safety of Fluoridation. *Evid Based Dent* 2008, *9* (2), 39–43. https://doi.org/10.1038/sj.ebd.6400578.
2. WHO. *A.14 Fluoride Toothpaste – Dental Caries*; Expert Committee on Selection and Use of Essential Medicines Application review; WHO, 2021.
3. *Sodium Fluoride*; Monograph; U.S. Pharmacopeia/National Formulary: Rockville, MD. https://doi.org/10.31003/USPNF_M76470_04_01.
4. *621 Chromatography*; General Chapter; U.S. Pharmacopeia/National Formulary: Rockville, MD. https://doi.org/10.31003/USPNF_M99380_01_01.
5. *1225 Validation of Compendial Procedures*; General Chapter; U.S. Pharmacopeia/National Formulary: Rockville, MD. https://doi.org/10.31003/USPNF_M99945_04_01.

CONTACT

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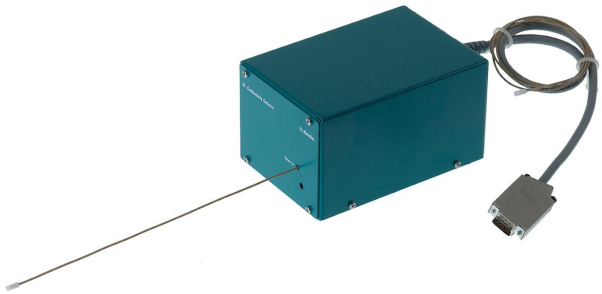
CONFIGURATION

930 Compact IC Flex Oven/SeS/PP/Deg

The 930 Compact IC Flex Oven/SeS/PP/Deg is the intelligent Compact IC instrument with column oven, sequential suppression, peristaltic pump for suppressor regeneration and built-in degasser. The instrument can be used with any separation and detection methods.

Typical areas of application:

- Anion or cation determinations with sequential suppression and conductivity detection



IC Conductivity Detector

Compact and intelligent high performance conductivity detector for intelligent IC instruments. Outstanding temperature stability, the complete signal processing within the protected detector block and the latest generation of DSP – Digital Signal Processing – guarantee the highest precision of the measurement. No change of measuring ranges (not even automatic ones) is required, due to the dynamic working range.

Metrosep A Supp 16 - 250/4.0

The Metrosep A Supp 16 is ideal for high-capacity separation problems and distinguishes itself with its outstanding resolution, even with complex separation problems. The Metrosep A Supp 16 separation column is based on a surface-functionalized polystyrene-divinylbenzene copolymer. The functional groups are bonded covalently. This and the surface structure of the anion exchanger results in unique selectivity. The high-capacity Metrosep A Supp 16 is used for solving complex problems.

The Metrosep A Supp 16 - 250/4.0 is characterized by outstanding resolution and solves the most difficult separation problems. The column is very well-suited for monitoring electroplating baths. Traces of anions can be determined in concentrated acids. Utilization in food analysis for the determination of maltose derivatives is just one more of the numerous applications of the high-capacity Metrosep A Supp 16 - 250/4.0.

Metrosep A Supp 16 Guard/4.0

The Metrosep A Supp 16 Guard/4.0 reliably protects the Metrosep A Supp 16 analytical separation columns against contamination. Thanks to the "On Column Guard System", the guard column is very easy to handle. The guard column screws easily onto the analytical column. No tools are required.

MSM Rotor A

Suppressor rotor for all IC instruments with MSM (Metrohm Suppressor Module)

919 IC Autosampler plus

The 919 IC Autosampler plus fulfills the requirements of laboratories with medium sample numbers. It enables automation of the full range of Metrohm IC instruments.