Application Note AN-C-197

Potassium assay in potassium citrate and citric acid oral solution

Method validation according to the U.S. Pharmacopeia (USP)

Potassium citrate and citric acid oral solutions are systemic alkalizers beneficial for health conditions where long-term maintenance of alkaline urine is desirable, and administration of sodium salts is contraindicated [1,2]. To comply with the strict quality standards for pharmaceutical products, validated methods such as those from the United States Pharmacopeia – National Formulary (USP-NF) are mandatory for manufacturers and laboratories. As part of the USP modernization initiative, the potassium monograph was updated, replacing the previous identification procedure of titration with ion chromatographic (IC) analysis [3]. For quality control, the USP specifies ion chromatography using a cation-exchange column with L76 column material and non-suppressed conductivity detection to quantify the potassium content [3].

The present IC method uses the Metrosep C 6 - 150/4.0 column (L76) to separate potassium from other potentially present ions. This method has been validated according to USP General Chapters <621> Chromatography [4] and <1225> Validation of Compendial Procedures [5]. All acceptance criteria for the potassium assay of the USP monograph «Potassium Citrate and Citric Acid Oral Solution» are fulfilled [3].

SAMPLE AND SAMPLE PREPARATION

The sample solutions are made using two distinct commercially available oral solutions of potassium citrate and citric acid. The labeled content was 1100 mg/334 mg potassium citrate monohydrate/citric acid monohydrate per 5 mL solution. For a sample stock solution (1000 mg/mL of potassium from potassium citrate and citric acid oral solutions), 1.26 mL of sample are transferred quantitatively to a 100 mL volumetric flask, then diluted to volume with ultrapure water and mixed well. For a sample solution (nominally 15.0 µg/mL of potassium), 1.5 mL of sample stock solution are added to a 100 mL volumetric flask, diluted to volume with ultrapure water, and mixed well.

The USP Reference Standard Potassium Citrate monohydrate (Cat#1548225 RS) is used as a standard solution.

EXPERIMENTAL

An 858 Professional Sample Processor with a peristaltic pump is used to aspirate samples or standard solutions into a 20 µL loop for direct injection (Figure 1). Cations are separated using the Metrosep C 6 - 150/4.0 column (L76) with a nitric acid eluent and detected with non-suppressed conductivity (Table 1).

The IC system is calibrated with a 6-point linear calibration fit in the concentration range of 3.0 to 22.5 µg/mL potassium. System suitability tests and solution stability tests are done with a working standard of 15.0 µg/mL potassium. Spiking recoveries are evaluated as triplicates. Repeatability studies are done with a 6-fold injection.

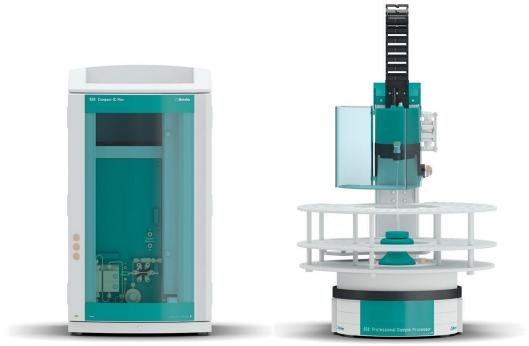

Figure 1. Instrumental setup including a 930 Compact IC Flex Oven/Deg and an 858 Professional Sample Processor.

Table 1. Parameters for the IC method as per USP Monograph «Potassium Citrate and Citric Acid Oral Solution» [3].

Column with L76 packing	Metrosep C 6 - 150/4.0
Eluent	4 mmol/L nitric acid
Flow rate	0.9 mL/min
Temperature	30 °C
Injection volume	20 µL
Detection	Direct conductivity

RESULTS

The IC method validation for the potassium assay in potassium citrate and citric acid oral solution was carried out according to the USP Monograph «Potassium Citrate and Citric Acid Oral Solution» [3]. The potassium peak was well resolved from other typical cations. The tailing factor was 1.3. Recovery results for samples spiked at three different levels were 99.2% (Table 2 and Figure 2).

Replicate tests for standards and samples always reached relative standard deviations (RSD) of less than 0.4%. Six standard solutions ranging from 3–22.5 mg/L potassium showed correlation coefficients of 0.99999 with a linear curve fit (only 0.999 was required). Intermediate precision was tested with two independent systems and analysts. The average results for the first and the second analyst did not differ by more than 0.5% (2% deviation was allowed) (Table 2).

