Application Note AN-S-379

Le fluorure dans les comprimés de fluorure de sodium à usage pharmaceutique

Method qualification according to the U.S. Pharmacopeia

Fluoride has been shown to be effective at preventing tooth decay and supporting remineralization of tooth enamel [1,2]. Aside from the fluorination of drinking water, milk, or salt, fluoride can also be encountered as a topical fluoride supplement such as fluoride tablets, toothpastes, mouthwashes, or gels [2,3]. However, its efficacy highly depends on concentration and dosage, which is also crucial to avoid overdosage and fluorosis [2].

Analytical methods, including ion chromatography (IC), are used to ensure that fluoride tablets meet the quality standards as given by the United States Pharmacopeia and National Formulary (USP-NF).

IC with suppressed conductivity detection has been approved by the USP as a validated method to quantify fluoride content in sodium fluoride tablets [4]. Using the Metrosep A Supp 16 - 250/4.0 (L91) column and applying a hydroxide eluent provides the required separation of fluoride and acetate. The qualification was performed according to USP General Chapters [5–7] and met all acceptance criteria from the USP Monograph «Sodium Fluoride Tablets» [4].

STANDARD AND SAMPLE PREPARATION

The system suitability solution and the standard solutions are prepared from a USP Sodium Fluoride RS certified standard by dilution with ultrapure water (UPW). The system suitability solution contains 2.0 µg/mL sodium fluoride (NaF) and 1.0 µg/mL of sodium acetate. The standard solutions contain 2.0 µg/mL NaF.

Samples were prepared from ground sodium fluoride tablets. A 0.215 g portion of the powder was accurately weighed and transferred into a 1000 mL volumetric flask. The flask was subsequently filled up to the mark with UPW.

To ensure complete dissolution, the mixture underwent ultrasonic agitation for 10 minutes. The resulting solution was then subjected to filtration using a 0.2 µm pore size membrane filter. The filtered solution was diluted 1:10 with UPW to achieve a final concentration of 2.0 µg/mL NaF.

EXPERIMENTAL

Samples and standard solutions were injected directly into the IC using an 858 Professional Sample Processor (Figure 1).

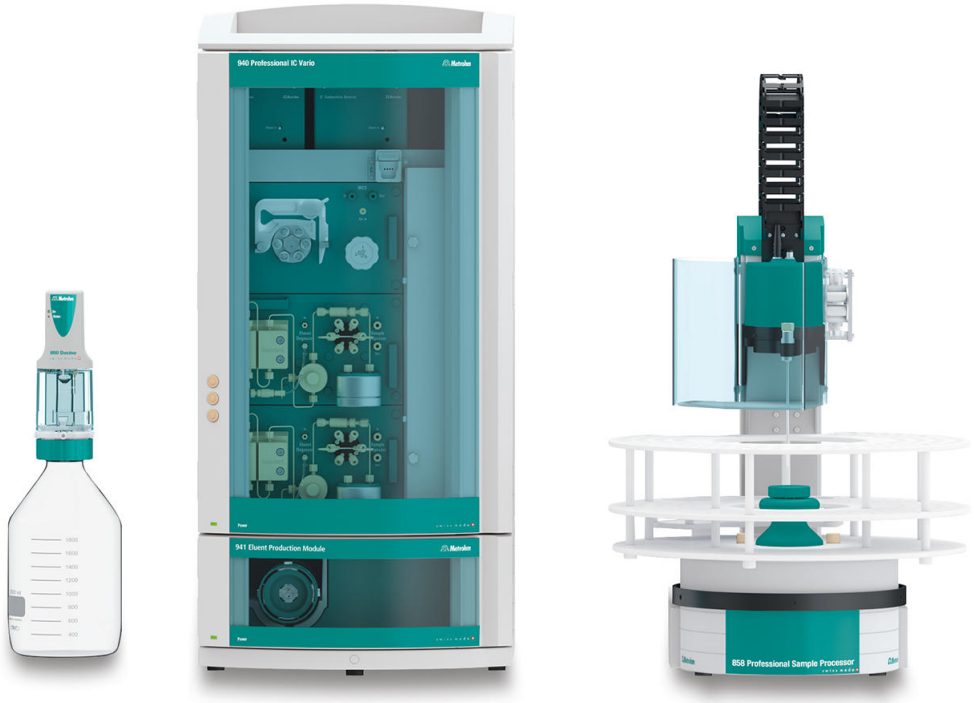

Figure 1. Instrumental setup including a 940 Professional IC Vario ONE SeS/PP/HPG, 858 Professional Sample Processor, and an 800 Dosino for Dosino regeneration of the Metrohm Suppressor Module (Metrohm Dosino Regeneration).

