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Potassium Assay in OTC Drug Products by Ion Chromatography

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PURPOSE

Pharmaceutical laboratories rely heavily on monographs from the United States Pharmacopeia and National Formulary (USP–NF) to build their analytical methods. USP has embarked on a global initiative to modernize monographs with selective and sensitive methodologies to replace outdated wet chemistry methods. In the current monograph for POTASSIUM BICARBONATE AND POTASSIUM CHLORIDE EFFERVESCENT TABLET FOR ORAL SUSPENSION, identification is performed by a wet chemistry method, and assay is determined by Atomic Absorption Spectroscopy (AAS). We propose a selective and sensitive ion chromatography (IC) method for the potassium assay drug product, which can also be used for the identification application.

METHOD

Ion chromatography (IC) is suitable for separation and quantification of mono- and divalent cations and many aliphatic amines in pharmaceutical matrices. Typically, a non-suppressed conductivity detection that resembles a standard HPLC flow path is the preferred method for cation species analysis. Key advantages of non-suppressed conductivity detection are:

- Linear calibration curve over a wide range
- Organic solvents as part of eluent composition
- No metal hydroxide formation
- Economical

In this case, a cation exchange column, Metrosep C6-150/4. 0mm with L76 packing and 4 mmol/L nitric acid as the eluent and a flow rate of 0. 9 mL/min, was used. We transferred and dissolved approximately 50 g of finely powdered Potassium 25 mEq tablets to a 2000 mL volumetric flask (equivalent to 10 tablets' weight), added 200 mL of DI water, swirled until effervescence ceased, diluted to volume with DI water, and mixed well. The method is validated according to USP General Chapter <1225> VALIDATION OF COMPENDIAL METHODS

RESULT

Optimized chromatographic conditions offered the best selectivity for potassium. Specificity was checked with diluent, resolution solution, standard solution, and sample solution to ensure no interference or co-elution with the potassium peak (Figure. 1). The linearity of potassium was investigated over the concentration range from 3. 75 mg/L to 22. 5 mg/L of potassium covering 25% to 150% of the expected potassium concentration. An overlay of these chromatograms is shown in Figure 2. The correlation coefficient was found to be 0. 9999 and the calculated Y-intercept bias was 0. 5% of the 100% linearity level response (figure. 3). Method validation elements of specificity, linearity, system suitability, solution stability, accuracy and precision, and intermediate precision and accuracy were investigated. Validation results met the acceptance criteria and are summarized in Table1. The data demonstrated that the assay procedure can be used for the ID of potassium in potassium bicarbonate and potassium chloride effervescent tablet for oral suspension.

Determination of Potassium in Potassium bicarbonate and potassium chloride effervescent tablets for oral suspension			
Parameters	**USP Requirement**	**Metrohm Procedure**	**Status**
Column (L76)	NA	Metrosep C 6 - 150/4.0 (L76) & Metrosep C 6 Guard/4.0	✓
Eluent	NA	4.0 mmol/L Nitric acid	✓
Flow	NA	0.9 mL/min	✓
Detection	NA	Non-Suppressed conductivity	✓
Injection Volume	NA	20 µL	✓
Run time	NA	20 minutes	✓
Column Temperature	NA	30° C	✓
Working Standard concentration	NA	10.0 mg/L Potassium standard	✓
Sample concentration	NA	10.0 mg/L Potassium	✓
Specificity			
Blank	No interference with Potassium peak	No interference with Potassium	✓
Tailing	Potassium peak Tailing in NMT 2.0 for Standard & Sample Solution	Standard = 1.37 / Sample = 1.38	✓
Interference/Co-elution	Resolution of the nearest peak from potassium is NLT 2.0 for Resolution Standard	Resolution Standard = 4.17	✓
Critical Pair	Resolution between potassium and adjacent impurity should be NLT 2.5 for sample solution	Sample = 11.3	✓
System Suitability			
10.0 mg/L Potassium standard	Six replicate injections RSD is NMT 0.5%	Potassium RSD = 0.10%	✓
Solution Stability			
10.0 mg/L Potassium standard & sample solutions	The change in peak area is NMT 2.0% from the initial time point - (µS/cm)*min	Potassium peak area change is 0.8%	✓
Linearity			
Six linearity solutions range from 25 - 150% (3.75, 7.5, 11.25, 15.0, 18.75 & 22.5 mg/L)	Correlation Coefficient (R) is NLT 0.999	0.9999	✓
	Y-Intercept	0.014	✓
	Y-Intercept bias: ≤ 2.0% of 100% linearity level response	0.51%	✓
Repeatability			
Repeatability solutions - analyze against Standard solution (six replicate injections of standard solution)	The average Assay result should be NLT 90.0% and NMT 110.0% of the label claim	The average Assay results was 104.6%	✓
	The RSD of the six Assay results should be NMT 1.0%.	The RSD of 6 Assay results was 0.66%	✓
Accuracy			
Accuracy solutions (Sample solutions are spiked with standard solutions at 50%, 75%, 100% and 150%). Prepare in triplicate at each level and analyze against average response of six replicate injections of Standard solution	The average recovery result at each spiked level should be within 100 ± 3%.	Average recovery for potassium Assay was 97.9%, 96.7% and 96.1% at 110%, 120% and 130% respectively.	✓
Intermediate Precision			
Second Analyst	Column: Metrosep C 6 - 150/4.0, ID No: 0033-2263	Date: 17/05/2018 to 18/05/2018	✓
Specificity			
Blank	No interference with Potassium peak	No interference with Potassium	✓
Tailing	Potassium peak Tailing in NMT 2.0 for Standard & Sample Solution	Standard = 1.44 / Sample = 1.46	✓
Interference/Co-elution	Resolution of the nearest peak from potassium is NLT 2.0 for Resolution Standard & Sample Solution	Resolution Standard = 4.62 / Sample = 11.01	✓
System Suitability			
10.0 mg/L Potassium standard	Six replicate injections RSD is NMT 0.5%	Potassium RSD = 0.18%	✓
Repeatability			
Repeatability solutions analyzed against Standard solution (six replicate injections of standard solution) by a different analyst on a different day and using a different batch of column	The average result should be NLT 90.0% and NMT 110.0% of the label claim	The average Assay results was 105.0%	✓
	The RSD of the six Assay results should be NMT 1.0%	The RSD of 6 Assay results was 0.22%	✓
	The two average results for first and second scientists do not differ by more than 2.0%	The difference was 0.19%	✓
Determination of Potassium in Potassium bicarbonate and potassium chloride effervescent tablets for oral suspension			✓
Parameters	**USP Requirement**	**Metrohm Procedure**	**Status**
Column (L76)	NA	Metrosep C 6 - 150/4.0 (L76) & Metrosep C 6 Guard/4.0	✓
Eluent	NA	4.0 mmol/L Nitric acid	✓
Flow	NA	0.9 mL/min	✓
Detection	NA	Non-Suppressed conductivity	✓
Injection Volume	NA	20 µL	✓
Run time	NA	20 minutes	✓
Column Temperature	NA	30° C	✓
Working Standard concentration	NA	10.0 mg/L Potassium standard	✓
Sample concentration	NA	10.0 mg/L Potassium	✓
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	The RSD of the six Assay results should be NMT 1.0%	The RSD of 6 Assay results was 0.22%	✓
	The two average results for first and second scientists do not differ by more than 2.0%	The difference was 0.19%	✓

