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%).

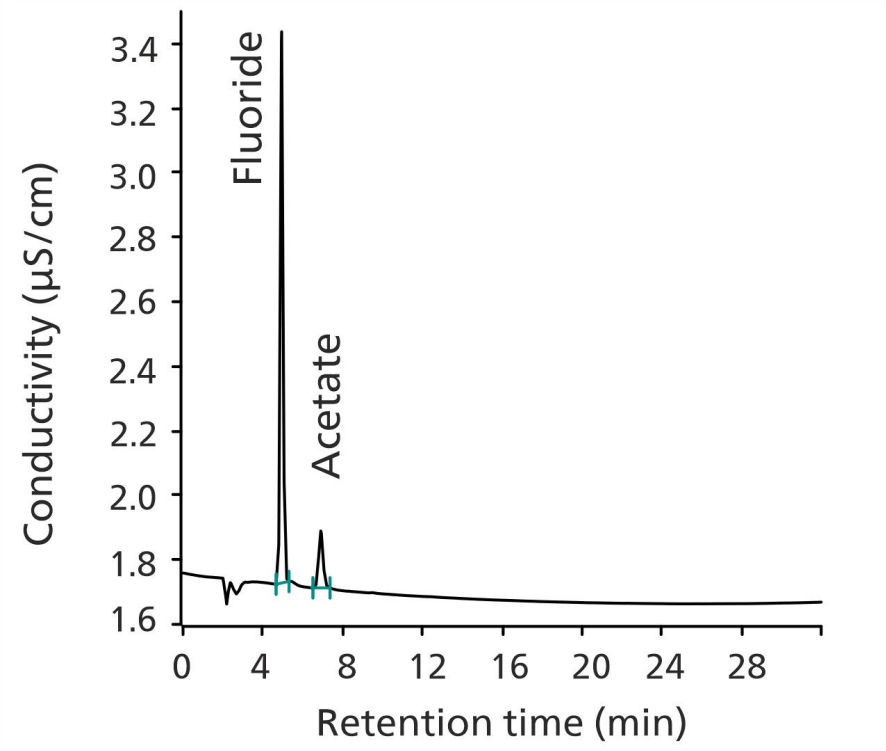

Figure 2. Chromatogram of the system suitability solution for the assay with 2.0 µg/mL sodium fluoride and 1.0 µg/mL sodium acetate.

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.

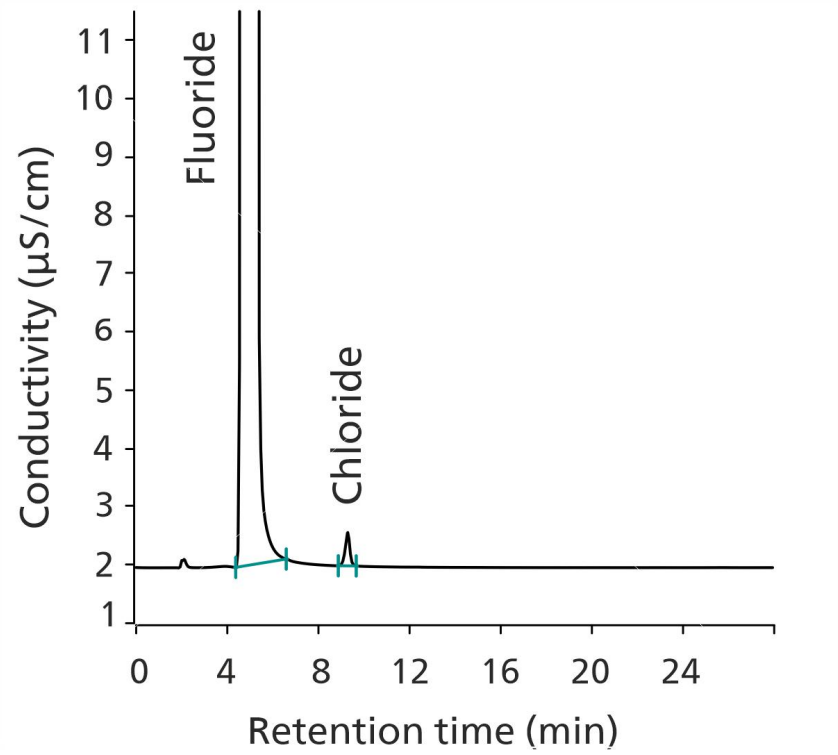

Figure 3. Chromatogram of the system suitability solution for the impurity chloride. The solution contained 1 mg/mL sodium fluoride and 1 µg/mL sodium chloride. The peaks are well resolved, and the signal-to-noise ratio for chloride was >740 (a value of more than 20 is required).

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

概要

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.
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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.

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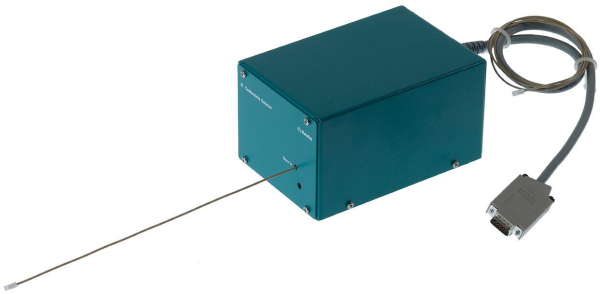
CONFIGURATION

930 Compact IC Flex Oven/SeS/PP/Deg

930 Compact IC Flex Oven/SeS/PP/Deg 是智能型 Compact 子色器,有**柱加炉**、**序列抑制**和**蠕**用于抑制器再生,以及内置的**脱气装置**。器可使用各分和方法。典型的用范:

- 子或子定,序列抑制法及



IC Conductivity Detector

用于智能型子色的智能型高性能器。卓越的温度定性,受保的器端子板内的整个信号理程以及最新一代的DSP(数字式信号理)均能保量的精性。功于工作范,无需行范更(也不是自行)。

Metrosep A Supp 16 - 250/4.0

Metrosep A Supp 16 最用于高容量分,即使在的分中也能保持佳的分辨率。Metrosep A Supp 16 分柱基于表面作用的聚乙/二乙基共聚物。官能均共价合。特征以及表面使子交具有独特的性。高容量 Metrosep A Supp 16 用于的分。

Metrosep A Supp 16 - 250/4.0 有佳的分辨率,可解决的分。柱非常用于控浴。可定酸中的子痕量。可在食品分析中用于定麦芽糖衍生物,只是高容量 Metrosep A Supp 16 - 250/4.0 的多用中的一。

Metrosep A Supp 16 Guard/4.0

Metrosep A Supp 16 Guard/4.0 保柱可有效保分析用分柱 Metrosep A Supp 16,使其免受染。保柱采用 «On Column Guard System» 技,其特征是操作便。只要将其到分析柱上即可。不需要任何工具。

MSM A

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919 IC Autosampler plus

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