Poster Note 71825

Ion Chromatography Assay for Lithium in Lithium Citrate

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Overview

Purpose: To develop an ion chromatography (IC) method using an RFIC™ system with suppressed conductivity detection as a candidate to replace the existing assay for lithium in the USP lithium citrate monograph.

Methods: Method development and validation were performed in accordance with guidelines prescribed in the USP General Chapter <1225> for the following parameters: 1) separation 2) sample analysis 3) calibration, LOD and LOQ 4) sample accuracy and determination 5) robustness

Results: The assay for lithium described here was validated and it met the analytical performance characteristics outlined in USP General Chapter <1225>, Validation of Compendial Procedures.

Introduction

Lithium is considered a primary therapeutic agent for acute and prophylactic treatment of biopolar disorder[1] . Practically, lithium is administered as salts such as lithium citrate. The USP has initiated an effort to modernize existing monographs across all compendia[2]. In response to this effort, this work describes an alternative method for lithium citrate analysis that is automated, fast, and uses an aqueous mobile phase (eluent). IC offers a significant improvement to the existing assays because it can simultaneously determine lithium, sodium, calcium, and other common cations in a single injection[3]. Moreover, using a Reagent-Free™ Ion Chromatography (RFIC) system with electrolytically generated methanesulfonic acid (MSA) eluent (Figure 1) simplifies the method and enhances reproducibility.

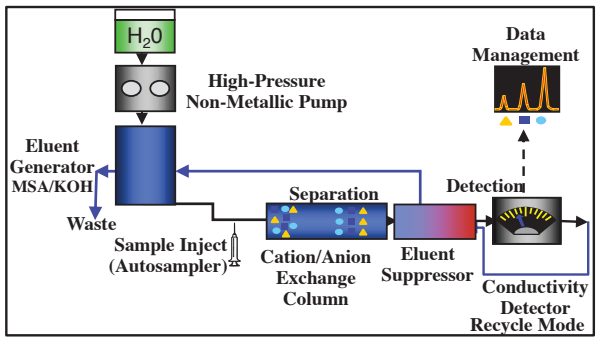
Methods

Equipment

•A Thermo Scientific Dionex ICS-2100 RFIC system was used in this work.

The Dionex ICS-2100 system is an integrated ion chromatograph that includes:
- Pump
- Column Heater
- Pump Degas
- EG Eluent Generator
- Thermo Scientific Dionex AS-AP Autosampler

Figure 1. RFIC principle.



Conditions

Columns:	Thermo Scientific Dionex IonPac CS12A-5µM, 3 x 150 mm Dionex IonPac CG12A-5µm Guard, 3 × 30 mm
Eluent:	8 mM MSA for 0 to 6 min, 67 mM MSA 6 to 8 min, 8 mM MSA for 8 to 20 min
Eluent Source:	Dionex ICS-2100 EG with Thermo Scientific Dionex CR-CTC Continuously Regenerated Cation Trap Column
Temperature:	33 °C
Flow Rate:	0.4 mL/min
Inj.Volume:	10 µL
Detection:	Thermo Scientific™ Dionex™ CERS™ 500 Cation Electrolytically Regenerated Suppresor 2 mm, 79 mA, recycle mode

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Robustness Study

Following the guidelines of USP Physical Tests, <621> Chromatography, we evaluated the robustness of this method by examining the retention time (RT), peak asymmetry and resolution after imposing small variations (±10%) in procedural parameters (e.g., flow rate, eluent concentration, column temperature)[4].

Results

Separation

Separation of lithium was achieved using a Dionex IonPac CS12A, 3 x 150 mm column under gradient elution conditions. Figure 2 shows separation of a 5 mg/L lithium solution prepared using lithium citrate. Figure 3 shows separation of a commercially available six cation standard mix using the proposed method. In order to achieve good separation from the nearest cation i.e. sodium, initial eluent concentration was maintained at 8 mM and then rapidly increased to 67 mM to elute the remaining cations quickly. The other four common cations elute within 10 min. The remaining 10 min prepare the column for the next sample injection.

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Figure 2. Determination of 5 mg/L lithium in deionized water.