Table 1: Validation Summary

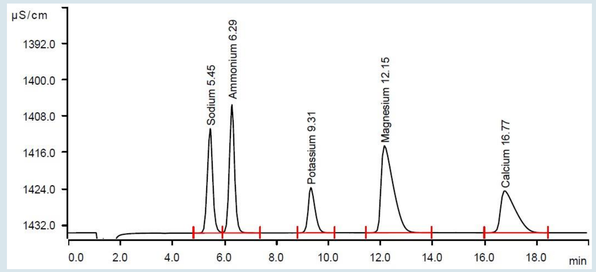
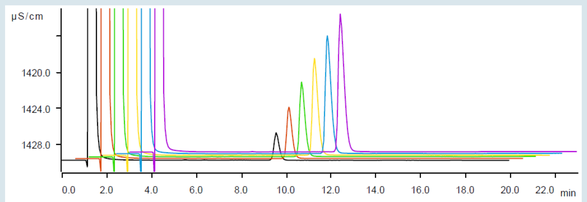


Fig 1: Specificity: Resolution solution



	Ident	Sample type	Volume	Legend	Display	Analysis
1	3.75 mg/L potassium standard	Standard 1	20.0		on	Cations
2	7.5 mg/L potassium standard	Standard 2	20.0		on	Cations
3	11.25 mg/L potassium standard	Standard 3	20.0		on	Cations
4	15.0 mg/L potassium standard	Standard 4	20.0		on	Cations
5	18.75 mg/L potassium standard	Standard 5	20.0		on	Cations
6	22.5 mg/L potassium standard	Standard 6	20.0		on	Cations

Fig 2: Linearity: Chromatograms overlay

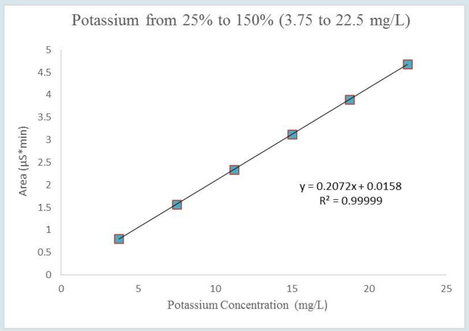


Fig 3: Linearity for Potassium

- Metrohm 940 Professional IC Vario
- Detection: Direct Conductivity Detection
- Column Temperature: 30° C
- Flow Rate: 0.9 mL/min
- Injection Volume: 20 µL
- Run Time: 20.0 min
- Eluent : 4 mmol/L nitric acid - Isocratic separation
- Metrosep C 6 - 150/4.0, 4mm × 150 mm, packing L76
- Metrosep C 6 Guard/4.0

Fig 3: Ion Chromatography instrument used for OTC Assay

CONCLUSION

We successfully developed and validated a single IC procedure for potassium assay and identification in potassium bicarbonate and potassium chloride for effervescent oral suspension. The optimized chromatographic conditions can be used for other cationic impurities, such as magnesium, calcium, sodium, and ammonium in potassium bicarbonate and potassium chloride for effervescent oral suspension. A single chromatographic method for assay and identification simplifies the overall QA/QC workflow.

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Metrohm USA Inc.