



Application Note AN-S-380

Monofluorophosphate and fluoride in sodium monofluorophosphate for pharmaceutical use

Method qualification according to the U.S. Pharmacopeia

RÉSUMÉ

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 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-

procedure was approved as a validated USP method [2–5].

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).

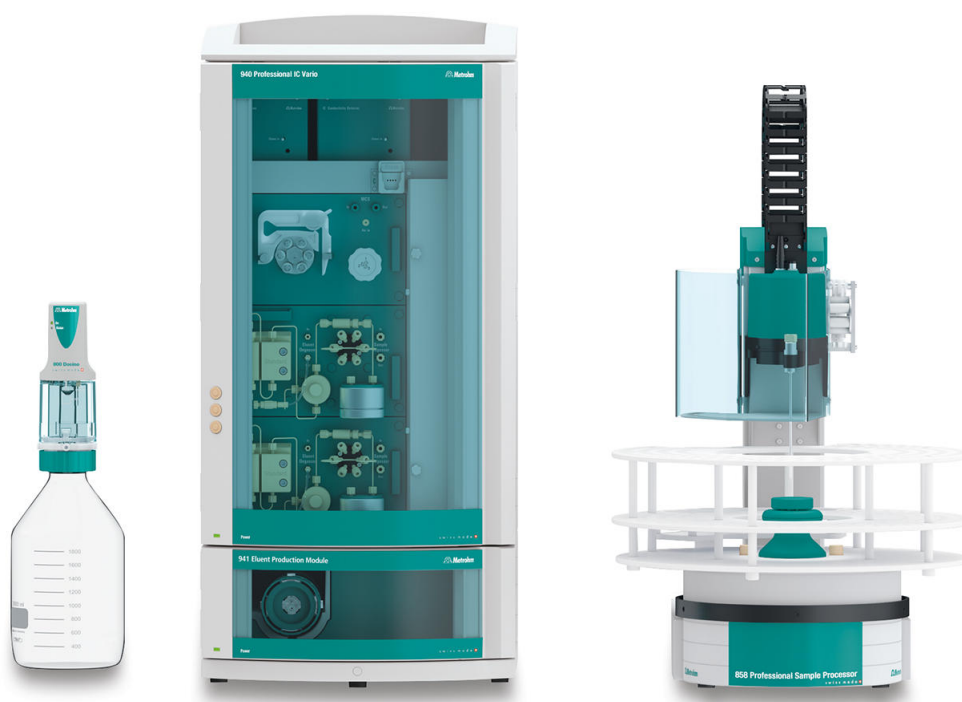


Figure 1. Instrumental setup including a 940 Professional IC Vario, 858 Professional Sample Processor, and an 800 Dosino for Dosino regeneration of the MSM (Metrohm Suppressor Module).

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

RESULTS

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

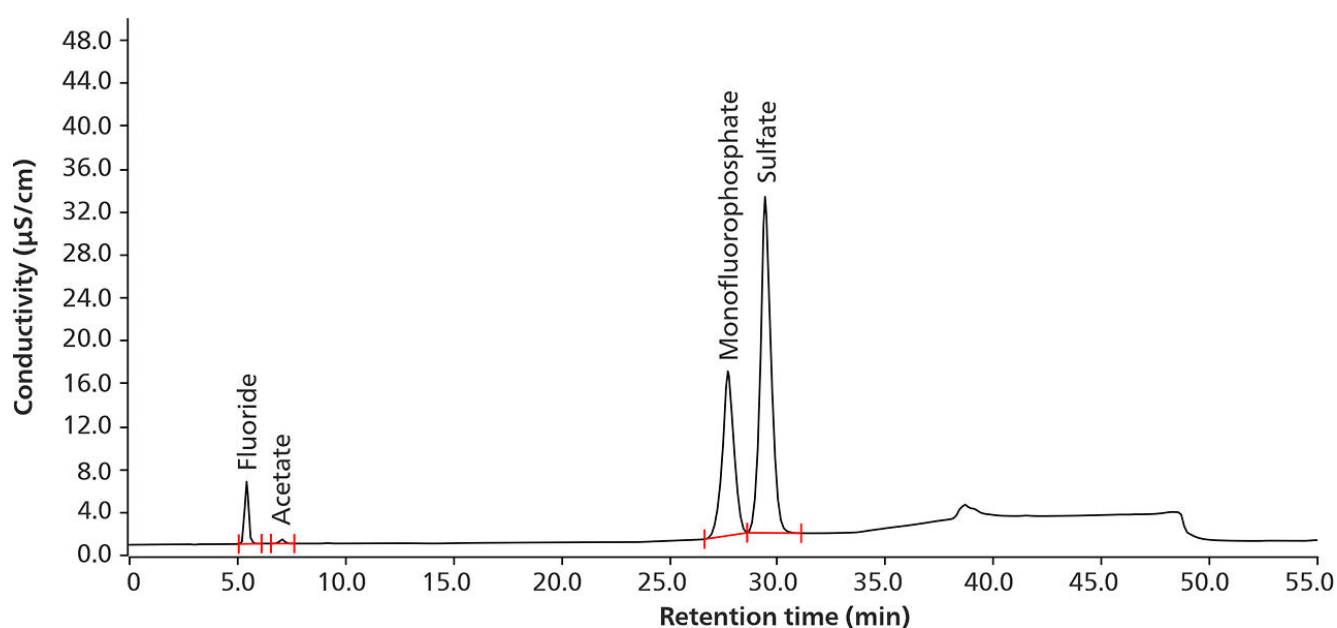


Figure 2. Chromatogram of the system suitability solution. The sodium fluoride concentration corresponds to 4.0 µg/mL, sodium acetate 1.4 µg/mL, sodium monofluorophosphate 150.0 µg/mL, and sodium sulfate 150.0 µg/mL.

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

RESULTS

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 ($\mu\text{g/mL}$) C_U = concentration of sodium monofluorophosphate in the sample solution ($\mu\text{g/mL}$)

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

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

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.

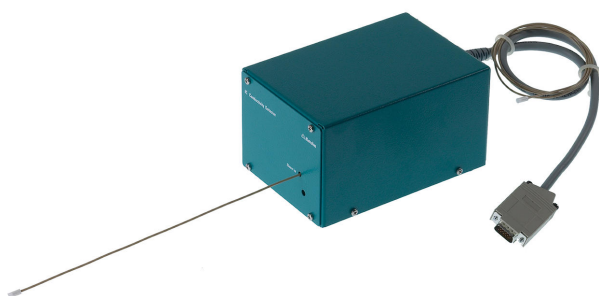


940 Professional IC Vario ONE/SeS/PP/HPG

Le 940 Professional IC Vario ONE/SeS/PP/HPG est l'appareil CI intelligent avec **suppression séquentielle**, **pompe péristaltique** pour la régénération du supprimeur 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.