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USP Modernization Initiative: Ionic Impurities in Drug Substances by Ion Chromatography

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PURPOSE

Chloride and sulfate are common impurities present in drug substances and drug products. Limit tests are based on turbidity and/or visual comparison methods as per USP general chapter. These methods lack specificity and data integrity.

One of the main goals of the USP monograph modernization initiative is to replace non-specific methods with highly selective and sensitive instrumental analysis methods. We propose a selective and sensitive ion chromatography (IC) method for chloride and sulfate detection in drug substances, potassium carbonate and potassium bicarbonate. The proposed method can be used for other anionic impurities, such as fluoride, bromide, nitrate and nitrate, if needed.

METHOD

Chloride and sulfate are separated using a strong anion exchange column L91 and detected by suppressed conductivity detection. Sequential suppression provided the lowest background conductivity and noise, offering the best possible quantification limits for these impurities in drug substances. Isocratic eluent composition of 7. 5mM Na_2CO_3, 0. 75mM NaOH was used at a flow rate of 0. 8 mL/min. The method was validated for specificity, system suitability, solution stability, linearity, accuracy and repeatability, intermediate precision and a sample impurities test.

RESULT

Specificity was tested with DI water used as diluent, standard solution (Figure 1), sample solution and spiked sample solution (Figure 2). Solution stability was tested for low level standard solution and the sample solution spiked at impurity level for 24 hours. A linear calibration curve with weighting 1 was used. In the provided samples, chloride and sulfate concentrations were found to be below the lowest standard level. Linear extrapolation was used to estimate chloride and sulfate concentration of the samples for calculating spiking recoveries. Repeatability studies and spiking tests fulfilled the acceptance criteria. Intermediate precision between two different columns (same type and same eluent) and two different analysts on different days was acceptable. The method validation results are summarized in Table 1 and the method robustness study results are summarized in Table 2.

Validation Summary: Chloride & Sulfate Impurities in Potassium Carbonate and Bicarbonate				
	Column: A Supp 16 150/4.0, 08 0054 2339		**Date:** 02/01-03/18	
Parameters	**USP Requirement**	**Potassium Carbonate**	**Potassium Bicarbonate**	**Status**
Column (L 91)	NA	A Supp 16 150/4.0 (L91)/Supp 16 guard (L91)	A Supp 16 150/4.0 (L91)/Supp 16 guard	✓
Eluent	NA	75mM Na_2CO_3/75mM NaOH	75mM Na_2CO_3/75mM NaOH	✓
Flow Rate	NA	0.8mL/Min	0.8mL/Min	✓
Detection	NA	Suppressed Conductivity	Suppressed Conductivity	✓
Injection Volume	NA	50µL	50µL	✓
Run time	NA	22 Minutes	22 Minutes	✓
Column Temperature	NA	45°C	45°C	✓
Specificity				
Blank	No interference with impurities	No interference with impurities	No interference with impurities	✓
Interference/mixed ion standard	Resolution of NLT 1.5 between impurity &	Chloride = 6.167 / Sulfate = 4.042	Chloride = 6.155/ Sulfate = 2.889	✓
Interference/sample spike	Resolution of NLT 1.5 between impurity &	Chloride = 17.5 / Sulfate = 4.137	Chloride = 4.97 / Sulfate = 3	✓
System Suitability				
Resolution (from system suitability solution)	Resolution of NLT 2.0 between main peak&	Chloride = 17.5 / Sulfate = 4.137	Chloride = 3.38 / Sulfate = 3	✓
Mean Tailing Factor from 6 replicates	NMT 2.0	Chloride = 1.376 / Sulfate = 1.193	Chloride = 1.02 / Sulfate = 0.98	✓
Retention Time	Report	Chloride = 5.72 / Sulfate = 17.04	Chloride = 6.1 / Sulfate = 18.1	✓
USP Signal to Noise	NLT 20	Chloride = 956 / Sulfate = 264	Chloride = 5952 / Sulfate = 1337	✓
System Precision (6 low level standards)	RSD of areas of replicate injections /Report value	Chloride = 0.613 / Sulfate = 0.936	Chloride = 3.2 / Sulfate = 4.9	✓
Solution Stability				
Low level standard & low level spike	Change in peak area NMT 10% from initial point (µS/cm)-Min	Chloride = 0.018/0.018 Sulfate = 0.013/0.013	Chloride = 0.071/0.088 Sulfate = 0.598/0.023	✓
Linearity				
6 point calibration	Correlation coeff: (R)NLT 0.99	Chloride = 0.998 / Sulfate = 0.999	Chloride = 0.999 / Sulfate = 0.999	✓
Accuracy				
Recovery (0.5% level)	100±20%	Chloride = 96% / Sulfate = 97%	Chloride = 98% / Sulfate = 96%	✓
Recovery (0.75% level)	100±10%	Chloride = 93.4% / Sulfate = 95.5%	Chloride = 99% / Sulfate = 95%	✓
Recovery (1.5% level)	100±10%	Chloride = 98.7% / Sulfate = 98.7%	Chloride = 104% / Sulfate = 101%	✓
Repeatability				
6 low level spikes	RSD of 6 recoveries: NMT 10.0%	Chloride = 3.295% / Sulfate = 2.500%	Chloride = 8% / Sulfate = 4%	✓
Sample impurities test				
Santa Cruz	Duplicate analysis & report average	<50mg/kg	<50 mg/kg	✓
Spectrum	Duplicate analysis & report average	Sulfate = 19mg/kg	<50 mg/kg	✓
Sigma	Duplicate analysis & report average	Sulfate = 10mg/kg	<50 mg/kg	✓
Intermediate Precision				
		Analyst: Jay Shaffer/**Column:** A Supp 16 150/4.0 SHF 003 3006	**Analyst:** Gabriele Zerbst/ **Column:** A Supp 16 150/4.0 SHF 0093 2004	
Specificity				
Blank	No interference with impurities	No interference with impurities	No interference with impurities	✓
Interference/mixed ion standard	Resolution of NLT 1.5 between impurity &	Chloride = 6.167 / Sulfate = 4.042	Chloride = 5.1 / Sulfate = No peak for	✓
Interference/sample spike	Resolution of NLT 1.5 between impurity &	Chloride = 17.39 / Sulfate = No peak for comparison	Chloride = 17.23 / Sulfate = No peak for comparison	✓
System Suitability				
Resolution (from system suitability solution)	Resolution of NLT 2.0 between main peak&	Chloride = 17.39 / Sulfate = No peak for comparison	Chloride = 17.21 / Sulfate = No peak for comparison	✓
Mean Tailing Factor from 6 replicates	NMT 2.0	Chloride = 1.376 / Sulfate = 1.193	Chloride = 1.06/ Sulfate = 1.20	✓
Retention Time	Report	Chloride = 6.05 / Sulfate = 17.59	Chloride = 5.92 / Sulfate = 17.45	✓
USP Signal to Noise	NLT 20	Chloride = 689 / Sulfate = 167	Chloride = 689 / Sulfate = 167	✓
System Precision (6 low level standards)	RSD of areas of replicate injections /Report	Chloride = 2.579 / Sulfate = 3.960	Chloride = 2.37% / Sulfate = 1.66	✓
RSD of 6 recoveries	NMT 10%	Chloride = 0.518% / Sulfate = 0.679	Chloride = 3.1% / Sulfate = 1.4%	✓
Average Recovery	100±20%	Chloride = 102% / Sulfate = 102%	Chloride = 107% / Sulfate = 95%	✓
Difference of Average Between Analyst 1& 2	NMT 20%	Chloride = 4% / Sulfate = 5%	Chloride = 6.1% / Sulfate = 4.1%	✓

