



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 ([L91](#)) 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 g/mL USP Sodium Fluoride RS, 1.4 g/mL of USP Sodium Acetate RS, 150.0 g/mL USP Sodium Monofluorophosphate RS, and 150.0 g/mL USP Sodium Sulfate RS. The standard solution contains 150.0 g/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 g/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**).

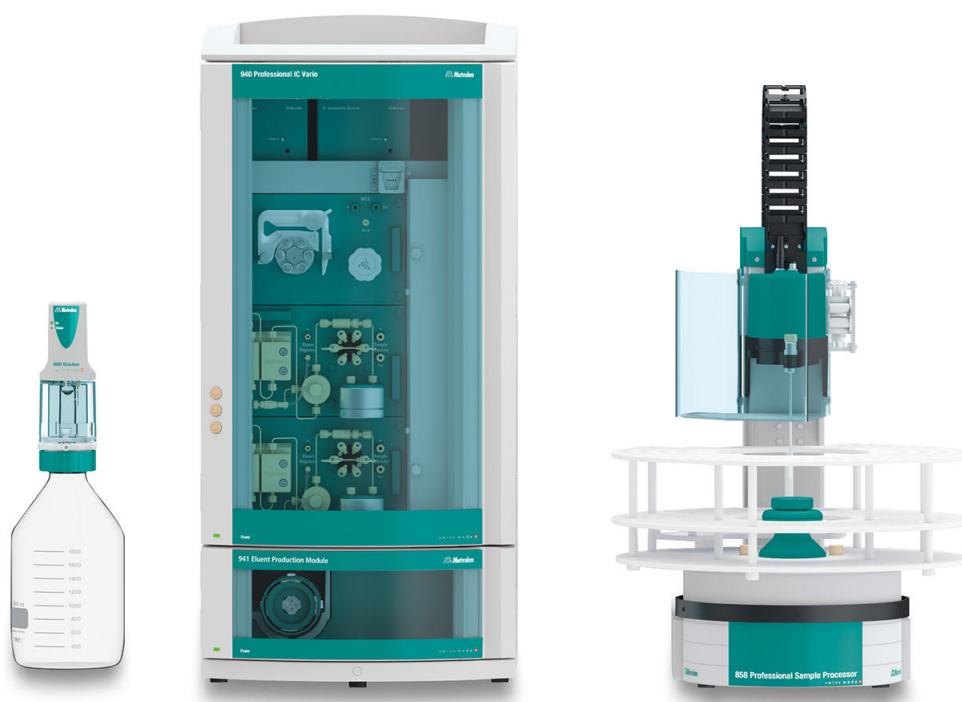


Figure 1. Instrumental setup including a 940 Professional IC Vario, 858 Professional Sample Processor, and an 800 Dosino for Dosino regeneration of the MSM (Metrohm Suppressor Module).

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 g/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 L
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**.