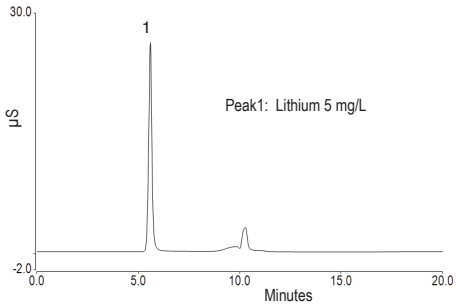
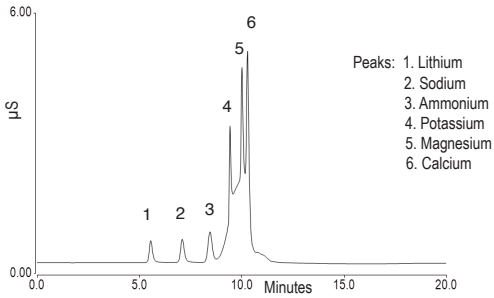


Figure 3. Separation of six common cations.



Calibration, LOD and LOQ

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the USP General Chapter <1225> guidelines recommend a minimum of five concentrations to establish linearity in an assay[5]. For a drug substance or finished product, the minimum specified range is from 80 to 120% of the test concentration. A minimum range from 50 to 120% is required for determination of an impurity. In this study, lithium was calibrated at 14 concentration levels ranging from 0.1 to 15 mg/L. The results yielded a linear relationship of peak area to concentration with a coefficient of determination (r^2) of 0.9999. The LOD and LOQ of lithium were 1.2 µg/L and 4 µg/L respectively.

Sample Accuracy and Precision

In order to test sample accuracy, recovery studies were performed after spiking lithium samples prepared using lithium citrate with lithium from lithium carbonate. Three different spike levels of 1, 5 and 10 mg/L lithium were studied and satisfactory recoveries were obtained for the spike. The results of the lithium spike recovery experiment are contained in Table 1.

Assay precision was evaluated by injecting seven replicates at three different concentration levels of 1, 5 and 10 mg/L lithium and expressed as the RSDs of RT and peak area from the series of measurements (Table 2).

Table 1. Retention time and peak area precisions of lithium solutions.

Target Lithium Concentration (mg/L)	Found (mg/L)	RT RSD (N=3)	Peak Area RSD (N=3)
1	0.99	0.01	0.35
5	5.02	0.04	0.34
10	10.07	0.05	0.32

Table 2. Recovery data for lithium spiked in lithium citrate solutions containing 5 mg/L lithium.

Lithium Concentration (mg/L)	Spike (mg/L)	Total Recovered (mg/L)	Spike Recovery (%)	RT RSD (N=3)	Peak Area RSD (N=3)
5	0	5.02	-	0.04	0.34
	1	6.01	101.5	0.03	0.37
	5	9.99	99.8	0.04	0.36
	10	14.99	99.9	0.04	0.23

Robustness Study

Assay robustness was evaluated by measuring the influence of small variations in procedural parameters on the RT, peak asymmetry and resolution from sodium on two columns from two different lots. A standard injection (5 mg/L lithium spiked with 0.1 mg/L sodium) was injected seven times (N=7) at each chromatographic condition. The results summarized in Table 3 indicate that the method is robust and suitable for lithium analysis.

Table 3. Robustness determined using a solution containing 5 mg/L lithium and 0.1 mg/L sodium.

Parameter	Value	Column 1			Column 2		
		Retention Time Difference (%)	Peak Asymmetry Difference (%)	Resolution (From Na) Difference (%)	Retention Time Difference (%)	Peak Asymmetry Difference (%)	Resolution (From Na) Difference (%)
Flow Rate (mL/min)	0.36	10.7	-1.28	2.32	10.73	-1.39	2.64
	0.40	-	-	-	-	-	-
	0.44	-8.75	0.64	-1.91	-8.63	0.35	-1.41
Column Temp (^{0}C)	30	0.26	1.28	3.35	0.31	0	4.44
	33	-	-	-	-	-	-
	36	-0.54	-0.64	-3.07	-0.52	-0.69	-3.99
MSA Eluent Initial Conc (mM)	7.2	8.06	-2.56	3.28	8.04	-2.43	3.79
	8.0	-	-	-	-	-	-
	8.8	-6.58	2.88	-2.86	-6.52	2.43	-2.51
MSA Eluent Final Conc (mM)	60.3	0	-0.96	-0.27	0	-0.35	0.32
	67.0	-	-	-	-	-	-
	73.7	-0.25	0.32	0	-0.21	-0.69	0.19

Conclusion

- The assay for lithium proposed here, was validated to meet the analytical performance characteristics outlined in USP General Chapter <1225>, Validation of Compendial Procedures, and was shown to measure accurately the lithium content of lithium citrate as per limits set in the USP monograph.
- Compared to the assay described in the USP lithium citrate monograph, this assay offers a simple, accurate, and robust measurement without handling hazardous reagents.
- This method is a candidate to replace the existing assay for lithium citrate in the USP monograph, and thereby modernize the monograph.

References

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