Application Note AN-S-373

Chloride in potassium bicarbonate and potassium chloride effervescent tablets for oral solution

Method validation according to the U.S. Pharmacopoeia

Potassium chloride and potassium bicarbonate effervescent tablets are used to prevent low levels of potassium in blood [1]. Using the monographs from the United States Pharmacopeia and National Formulary (USP-NF) allows pharmaceutical manufacturers and labs to fulfill strict quality regulations for drugs and formulations.

The USP has embarked on a global initiative to modernize many existing monographs. The monograph «Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution» comprises different methods to determine potassium, sodium, but also chloride in these tablets [2]. Ion chromatography (IC) with suppressed conductivity detection has been approved by the USP as a validated method to quantify chloride content in potassium bicarbonate and potassium chloride effervescent tablets for oral suspension [2]. The Metrosep A Supp 16 - 100/4.0 (L91) column provides the required separation of chloride. The method is validated according to USP General Chapter <621> Chromatography, system suitability [3].

SAMPLE AND SAMPLE PREPARATION

Sample analyses are performed with a solution of the respective effervescent tablets. No additional sample preparation is required.

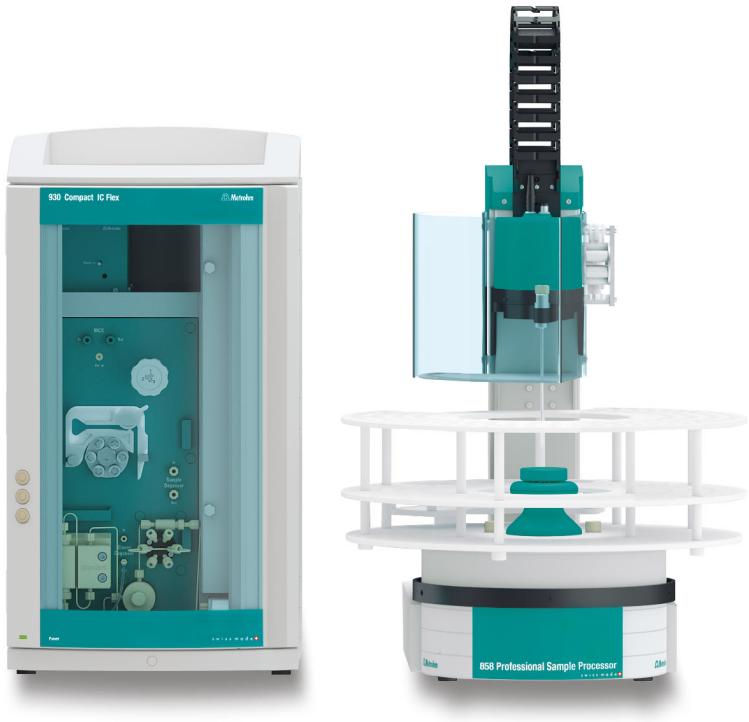

Figure 1. Instrumental setup including a 930 Compact IC Flex Oven/SeS/PP and an 858 Professional Sample Processor.

EXPERIMENTAL

A sample stock solution (nominally 4434.52 µg/mL chloride) is prepared by adding 50 g (equivalent to 10 tablets weight) of finely powdered potassium bicarbonate and potassium chloride effervescent tablets for oral solution to a 2000 mL volumetric flask. The powder is dissolved in 200 mL ultrapure water (UPW). After effervescence ceases, the volumetric flask is filled up to the mark. A small volume (1.692 mL) of this stock solution is transferred to a 500 mL volumetric flask and filled up to the mark with UPW. This final sample solution nominally contains 15.0 µg/mL chloride.

The working standard solution of 15 µg/mL is prepared from a USP Potassium Chloride RS standard.

Samples and standard solutions are injected directly into the IC using an 858 Professional Sample Processor (**Figure 1**). Separation of chloride from other anions is performed using a Metrosep A Supp 16 - 100/4.0 column. This anion-exchange column, consisting of a strong ion exchanger made from monodisperse porous polystyrene/divinyl benzene beads combined with quaternary amines, qualifies for certain USP methods using the USP chromatographic column packing L91.

The calibration is performed with a 6-point linear calibration curve using a concentration range of 2.25–22.50 µg/mL chloride. The sample is then analyzed in duplicate.

Table 1. Requirements for the IC method for chloride determination as per USP Monograph «Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution» [2].

Column with L91 packing	Metrosep A Supp 16 - 100/4.0
Eluent	15 mmol/L sodium carbonate, 1.5 mmol/L sodium hydroxide
Flow rate	0.8 mL/min
Temperature	45 ° C
Injection volume	20 µL
Detection	Suppressed conductivity

RESULTS

The IC assay for chloride content was validated according to the USP Monograph «Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution» [2]. The accuracy of the chloride determination in the sample was calculated as 101.2% (**Figure 2**) and falls into the acceptance criteria. All analytical quality requirements were fulfilled, e.g., the correlation coefficient for chloride was 0.9998, and the relative standard deviation of repeated standard solutions was 0.05% (n = 6) (**Table 2**).

Table 2. Analytical quality criteria for method acceptance according to USP Monograph «Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution» [2].

