Application Note AN-S-380

Monofluorophosphate and fluoride in sodium monofluorophosphate for pharmaceutical use

Method qualification according to the U.S. Pharmacopeia

Monofluorophosphate (MFP) is often used for tooth enamel remineralization and to prevent dental caries (cavities) [1]. Pharmaceutical manufacturers and laboratories are obliged to use the Monographs from the United States Pharmacopeia and National Formulary (USP-NF) for the assessment of drug and formulation quality, including MFP.

The USP has initiated a global initiative to modernize many of their existing Monographs. Ion chromatography (IC) with suppressed conductivity detection has been approved by the USP as a validated method to quantify the MFP content in sodium monofluorophosphate [2].

The required separation of MFP from sulfate is possible by using the Metrosep A Supp 16 - 250/4.0 column and a hydroxide gradient. All acceptance criteria for the USP Monograph «Sodium Monofluorophosphate» are fulfilled and the procedure was approved as a validated USP method [2–5].

STANDARD AND SAMPLE PREPARATION

The system suitability solution and the standard solution are prepared from USP certified standards by dilution with ultrapure water (UPW).

The system suitability solution contains 4.0 µg/mL USP Sodium Fluoride RS, 1.4 µg/mL of USP Sodium Acetate RS, 150.0 µg/mL USP Sodium Monofluorophosphate RS, and 150.0 µg/mL USP Sodium Sulfate RS. The standard solution contains 150.0 µg/mL USP Sodium Monofluorophosphate RS.

Sample analyses were performed with customer-provided sodium monofluorophosphate (Na_2PFO_3). Of this, 1.5 g was weighed and added to a 1000 mL volumetric flask. The flask was filled up to the mark with UPW, sonicated for 15 minutes, and finally filtered through filter paper with a pore size of 0.2 µm. This sample stock solution was further diluted 1:10 with UPW. The final concentration corresponds to 150 µg/mL monofluorophosphate. No additional sample preparation is required.

EXPERIMENTAL

System suitability solution, samples, and standard solutions were injected directly into the IC using an 858 Professional Sample Processor (Figure 1).

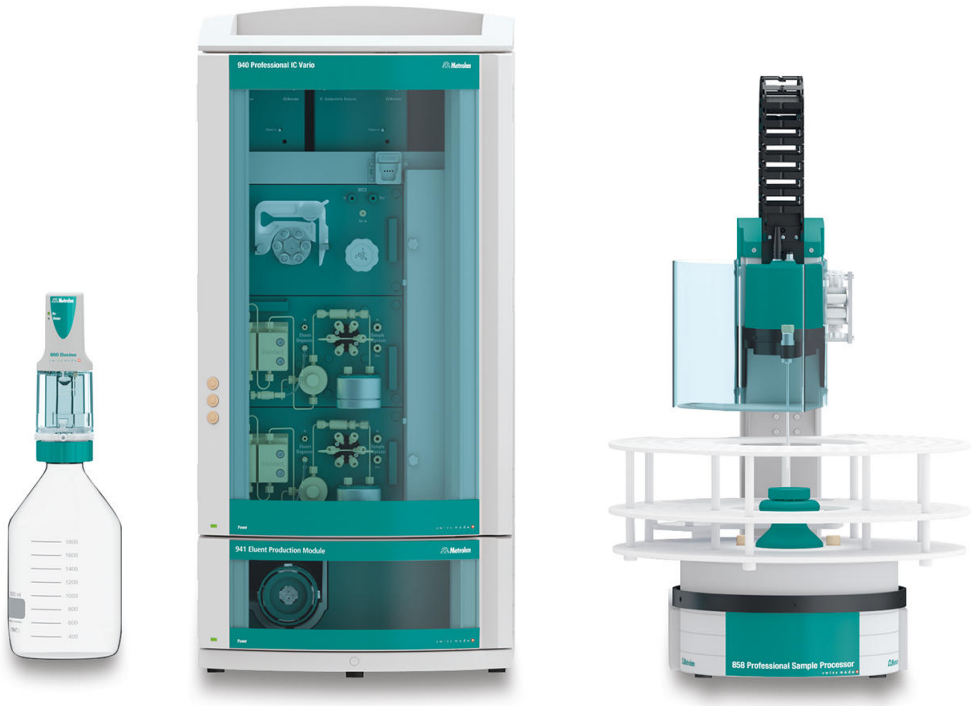

Figure 1. Instrumental setup including a 940 Professional IC Vario, 858 Professional Sample Processor, and an 800 Dosino for Dosino regeneration of the MSM (Metrohm Suppressor Module).