Table 1: Validation Summary

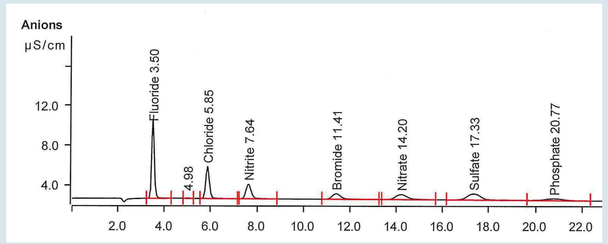

Fig 1. Specificity: Mixed anion standard

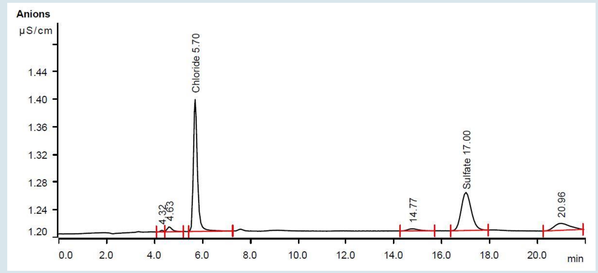

Fig 2: 100 ppb spike in santa K_2CO_3 sample

Robustness study results from System suitability								
Actual Method Conditions		Column temperature: 45°						
		Flow rate: 0.8 mL/min						
		Eluent strength: 7.5mM Na2CO3/0.75mM NaOH						
Flow Rate Variation from 0.6 (mL/min), 0.8(mL/min) and 1.0(mL/min)								
Column oven temperature Variation from 41°, 45°and 50°								
Eluent strength Variation from 6.0mMNa2CO3/0.6mM NaOH, 7.5mM/0.75 and 8.5mM/0.85mM								
Parameter	Variation	Retention Time		Resolution between	USP Tailing		%RSD	
		Cl	SO4	Cl & SO4	Cl	SO4	Cl	SO4
Flow rate (mL/Min)	0.6	7.54	22.13	23.7	1.29	1.19	0.55	1.05
	0.8	5.72	17.03	22.00	1.38	1.19	0.61	0.93
	1	4.55	13.30	20.5	1.51	1.23	0.47	1.40
Column Oven Temperature (°)	41	5.82	17.00	21.92	1.39	1.20	0.49	0.98
	45	5.72	17.03	22.00	1.38	1.19	0.61	0.93
	50	5.63	17.38	23.48	1.38	1.20	1.80	1.39
Eluent Strength (mM)	6.0/0.60	6.21	21.94	25.86	1.38	1.19	0.46	2.03
	7.5/0.75	5.72	17.03	22.00	1.38	1.19	0.61	0.93
	8.5/0.85	5.47	14.88	20.83	1.63	2.75	0.68	0.83

Table 2: Robustness summary

- Metrohm 940 Professional IC Vario
- Detection: Conductivity Detection after Sequential Suppression
- Column Temperature: 30° C
- Flow Rate: 0.8 mL/min
- Injection Volume: 10 µL
- Eluent : 7. 5mM Na_2CO_3, 0. 75mM NaOH
- Column: Metrosep A Supp 10-250/4.0, packing L91

Fig 3: Ion Chromatography instrument used for drug substance impurity

CONCLUSION

We successfully validated an IC method to determine chloride and sulfate in drug substances, potassium bicarbonate and potassium carbonate. The proposed IC method overcomes limitations of the turbidimetry / visual comparison methods.

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