Parameter	Actual	USP requirement	Status
% RSD	0.05	NMT 0.5	Pass
Tailing factor	1.27	NMT 2.0	Pass
Recovery	101.2%	90–110%	Pass
Resolution	2.48	NLT 1.5	Pass

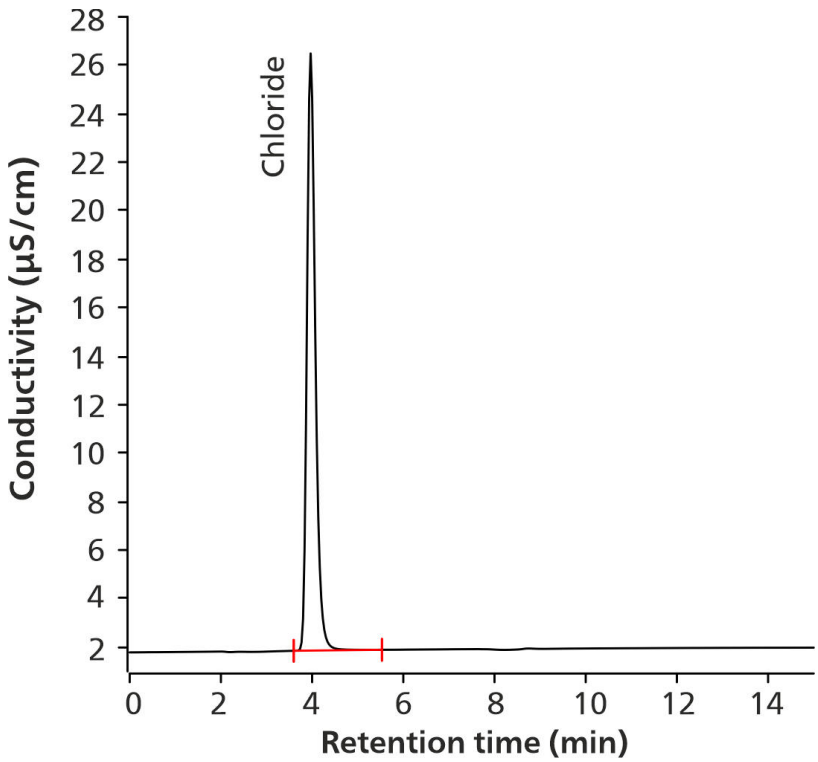

Figure 2. Chromatogram of 15.0 µg/mL chloride in the sample solution (101.1% recovery of the nominal concentration).

The presented IC method for chloride in potassium bicarbonate and potassium chloride effervescent tablets for oral solution is officially included into the USP [**2**]. Chloride separation is performed with a strong anion-exchanger – the Metrosep A Supp 16 - 100/4.0 column, corresponding to packing material L91. Robustness and reliability of the method was demonstrated following the guidelines of the USP General Chapter <621> [**3**]. The presented setup is suitable to quantify chloride according to the USP requirements. Further USP methods are summarized in the flyer «Bring your USP methods up to date!» [**4**].

REFERENCES

1. Kardalas, E.; Paschou, S. A.; Anagnostis, P.; et al. Hypokalemia: A Clinical Update. *Endocr Connect* **2018**, *7* (4), R135–R146. https://doi.org/10.1530/EC-18-0109.
2. *Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution*; Monograph; U.S. Pharmacopeia/National Formulary: Rockville, MD. https://doi.org/10.31003/USPNF_M67253_02_01.
3. *<621> Chromatography, General Chapter*; U.S. Pharmacopeia/National Formulary: Rockville, MD. https://www.uspnf.com/notices-gc-621-nitr-20220826.
4. Metrohm AG. Bring Your USP Methods up to Date!, 2023. 8.000.5436EN

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CONFIGURATION

Metrosep A Supp 16 - 100/4.0

Metrosep A Supp 16 是一种高容量分离柱,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。因阴离子交换剂的形态而具有独特的选择性。此外,该柱型还具有机械强度高、化学稳定性好的特点。

该柱非常适用于离子负载较高、但对分辨率的要求相对较小的应用。通过三碘化物方法(EPA 326,DIN EN ISO 11206)测定水样中的溴酸盐是 Metrosep A Supp 16 - 100/4.0 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。

930 Compact IC Flex Oven/SeS/PP/Deg

930 Compact IC Flex Oven/SeS/PP/Deg 是智能型 Compact 离子色谱仪器,带有**柱加热炉**、**序列抑制**和**蠕动泵**用于抑制器再生,以及内置的**脱气装置**。该仪器可使用各种分离和检测方法。

典型的应用范围:

- 阴离子或阳离子测定,序列抑制法及电导检测

858 Professional Sample Processor

858 Professional Sample Processor 可处理体积在 500 µL 至 500 mL 之间的样品。进行样品转移时,既可以使用 850 Professional IC System 上的蠕动泵、也可通过 800 Dosino 来进行。

USP

本宣传页中对 USP 近期完成的色谱更新进行了概述,其现在已规定了用于多种 API、杂质和赋形剂药物分析的离子色谱法。