EXPERIMENTAL

Baseline separation of fluoride, acetate, monofluorophosphate, and sulfate was ensured by applying a potassium hydroxide gradient (Table 2, eluent A 100 mmol/L potassium hydroxide, eluent B ultrapure water) and using the Metrosep A Supp 16 column (USP listing L91). Detection of analytes was achieved with chemically suppressed conductivity detection.

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

Table 1. Requirements for the IC method as per USP Monograph «Sodium Monofluorophosphate» [2].

Column with L91 packing	Metrosep A Supp 16 - 250/4.0
Flow rate	1.0 mL/min
Eluent	Eluent A: 100.0 mmol/L Potassium hydroxide Eluent B: Ultrapure water
Temperature	40 °C
Injection volume	10 µL
Detection	Suppressed conductivity

Table 2. Binary gradient program for the USP Monograph «Sodium Monofluorophosphate» [2].

Time (minutes)	Eluent A (%)	Eluent B (%)
0.0	15	85
20.0	15	85
30.0	30	70
35.0	60	40
45.0	60	40
45.1	15	85
50.0	15	85

The IC method for the determination of monofluorophosphate content is qualified according to the USP Monograph «Sodium Monofluorophosphate» following the USP references for method validation procedures [2–5]. A chromatogram for the system suitability approval is shown in Figure 2.

RESULTS

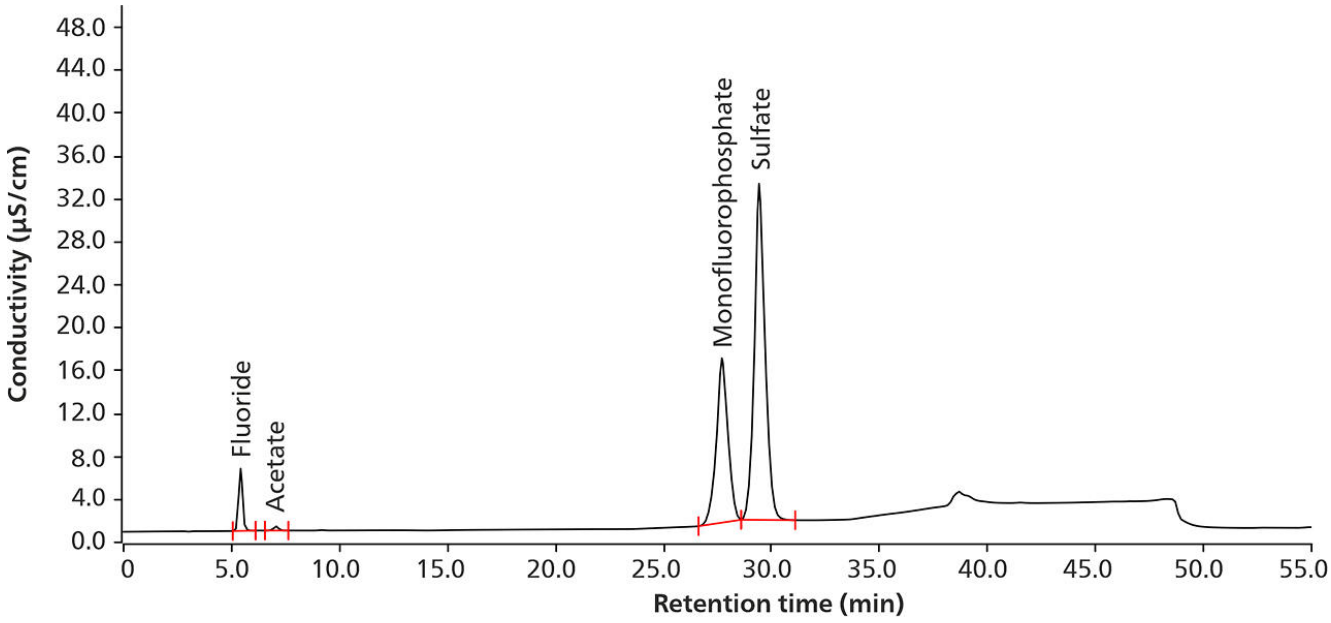

Figure 2. Chromatogram of the system suitability solution. The sodium fluoride concentration corresponds to 4.0 µg/mL, sodium acetate 1.4 µg/mL, sodium monofluorophosphate 150.0 µg/mL, and sodium sulfate 150.0 µg/mL.

