



Application Note AN-S-375

Fluoruro in fluoruro di sodio per uso farmaceutico

Convalida del metodo secondo la Farmacopea statunitense

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%).

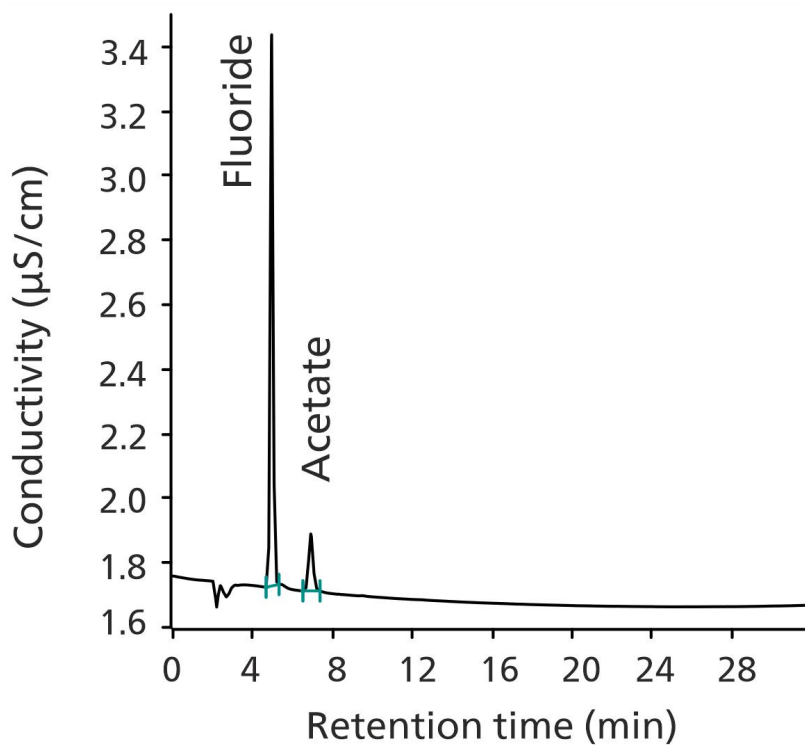


Figure 2. Chromatogram of the system suitability solution for the assay with 2.0 µg/mL sodium fluoride and 1.0 µg/mL sodium acetate.

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.

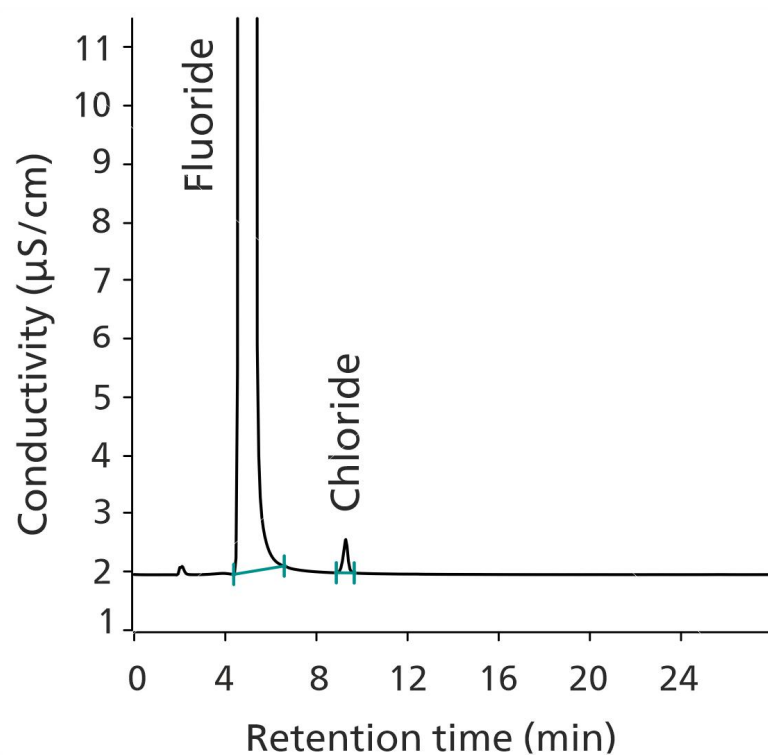


Figure 3. Chromatogram of the system suitability solution for the impurity chloride. The solution contained 1 mg/mL sodium fluoride and 1 µg/mL sodium chloride. The peaks are well resolved, and the signal-to-noise ratio for chloride was >740 (a value of more than 20 is required).

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

SOMMARIO

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

Metrohm Italiana Srl
Via G. Di Vittorio, 5
21040 Origgio (VA)

info@metrohm.it

CONFIGURATION



930 Compact IC Flex Oven/SeS/PP/Deg

Il 930 Compact IC Flex Oven/SeS/PP/Deg è l'intelligente strumento Compact-IC con **forno della colonna**, **soppressione sequenziale** e **pompa peristaltica** per la rigenerazione del soppressore, nonché **Degasser** incorporato. Lo strumento può essere impiegato con qualsiasi metodo di separazione e di rilevamento.

Campi d'impiego tipici:

- Determinazione di anioni o cationi con soppressione sequenziale e rilevamento della conduttività



IC Conductivity Detector

Rilevatore della conducibilità ad alte prestazioni compatto e intelligente per gli strumenti IC intelligenti. Eccellente stabilità di temperatura, la completa elaborazione del segnale all'interno del blocco del rivelatore protetto e DSP – Digital Signal Processing – di ultima generazione garantiscono la massima precisione della misura. Grazie al range dinamico di lavoro non sono necessari cambiamenti (anche non automatici) del range di misura.



Metrosep A Supp 16 - 250/4,0

La Metrosep A Supp 16 è particolarmente adatta per problemi di separazione ad alta capacità e si contraddistingue per l'eccellente risoluzione anche nel caso di problemi di separazione complessi. La colonna di separazione Metrosep A Supp 16 è basata su un copolimero di polistirene/divinilbenzene a superficie funzionalizzata. I gruppi funzionali sono collegati in modo covalente. Questo fatto e la struttura superficiale dello scambiatore di anioni permettono una selettività unica. La Metrosep A Supp 16 ad alta capacità viene impiegata per la soluzione di problemi complessi.

La Metrosep A Supp 16 - 250/4,0 possiede una risoluzione eccellente e risolve i più complessi problemi di separazione. La colonna è particolarmente adatta per il monitoraggio di bagni galvanici. Tracce di anioni sono rilevabili in acidi concentrati. L'impiego nell'analisi degli alimenti per la determinazione di derivati di maltosio è solo una tra le numerose applicazioni della Metrosep A Supp 16 - 250/4,0.



Metrosep A Supp 16 Guard/4,0

La Metrosep A Supp 16 Guard/4,0 protegge efficacemente le colonne di separazione Metrosep A Supp 16 dai contaminanti. Grazie all'«On Column Guard System», la precolonna si contraddistingue per l'estrema facilità d'uso. La precolonna viene semplicemente avvitata sulla colonna analitica. L'operazione non richiede utensili.



Rotore MSM A

Rotore del soppressore per tutti gli strumenti IC con MSM



919 IC Autosampler plus

L'919 IC Autosampler plus soddisfa i requisiti di laboratori con una media quantità di campioni. Con esso è possibile automatizzare i vari cromatografi ionici della gamma Metrohm.