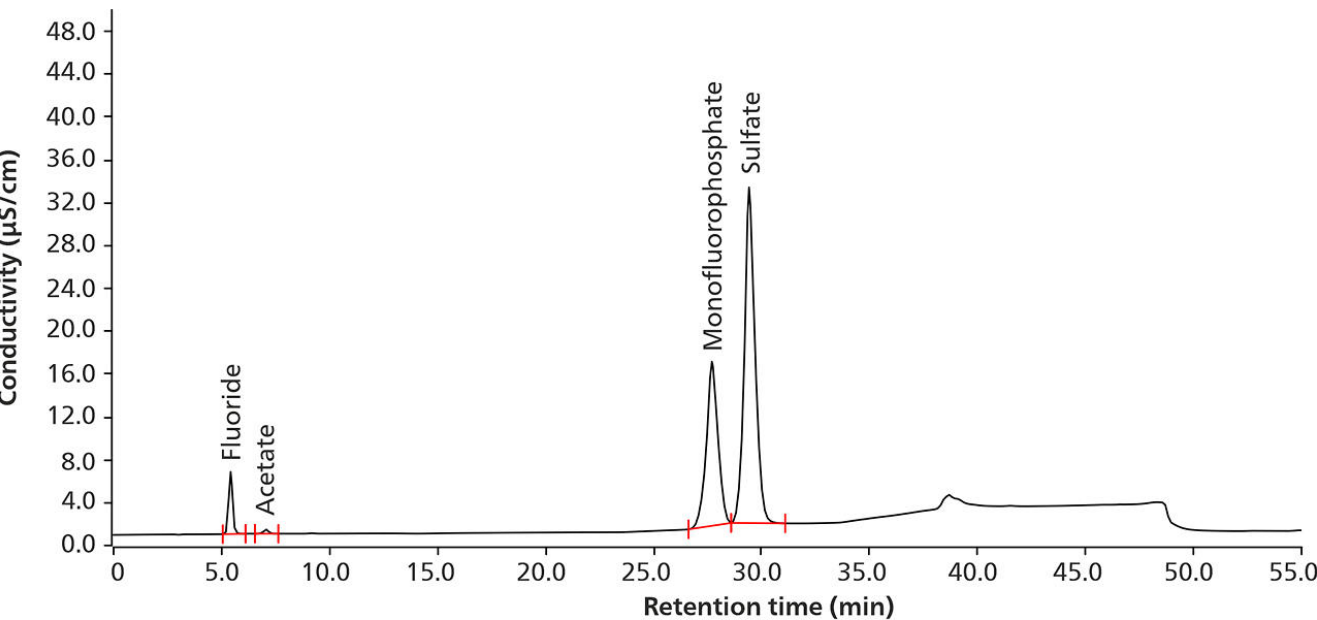


Figure 2. Chromatogram of the system suitability solution. The sodium fluoride concentration corresponds to 4.0 µg/mL, sodium acetate 1.4 µg/mL, sodium monofluorophosphate 150.0 µg/mL, and sodium sulfate 150.0 µg/mL.

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:

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

RESULTS

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:

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

RESULTS

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 (g/mL) C_U = concentration of sodium monofluorophosphate in the sample solution (g/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.

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CONFIGURATION



Metrosep A Supp 16 - 250/4.0

Metrosep A Supp 16 适用于高容量分离问题,即使在复杂的分离问题中也能保持优良的分辨率。Metrosep A Supp 16 分离柱基于表面作用的聚苯乙烯/二乙烯基苯共聚物。官能组均为共价键合。该特征以及表面结构使阴离子交换剂具有独特的选择性。高容量 Metrosep A Supp 16 适用于复杂的分离问题。

Metrosep A Supp 16 - 250/4.0 拥有优良的分辨率,可解决复杂的分离问题。该柱非常适用于监控电镀浴。可测定浓酸中的阴离子痕量。可在食品分析中用于测定麦芽糖衍生物,这只是高容量 Metrosep A Supp 16 - 250/4.0 的众多应用中的一种。



Metrosep A Supp 16 Guard/4.0

Metrosep A Supp 16 Guard/4.0 保护柱可有效保护分析用分离柱 Metrosep A Supp 16,使其免受污染。该保护柱采用 «On Column Guard System» 技术,其特征是操作简便。只要将其拧到分析柱上即可。不需要任何工具。

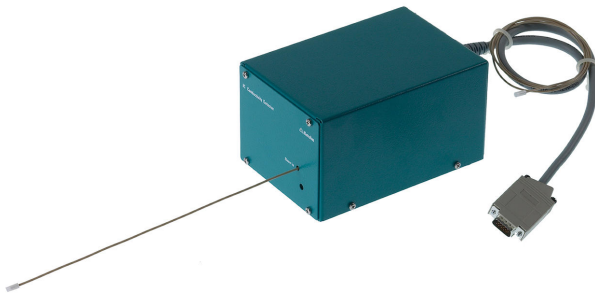


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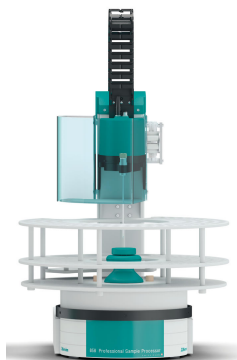
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IC Conductivity Detector

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858 Professional Sample Processor – Pump

858 Professional Sample Processor – Pump 500 L
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