The relative retention times for fluoride, acetate, monofluorophosphate, and sulfate are 0.20, 0.26, 1.00, and 1.06, 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, monofluorophosphate)

All acceptance criteria for the system suitability (resolution, tailing factor, and relative standard deviation of replicate standard injections) are fulfilled (Table 3).

Table 3. System suitability requirements as per USP.

Parameter	Actual	USP required	Status
Resolution monofluorophosphate / sulfate	1.84	NLT 1.5	Pass
Tailing factor	1.02	NMT 2.5	Pass
*RSD (%); n=6	0.38	NMT 2.0	Pass

The results for the sample solution (Table 4) are calculated as follows:

$$Result\ (\%) = \left(\frac{r_U}{r_S}\right) \times \left(\frac{C_S}{C_U}\right) \times 100$$

r_U = peak response of monofluorophosphate from the sample solution r_S = peak response of monofluorophosphate from the standard solution C_S = concentration of USP Sodium Monofluorophosphate RS in the standard solution (µg/mL) C_U = concentration of sodium monofluorophosphate in the sample solution (µg/mL)

Table 4. Sodium monofluorophosphate sample analysis and requirements as per USP.

Analyte	Actual	USP requirement	Status
Sodium MFP [%]	95.56	91.7–100.5	Pass

CONCLUSION

The presented IC method has been successfully qualified for assessing the content of monofluorophosphate in accordance with the USP Monograph «Sodium Monofluorophosphate». This qualification strictly followed the USP validation specifications.

The system suitability met all acceptance criteria, including resolution, tailing factor, and the relative standard deviation of replicate standard injections. Furthermore, the sample analysis also fulfilled the USP requirements.

As a result, analysis with ion chromatography has been proven to be a reliable and appropriate approach for the determination of monofluorophosphate in pharmaceutical formulations. Manufacturers of sodium monofluorophosphate benefit from the high degree of automation and its ease of use.

REFERENCES

1. Vogel, G. L.; Mao, Y.; Chow, L. C.; et al. Fluoride in Plaque Fluid, Plaque, and Saliva Measured for 2 Hours after a Sodium Fluoride Monofluorophosphate Rinse. *Caries Research* **2000**, *34* (5), 404–411. https://doi.org/10.1159/000016615.
2. U. S. Pharmacopeia/National Formulary. *USP Monographs, Sodium Monofluorophosphate*; USP/NF, Rockville, MD, USA.
3. U. S. Pharmacopeia/National Formulary. <621> Chromatography. In *General Chapter*; USP/NF, Rockville, MD, USA.
4. U. S. Pharmacopeia/National Formulary. *General Chapter, <1065> Ion Chromatography*; USP-NF: Rockville, MD, USA, 2023. https://doi.usp.org/USPNF/USPNF_M897_01_01.html.
5. U. S. Pharmacopeia/National Formulary. *General Chapter, <1225> Validation of Compendial Procedures*; USP-NF: Rockville, MD, USA, 2023. https://doi.org/10.31003/USPNF_M99945_04_01.

CONTACT

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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

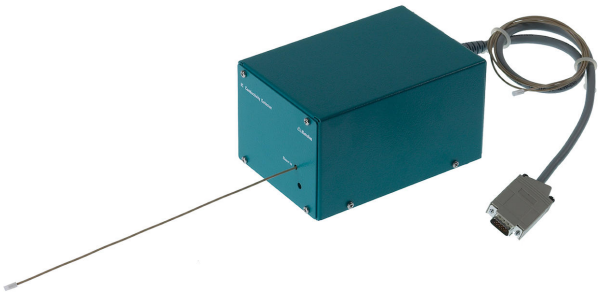
The Metrosep A Supp 16 Guard/4.0 reliably protects the Metrosep A Supp 16 analytical separation columns against contamination. Thanks to the "On Column Guard System", the guard column is very easy to handle. The guard column screws easily onto the analytical column. No tools are required.

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.