

# 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				
	Column: A Supp 10-250/4.0, SR 0054-0039	Date: 02/01/2018		
Parameters	USP Requirement	Potassium Carbonate	Potassium Bicarbonate	Status
Column (L91)	NA	A Supp 10-250/4.0 (SR 0054-0039)	A Supp 10-250/4.0 (SR 0054-0039)	✓
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	20µL	20µL	✓
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/related ion standard	Resolution of NLT 3.5 between impurity &	Chloride = 6.167 / Sulfate = 0.042	Chloride = 6.152 / Sulfate = 0.089	✓
Interference/sample spike	Resolution of NLT 3.5 between impurity &	Chloride = 17.3 / Sulfate = 4.137	Chloride = 17.3 / Sulfate = 4	✓
System Suitability				
Resolution (flow system suitability solution)	Resolution of NLT 2.0 between main peak	Chloride = 17.3 / Sulfate = 4.137	Chloride = 17.3 / Sulfate = 4	✓
Mean Tailing Factor from 6 replicates	NMT 2.0	Chloride = 1.376 / Sulfate = 1.183	Chloride = 1.02 / Sulfate = 0.36	✓
Retention Time	Report	Chloride = 5.72 / Sulfate = 17.04	Chloride = 5.7 / Sulfate = 16.1	✓
USP Signal to Noise	NLT 20	Chloride = 952 / Sulfate = 264	Chloride = 952 / Sulfate = 137	✓
System Precision (6 low level standards)	RSD of areas of replicate injections/Report value	Chloride = 0.63 / Sulfate = 0.391	Chloride = 3.2 / Sulfate = 4.9	✓
Solution Stability				
Low level standard & low level spike	Chloride in peak area NMT 30% from initial point	Chloride = 0.071/0.088	Sulfate = 0.080/0.023	✓
Linearity				
System calibration	Correlation coeff. (NLT) 0.99	Chloride = 0.998 / Sulfate = 0.999	Chloride = 0.999 / Sulfate = 0.999	✓
Accuracy				
Recovery (0.2% level)	100±2%	Chloride = 99% / Sulfate = 99%	Chloride = 99% / Sulfate = 99%	✓
Recovery (0.25% level)	100±1%	Chloride = 93.8% / Sulfate = 95.5%	Chloride = 99% / Sulfate = 95%	✓
Recovery (1.5% level)	100±1%	Chloride = 98.7% / Sulfate = 98.7%	Chloride = 104% / Sulfate = 102%	✓
Repeatability				
6 low level spikes	RSD of 6 recoveries: NMT 10.0%	Chloride = 3.250% / Sulfate = 2.502%	Chloride = 3% / Sulfate = 4%	✓
Sample impurities test				
Santa Oro	Duplicate analysis & report average	<50 ng/g	<50 ng/g	✓
Spectrum	Duplicate analysis & report average	Sulfate = 136 ng/g	<50 ng/g	✓
Name	Duplicate analysis & report coverage	Sulfate = 30 ng/g	<50 ng/g	✓
Intermediate Precision				
	Analyst: Jay Shaffer/Column: A Supp 10-250/4.0 (SR 0054-0039)	Analyst: Gabriela Zierler/Column: A Supp 10-250/4.0 (SR 0054-0039)		
Specificity				
Blank	No interference with impurities	No interference with impurities	No interference with impurities	✓
Interference/related ion standard	Resolution of NLT 3.5 between impurity &	Chloride = 6.167 / Sulfate = 0.042	Chloride = 5.7 / Sulfate = No peak for comparison	✓
Interference/sample spike	Resolution of NLT 3.5 between impurity &	Chloride = 17.3 / Sulfate = No peak for comparison	Chloride = 17.3 / Sulfate = No peak for comparison	✓
System Suitability				
Resolution (flow system suitability solution)	Resolution of NLT 2.0 between main peak	Chloride = 17.3 / Sulfate = No peak for comparison	Chloride = 17.3 / Sulfate = No peak for comparison	✓
Mean Tailing Factor from 6 replicates	NMT 2.0	Chloride = 6.092 / Sulfate = 1.139	Chloride = 1.08 / 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 = 889 / Sulfate = 167	Chloride = 889 / Sulfate = 167	✓
System Precision (6 low level standards)	RSD of areas of replicate injections/Report	Chloride = 2.579 / Sulfate = 3.960	Chloride = 3.17% / Sulfate = 3.66	✓
RSD of 6 recoveries	NMT 10%	Chloride = 0.518% / Sulfate = 0.479	Chloride = 3.12% / Sulfate = 1.8%	✓
Average Recovery	100±20%	Chloride = 102% / Sulfate = 102%	Chloride = 107% / Sulfate = 98%	✓
Difference of Average Between Analysts	NMT 20%	Chloride = 9% / Sulfate = 5%	Chloride = 0.1% / Sulfate = 4.1%	✓

