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.

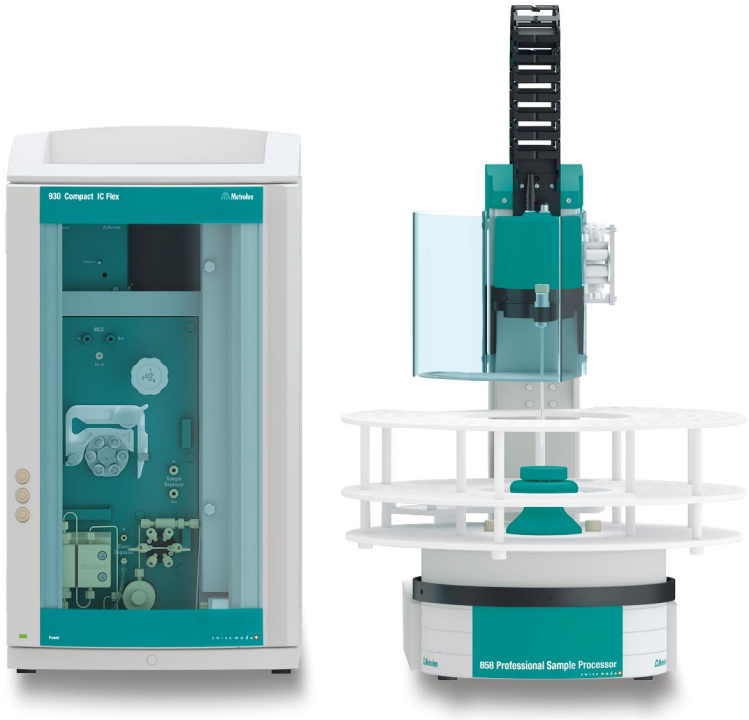

Figure 1. Instrumental setup including a 930 Compact IC Flex Oven/SeS/PP and an 858 Professional Sample Processor.

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

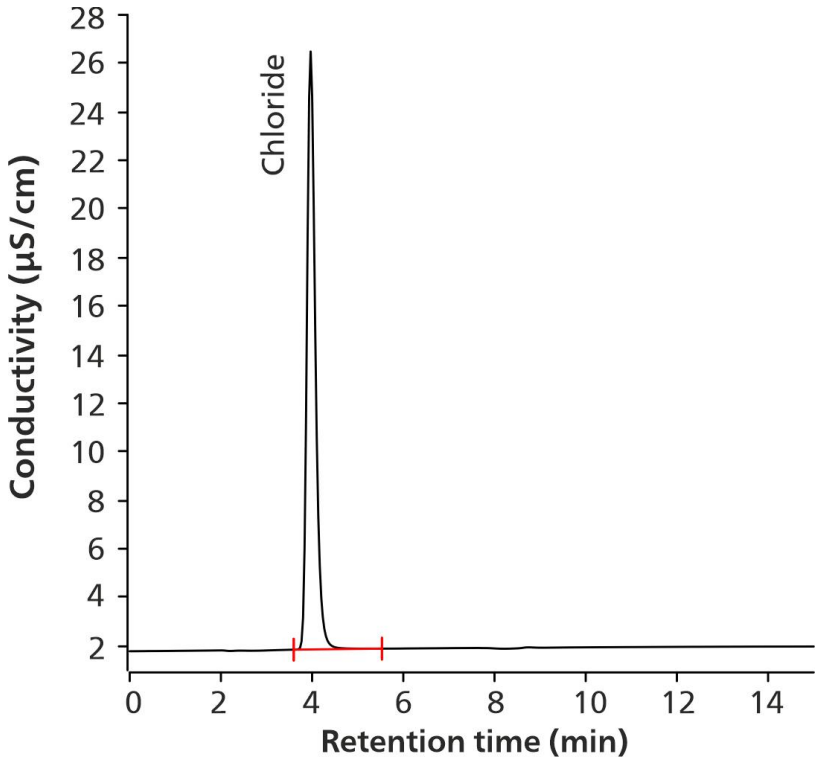

Figure 2. Chromatogram of 15.0 µg/mL chloride in the sample solution (101.1% recovery of the nominal concentration).

CONCLUSION

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

The Metrosep A Supp 16 is a high capacity separation column based on a surface-functionalized polystyrene-divinylbenzene copolymer. The functional groups are bonded covalently. The morphology of the anion exchanger results in unique selectivity. In addition, this column type is noteworthy for its high mechanical and chemical resilience.

The column is well-suited to applications with a high ionic load but which require only relatively low resolution. Using the Metrosep A Supp 16 - 100/4.0 to determine bromate in water by means of the triiodide method (EPA 326, DIN EN ISO 11206) is another of its numerous applications.

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.

930 Compact IC Flex Oven/SeS/PP/Deg

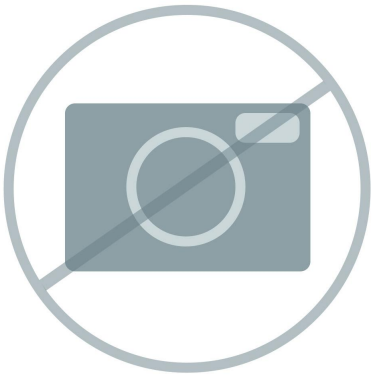
The 930 Compact IC Flex Oven/SeS/PP/Deg is the intelligent Compact IC instrument with **column oven**, **sequential suppression**, **peristaltic pump** for suppressor regeneration and built-in **degasser**. The instrument can be used with any separation and detection methods.

Typical areas of application:

- Anion or cation determinations with sequential suppression and conductivity detection

858 Professional Sample Processor

The 858 Professional Sample Processor processes samples from 500 µL to 500 mL. The sample transfer takes place either by means of a peristaltic pump on the 850 Professional IC system or with an 800 Dosino.



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The USP is a global authority for defining standards for pharmaceutical analyses. Ion chromatography systems from Metrohm are the ideal solution for pharmaceutical testing of APIs, impurities, and excipients. Metrohm IC systems are fully compliant with the guidelines of USP and GLP and meet all requirements regarding data integrity, security, and traceability as per FDA 21 CFR Part 11, ALCOA, and ALCOA+.