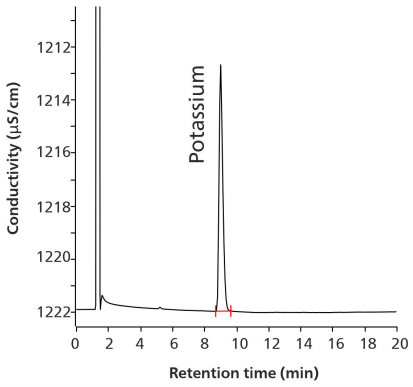

Figure 2. Chromatogram of a potassium citrate and citric acid oral solution containing 19 µg/mL potassium.

Table 2. Exemplary results and USP requirements from the IC method validation for potassium in potassium citrate and citric acid oral solution as per USP [3].

Parameter	Result	USP requirement
Tailing factor	1.3	NMT 2.0
Resolution K^+/Mg^{2+}	4.6	NLT 2.0
RSD % (n = 6)	<0.4%	NMT 0.5%
Linear correlation coefficient R	0.99999	NLT 0.999
Spiking recovery	99.2%	100 ± 3%
Intermediate precision	0.5%	NMT 2%

CONCLUSION

As per USP «Potassium Citrate and Citric Acid Oral Solution» [3], the assay for potassium is carried out with an IC using a Metrosep C 6 separation column (packing material L76). All validation results fulfilled the requirements of the monograph and followed the guidelines of the USP General Chapters <621> [4] and <1225> [5]. The presented IC method is suitable to quantify potassium in potassium citrate and citric acid oral solutions.

REFERENCES

1. National Institutes of Health (NIH) (.gov). *Potassium Citrate and Citric Acid Oral Solution USP*. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ce42122f-8087-471f-b0a3-5524bdbd4526&type=display (accessed 2024-08-26).
2. Doizi, S.; Poindexter, J. R.; Pearle, M. S.; et al. Impact of Potassium Citrate vs Citric Acid on Urinary Stone Risk in Calcium Phosphate Stone *Formers. Journal of Urology* 2018. DOI:10.1016/j.juro.2018.07.039
3. U.S. Pharmacopeia. USP-NF Potassium Citrate and Citric Acid Oral Solution. *Monograph*. DOI:10.31003/USPNF_M67530_04_01
4. *<621> Chromatography, General Chapter*, U.S. Pharmacopeia/National Formulary: Rockville, MD.
5. *1225 Validation of Compendial Procedures*; General Chapter; U.S. Pharmacopeia/National Formulary: Rockville, MD. DOI:10.31003/USPNF_M99945_04_01

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CONFIGURATION

Metrosep C 6 - 150/4.0

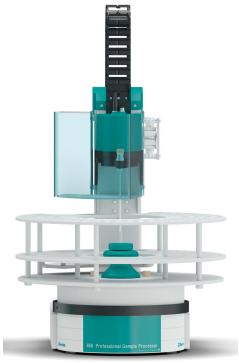
The high-capacity C 6 material makes the Metrosep C 6 - 150/4.0 separation column the optimum solution for separating standard cations with high differences in concentration in conjunction with reasonable retention times. Drinking water with low ammonium contents can be determined with this column.

930 Compact IC Flex Oven/Deg

The 930 Compact IC Flex Oven/Deg is the intelligent Compact IC instrument with **column oven**, **without suppression** and with built-in **degasser**. The instrument can be used with any separation and detection methods.

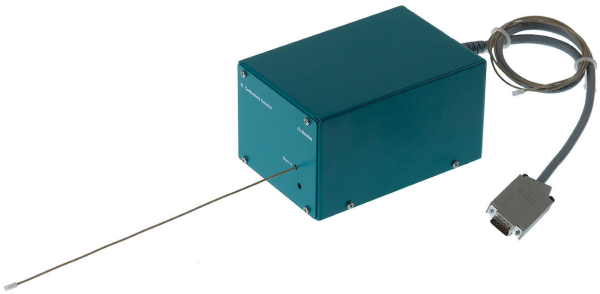
Typical areas of application:

- Anion and cation determinations without suppression with conductivity detection
- Simple applications with UV/VIS or amperometric detection



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.



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.