Fluoride was separated from acetate by applying a binary potassium hydroxide gradient (Tables 1 and 2) and using the Metrosep A Supp 16 column (L91) followed by chemically suppressed conductivity detection.

Table 1. Requirements for the IC method as per USP Monograph «Sodium Fluoride Tablets» [4].

Column with L91 packing	Metrosep A Supp 16 - 250/4.0
Flow rate	1.0 mL/min
Eluent	A: 100 mmol/L Potassium hydroxide B: Ultrapure water
Temperature	40 °C
Injection volume	20 µL
Detection	Suppressed conductivity

Table 2. Binary gradient program for USP Monograph «Sodium Fluoride Tablets» [4].

Time (minutes)	Eluent A (%)	Eluent B (%)
0.0	15	85
7.0	15	85
8.0	80	20
15.0	80	20
15.1	15	85
25.0	15	85

RESULTS

The IC method presented for fluoride determination in sodium fluoride tablets was qualified according to the general requirements of USP and the USP Monograph «Sodium Fluoride Tablets» [4–7].

The appropriate separation of fluoride and acetate on the A Supp 16 column was achieved by applying a hydroxide gradient (Table 3). The chromatogram is shown in Figure 2.

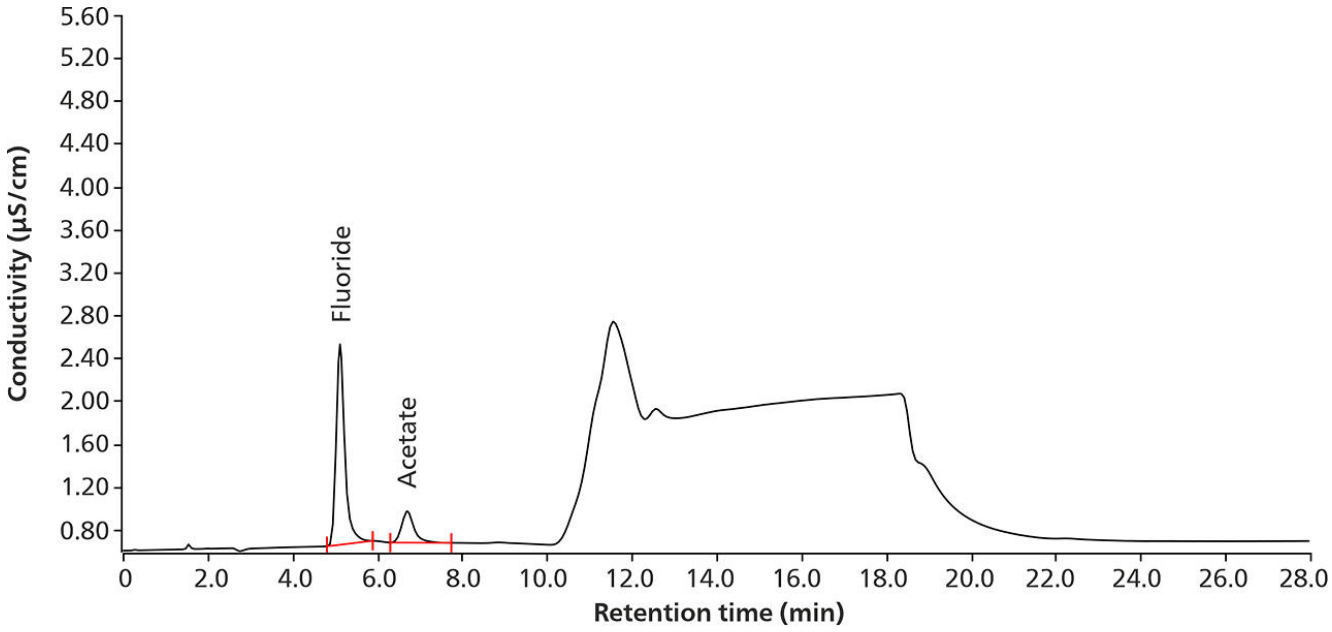

Figure 2. Chromatogram of the system suitability solution. The concentration of sodium fluoride was 2.0 µg/mL. Acetate was not quantified (nominal concentration 1.0 µg/mL).

The relative retention times (r_G, unadjusted) for fluoride and acetate are 1.0 and 1.3, respectively. These unitless values are automatically calculated with the MagIC Net software by applying the following formula:

$$r_G = \frac{t_{Ri}}{t_{Rst}}$$

r_G = relative retention time, unadjusted t_{Ri} = retention time peak of interest t_{Rst} = retention time peak of reference peak (peak corresponding to the substance to be examined, sodium fluoride)

Table 3 shows that the system suitability criteria are met, including resolution, tailing factor, and relative standard error (RSD) of multiple standard injections [4].

Table 3. System suitability test requirements and results from the study.