Table 1: Validation Summary

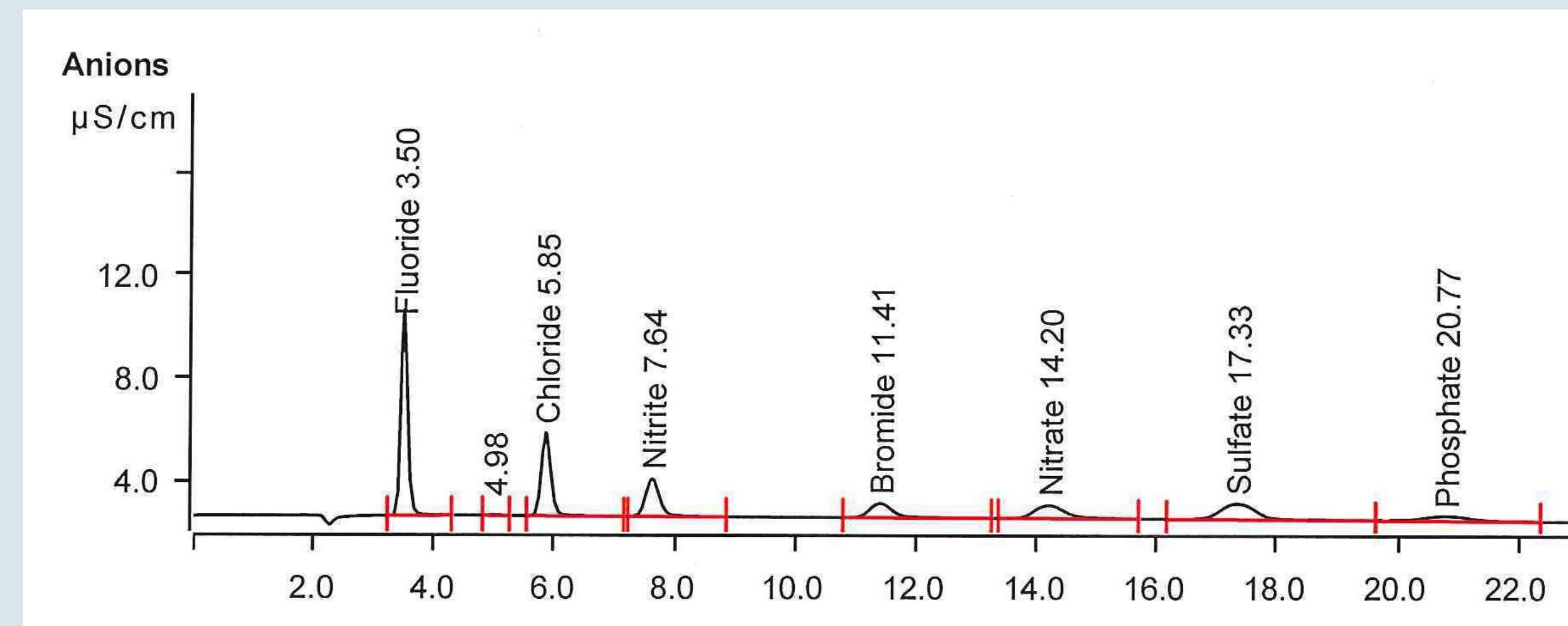


Fig 1. Specificity: Mixed anion standard

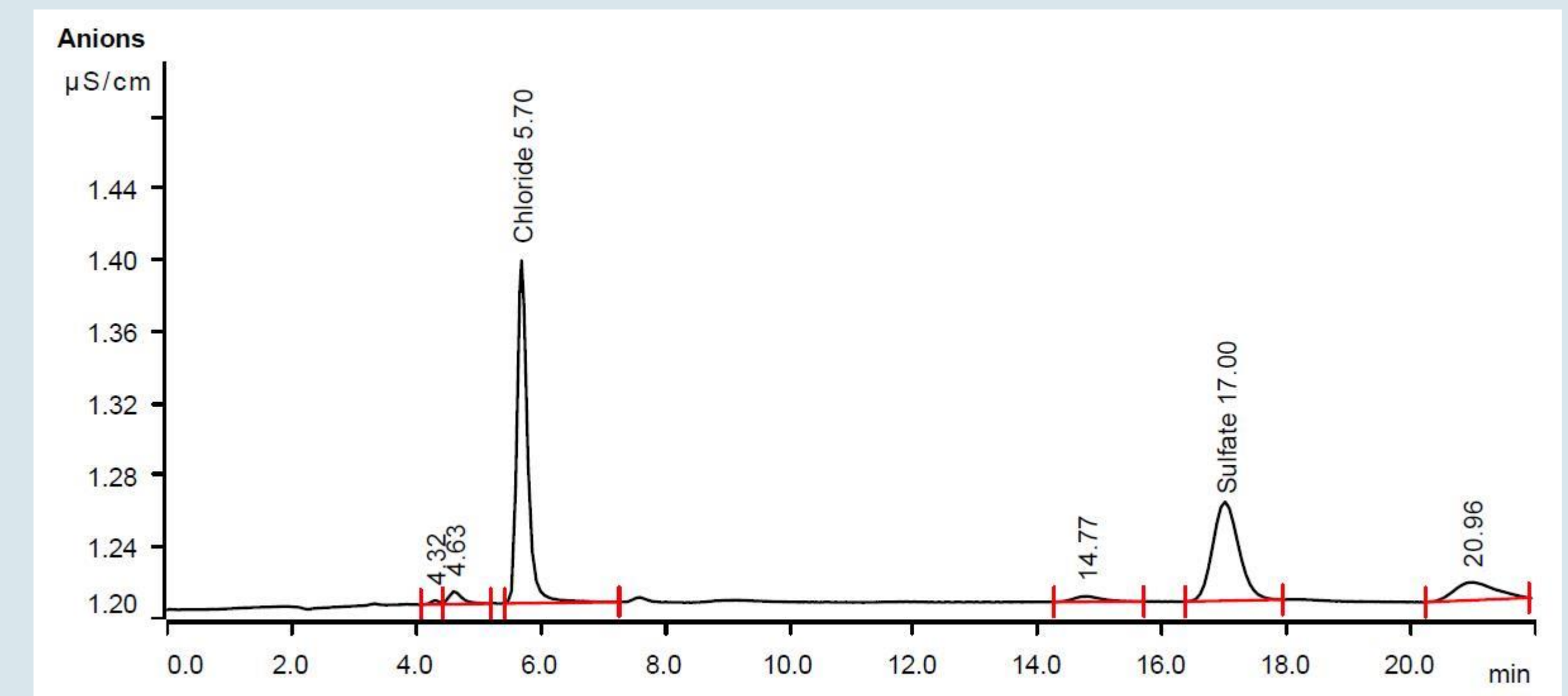


Fig 2: 100 ppb spike in santa K<sub>2</sub>CO<sub>3</sub> sample

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	1.93
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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