Application Note AN-S-379

Fluoride in sodium fluoride tablets for pharmaceutical use

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 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).

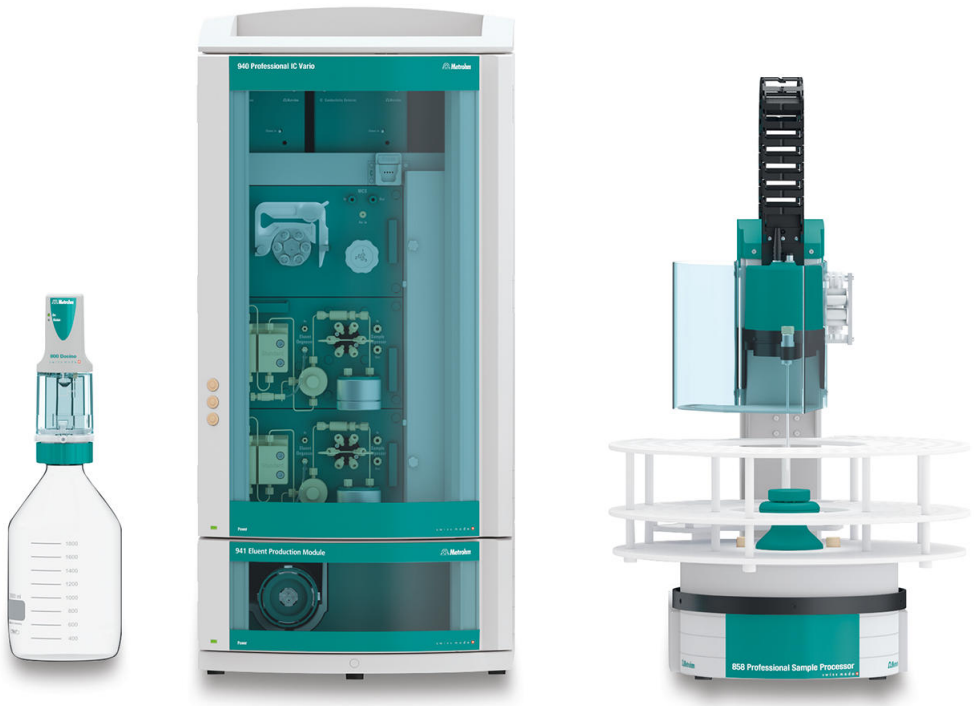

Figure 1. Instrumental setup including a 940 Professional IC Vario ONE SeS/PP/HPG, 858 Professional Sample Processor, and an 800 Dosino for Dosino regeneration of the Metrohm Suppressor Module (Metrohm Dosino Regeneration).

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.

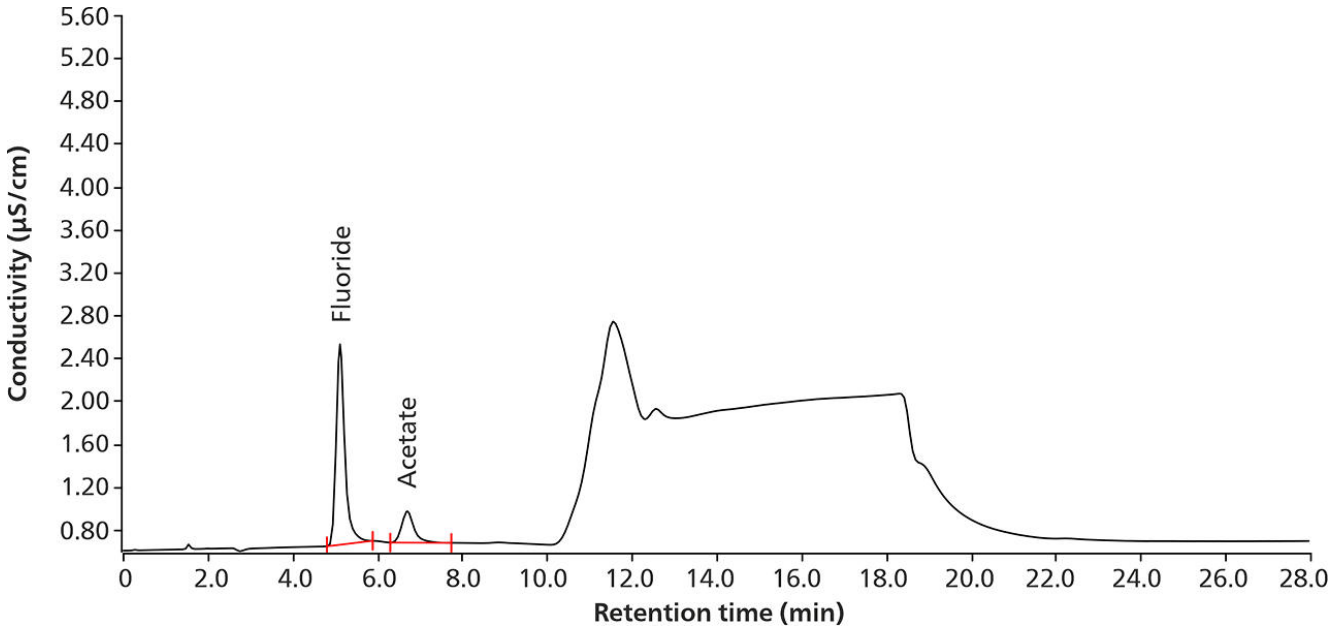

Figure 2. Chromatogram of the system suitability solution. The concentration of sodium fluoride was 2.0 µg/mL. Acetate was not quantified (nominal concentration 1.0 µg/mL).

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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CONFIGURATION

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

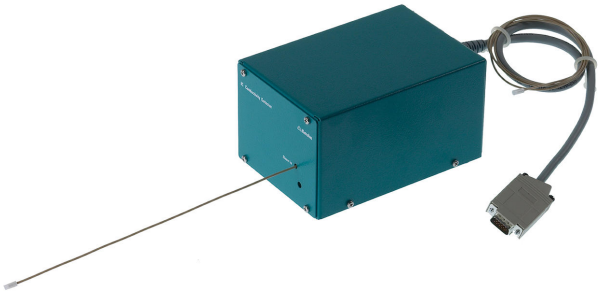
The Metrosep A Supp 16 Guard/4.0 reliably protects the Metrosep A Supp 16 analytical separation columns against contamination. Thanks to the "On Column Guard System", the guard column is very easy to handle. The guard column screws easily onto the analytical column. No tools are required.

940 Professional IC Vario ONE/SeS/PP/HPG

The 940 Professional IC Vario ONE/SeS/PP/HPG is the intelligent IC instrument with **sequential suppression**, a **peristaltic pump** for suppressor regeneration and **binary high-pressure gradient**. It can be extended with the 942 Extension Modules to up to a quaternary gradient system. The instrument can be used with any separation and detection methods.

Typical areas of application:

- Gradient applications for anion or cation determinations with sequential suppression



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.

858 Professional Sample Processor – Pump

The 858 Professional Sample Processor – Pump processes samples from 500 µL to 500 mL. The sample transfer takes place either with the installed bidirectional two-channel peristaltic pump or with an 800 Dosino.