Parameter	Actual	USP requirement	Status
Resolution fluoride/acetate	3.7	NLT 1.5	Pass
Tailing factor for fluoride	1.4	NMT 2.0	Pass
RSD fluoride (%, n=5)	0.4	NMT 2.0	Pass

The calibration for the sample analysis was performed using a single standard at 2.0 µg/mL NaF injected six times. The sample was analyzed in duplicate and fulfilled the respective USP validation criteria as shown in Table 4.

Table 4. Sample test showing the calculated percentage of the labeled amount of sodium fluoride (NaF) in the used tablets reached in the analysis.

Parameter	Actual	USP requirement	Status
Fluoride sample [%]	99.4	90–110	Pass

CONCLUSION

Ion chromatography (IC) has successfully passed the qualification tests for quantifying the fluoride content in pharmaceutical tablets, in full compliance with the USP Monograph «Sodium Fluoride Tablets». The qualification was conducted in accordance with the guidelines set by the USP.

Regarding system suitability and sample analysis, the IC method passed all predefined acceptance criteria including resolution, tailing factor, and the relative standard deviation for repeated standard injections as well as for the sample result. Consequently, ion chromatography has qualified as a reliable and highly automated method for fluoride quantification in pharmaceutical compounds, offering both user-friendliness and accurate results.

REFERENCES

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CONTACT

Metrohm Suisse SA
Industriestrasse 13
4800 Zofingen

info@metrohm.ch

CONFIGURATION

Metrosep A Supp 16 - 250/4,0

La Metrosep A Supp 16 est idéale pour les problèmes de séparation à haute capacité et se caractérise par une excellente résolution, même pour les problèmes de séparation complexes. La colonne de séparation Metrosep A Supp 16 est basée sur un copolymère de polystyrène/divinylbenzène à surface fonctionnalisée. Les groupes fonctionnels sont liés par covalence. Une sélectivité hors pair est obtenue grâce à cette caractéristique et à la structure superficielle de l'échangeur d'anions. La Metrosep A Supp 16 de haute capacité est utilisée lorsqu'il s'agit de résoudre des problèmes complexes.

La Metrosep A Supp 16 - 250/4,0 possède une excellente résolution et résout les problèmes de séparation les plus complexes. Cette colonne convient parfaitement au contrôle des bains galvaniques. Il est possible de déterminer des anions à l'état de traces dans des acides concentrés. Son utilisation pour l'analyse des produits alimentaires pour la détermination des dérivés du maltose est une autre des nombreuses applications de cette Metrosep A Supp 16 - 250/4,0 haute capacité.

Metrosep A Supp 16 Guard/4,0

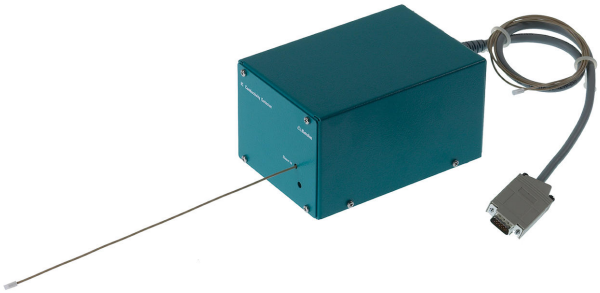
La Metrosep A Supp 16 Guard/4,0 protège efficacement les colonnes de séparation analytiques Metrosep A Supp 16 contre les contaminations. La manipulation de la colonne Guard est fort simple grâce au système « On Column Guard ». La colonne Guard est simplement vissée sur la colonne analytique. Aucun outil n'est requis pour ce faire.

940 Professional IC Vario ONE/SeS/PP/HPG

Le 940 Professional IC Vario ONE/SeS/PP/HPG est l'appareil CI intelligent avec **suppression séquentielle**, **pompe péristaltique** pour la régénération du suppresseur et **gradient haute pression binaire**. Il peut être développé avec le 942 Extension Module jusqu'au niveau d'un système gradient quaternaire. L'appareil peut être utilisé avec n'importe quelles méthodes de séparation et de détection.

Domaines d'application typiques :

- Applications en gradient pour les déterminations d'anions ou de cations avec suppression séquentielle



IC Conductivity Detector

Détecteur de conductivité haute performance compact et intelligent destiné aux appareils CI intelligents. Excellente constance de la température, tout le traitement du signal au sein du bloc de détecteur protégé et DSP – Digital Signal Processing – de la dernière génération garantissent une précision de mesure optimale. Grâce à la plage de travail dynamique, aucun changement de plage n'est nécessaire (même automatique).

858 Professional Sample Processor – Pump

Le 858 Professional Sample Processor – Pump traite des échantillons de 500 µL à 500 mL. Le transfert des échantillons s'opère soit au moyen de la pompe péristaltique bidirectionnelle à deux voies intégrée soit par un 800 Dosino.