

# 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 nitrite, 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<sub>2</sub>CO<sub>3</sub>, 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				
Parameters	USP Requirement	Potassium Carbonate	Potassium Bicarbonate	Status
Column ID (B1)	NA	A Supp 10-250/4.0 (L91) Supp 10-250/4.0 (L91)	A Supp 10-250/4.0 (L91) Supp 10-250/4.0 (L91)	✓
Eluent	NA	7.5mM Na <sub>2</sub> CO <sub>3</sub> /0.75mM NaOH	7.5mM Na <sub>2</sub> CO <sub>3</sub> /0.75mM 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	✓
<b>Specificity</b>				
Blank	No interference with impurities	No interference with impurities	No interference with impurities	✓
Interference/related ion standard	Resolution of NET 1.5 between impurity & component	Chloride = 6.127 / Sulfate = 4.042	Chloride = 6.1152 / Sulfate = 4.049	✓
Interference/impurity spike	Resolution of NET 1.5 between impurity & component	Chloride = 17.33 / Sulfate = 4.137	Chloride = 17.33 / Sulfate = 4.137	✓
<b>System Suitability</b>				
Resolution (from system suitability solution)	Resolution of NET 2.0 between main peak	Chloride = 17.33 / Sulfate = 4.137	Chloride = 17.33 / Sulfate = 4.137	✓
Mean Tailing Factor from 6 replicates	NMT 2.0	Chloride = 1.376 / Sulfate = 1.351	Chloride = 1.32 / Sulfate = 0.98	✓
Retention Time	Report	Chloride = 5.72 / Sulfate = 17.03	Chloride = 5.72 / Sulfate = 17.03	✓
USP Signal to Noise	NLT 20	Chloride = 956 / Sulfate = 264	Chloride = 952 / Sulfate = 137	✓
System Precision (at low level standard)	RSD of areas of replicate injections / Report value	Chloride = 0.63 / Sulfate = 0.55	Chloride = 0.2 / Sulfate = 0.9	✓
<b>Solution Stability</b>				
Low level standard & low level spike	Change in peak area NMT 3.0% from initial point 60/30min	Chloride = 0.024/0.028 / Sulfate = 0.024/0.023	Chloride = 0.071/0.088 / Sulfate = 0.020/0.023	✓
<b>Linearity</b>				
6-point calibration	Correlation coeff. ≥0.99 / 0.99	Chloride = 0.998 / Sulfate = 0.999	Chloride = 0.999 / Sulfate = 0.999	✓
<b>Accuracy</b>				
Recovery (0.1% level)	100±20%	Chloride = 99% / Sulfate = 99%	Chloride = 99% / Sulfate = 99%	✓
Recovery (0.5% level)	100±10%	Chloride = 93.8% / Sulfate = 95.5%	Chloride = 99% / Sulfate = 95%	✓
Recovery (1.5% level)	100±10%	Chloride = 98.7% / Sulfate = 98.7%	Chloride = 104% / Sulfate = 102%	✓
<b>Repeatability</b>				
6 low level spikes	RSD of 6 recoveries: NMT 10.0%	Chloride = 3.250% / Sulfate = 2.520%	Chloride = 3% / Sulfate = 4%	✓
<b>Sample impurities test</b>				
Sample Use	Duplicate analysis & report average	<50ng/g	<50 ng/g	✓
Spectrum	Duplicate analysis & report average	Sulfate = 136ng/g	<50 ng/g	✓
Spms	Duplicate analysis & report average	Sulfate = 130ng/g	<50 ng/g	✓
<b>Intermediate Precision</b>				
Analyst: Day 1/Analyst: Day 2	Analyst: Day 1/Analyst: Day 2	Analyst: Day 1/Analyst: Day 2	Analyst: Day 1/Analyst: Day 2	
<b>Specificity</b>				
Blank	No interference with impurities	No interference with impurities	No interference with impurities	✓
Interference/related ion standard	Resolution of NET 1.5 between impurity & component	Chloride = 6.127 / Sulfate = 4.042	Chloride = 5.7 / Sulfate = No peak for comparison	✓
Interference/impurity spike	Resolution of NET 1.5 between impurity & component	Chloride = 17.33 / Sulfate = 4.137	Chloride = 17.33 / Sulfate = 4.137	✓
<b>System Suitability</b>				
Resolution (from system suitability solution)	Resolution of NET 2.0 between main peak	Chloride = 17.33 / Sulfate = 4.137	Chloride = 17.33 / Sulfate = 4.137	✓
Mean Tailing Factor from 6 replicates	NMT 2.0	Chloride = 0.926 / Sulfate = 1.139	Chloride = 1.08 / Sulfate = 1.20	✓
Retention Time	Report	Chloride = 6.25 / Sulfate = 17.53	Chloride = 5.92 / Sulfate = 17.45	✓
USP Signal to Noise	NLT 20	Chloride = 689 / Sulfate = 167	Chloride = 689 / Sulfate = 167	✓
System Precision (at low level standard)	RSD of areas of replicate injections / Report	Chloride = 2.579 / Sulfate = 1.950	Chloride = 2.37% / Sulfate = 1.66	✓
RSD of 6 recoveries	NMT 3.0%	Chloride = 0.519% / Sulfate = 0.479	Chloride = 3.1% / Sulfate = 1.0%	✓
Average Recovery	100±20%	Chloride = 102% / Sulfate = 102%	Chloride = 107% / Sulfate = 99%	✓
Difference of Average Between Analysts 1 & 2	NMT 20%	Chloride = 6% / Sulfate = 5%	Chloride = 4.2% / Sulfate = 4.2%	✓

Table 1: Validation Summary

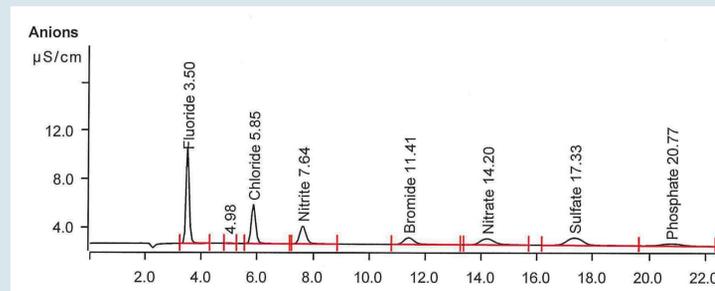


Fig 1. Specificity: Mixed anion standard

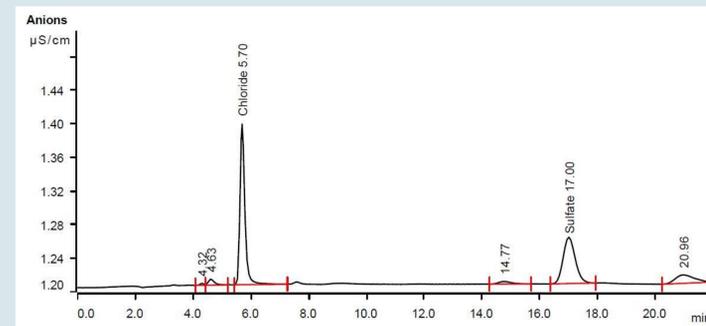


Fig 2: 100 ppb spike in sample K<sub>2</sub>CO<sub>3</sub>

Robustness study results from System suitability								
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 (°C)	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	0.81	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<sub>2</sub>CO<sub>3</sub>, 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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