Application Note 1144

Ion Chromatography Assay for Lithium in Lithium Hydroxide

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Key Words
Dionex IonPac CS16 Column, Suppressed Conductivity Detection, Pharmaceutical, USP Monograph

Goal
To develop an IC method for the determination of lithium in lithium hydroxide using an RFIC system with suppressed conductivity detection.

Introduction
Lithium is considered the primary therapeutic agent for acute and prophylactic treatment for biopolar disorder.[1] Practically, lithium is administered as salts such as lithium hydroxide. The United States Pharmacopoeia (USP) monograph for lithium hydroxide describes a titration-based assay.[2] This assay involves mixing lithium hydroxide with hydrochloric acid followed by observing the color change to calculate lithium content. This method is tedious and requires a hazardous/corrosive chemical.

The USP has initiated an effort to modernize existing monographs across all compendia.[3] In response to this effort, this application note describes an alternative method to assay the lithium content of lithium hydroxide that is automated, faster, and uses an aqueous mobile phase (eluent). This method uses ion chromatography (IC) and offers significant improvement over existing assays because it can simultaneously determine lithium, sodium, calcium, and other common cations.[4] Moreover, using a Thermo Scientific™ Reagent-Free™ Ion Chromatography (RFIC™) system with electrolytically generated methanesulfonic acid (MSA) eluent simplifies the method and enhances reproducibility. This approach was successfully used to design methods for lithium quantification in lithium carbonate[5] and lithium citrate[6].

The IC-based method described in this application note uses a Thermo Scientific™ Dionex™ IonPac™ CS16 cation-exchange column, an electrolytically generated MSA eluent, and suppressed conductivity detection to determine lithium in lithium hydroxide. The Dionex IonPac CS16 column is a high-capacity cation-exchange column packed with resin functionalized with carboxylic acid groups. This column is specifically designed for the separation of alkali metals, alkaline earth metals, and ammonium at diverse concentration ratios. Therefore, the Dionex IonPac CS16 column is suited for applications involving separation of lithium from low concentrations of other cationic contaminants, when the determination of the cationic contaminants is required as is true here, where we applied the same method to determine a low amount of calcium in lithium hydroxide samples. The eluent is generated using a Thermo Scientific Dionex EGC III MSA Eluent Generator Cartridge and purified online using a Thermo Scientific Dionex CR-CTC II Continuously Regenerated Cation Trap Column. The Thermo Scientific™ Dionex™ CERS™ 500 (2 mm) Cation Electrolytically Regenerated Suppressor produces the regenerant ions necessary for eluent suppression and allows continuous operation with minimum maintenance.

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Because the RFIC system requires only deionized (DI) water as the carrier, it significantly simplifies system operation and improves analytical reproducibility. The method proposed in this application note was validated following the guidelines outlined in USP General Chapter <1225>, Validation of Compendial Procedures[7] to meet the requirements for lithium and calcium quantification prescribed in the lithium hydroxide USP monograph.

Equipment

- A Thermo Scientific™ Dionex™ ICS-5000⁺ RFIC system was used in this work. The Dionex ICS-5000⁺ is an integrated ion chromatograph that includes:
  - SP single pump module (P/N 061707) or DP Dual Pump (P/N 061712) with degas option
  - DC detector compartment (P/N 061767) with single-temperature zone
- Thermo Scientific Dionex AS-AP Autosampler with 10 µL injection loop
- Dionex EGC III MSA Cartridge (P/N 074535)
- Thermo Scientific™ Autoselect™ Polyvial™ 10 mL Autosampler Vials with caps and septa (P/N 055058)
- Dionex CERS 500 Suppressor, 2 mm (P/N 082543)
- Thermo Scientific™ Dionex™ Chromeleon™ Chromatography Data System (CDS) software version 7.2

Reagents and Standards

- DI Water, Type I reagent grade, 18 MΩ-cm resistance or better
- Lithium carbonate, 300 mg, USP Reference Standard (USP P/N 1369000, Lot Number GIJ227)
- Lithium hydroxide (monohydrate, $LiOH•H_2O$), Sigma-Aldrich®, P/N 450197-25G-F, Lot Number MKBD3360
- Thermo Scientific Dionex Six Cation-II Standard (P/N 046070, Lot Number 150216)

Conditions	
Columns:	Dionex IonPac CS16, Analytical, 3 x 250 mm (P/N 059596) Dionex IonPac CG16 Guard, 3 x 50 mm (P/N 059595)
Eluent:	10 mM MSA, 0–11 min; 65 mM MSA, 11–16 min; 10 mM MSA, 16–22 min
Eluent Source:	Dionex EGC III MSA cartridge (P/N 074535) with Dionex CR-CTC II trap column (P/N 066262)
Flow Rate:	0.45 mL/min
Background Conductance:	~0.3 µS
Detection:	Suppressed conductivity, Dionex CERS 500 suppressor, 2 mm (P/N 082543) recycle mode, 86 mA current
Noise:	~1–2 nS/min peak-to-valley
Run Time:	22 min
Injection Volume:	10 µL in Push-Full mode
Column Temperature:	40 °C

Preparation of Solutions and Reagents

Sample Preparation

Lithium Stock Solution 1000 mg/L, Prepared Using Lithium Carbonate, USP

Accurately weigh 0.5322 g of USP lithium carbonate and dissolve in DI water in a 125 mL polypropylene bottle and adjust the weight to 100 g with DI water.

Lithium Stock Solution 1000 mg/L, Prepared Using Lithium Hydroxide

Accurately weigh 0.6993 g of lithium hydroxide (hydrate) and dissolve in DI water in a 125 mL polypropylene bottle and adjust the weight to 100 g with DI water.

Working Lithium Carbonate Standard and Lithium Hydroxide Sample Solutions

To prepare working standard and sample solutions, the stock solutions were diluted appropriately with 10 mM acetic acid (final pH ~4).

Note – Use 10 mM acetic acid for sample preparation. This reduces sample pH and inhibits potential retention of divalent cations at weak cation exchange sites that are sometimes formed along the flow path. This can result in inaccurate reading for divalent cations. For more details refer to Product Manual for Dionex IonPac CS16 column, Document Number 031747-05.

Robustness Study

Following the guidelines of USP Physical Tests, <621> Chromatography,[8] evaluate 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 gradient concentration, column temperature). Inject a standard mixture containing 10 mg/L lithium, 0.12 mg/L sodium, 0.06 mg/L magnesium, and 0.06 mg/L calcium in 10 mM acetic acid. Apply the same procedure to another column set from a different lot. Test the following variations:

- Flow rate: 0.405, 0.45, and 0.495 mL/min
- Column temperature: 36, 40, and 44 °C
- MSA eluent initial concentrations: 9, 10, and 11 mM
- MSA eluent final concentrations: 58.5, 65, and 71.5 mM

Results and Discussion

Separation

Separation of lithium was achieved with a Dionex IonPac CS16, 3 x 250 mm column using initial isocratic elution followed by a step change to a higher concentration that was used to elute the remaining cations. Figure 1 shows separation of a 10 mg/L lithium solution prepared using lithium hydroxide. Figure 2 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, the initial eluent concentration was kept at 10 mM and then rapidly increased to 65 mM to elute the remaining cations quickly.

The other four common cations elute within next six minutes and the remaining time is used to re-equilibrate to starting conditions. This method can also be executed using manually prepared eluents, but the performance, especially for retention time reproducibility, will not be as good.

Columns:	Dionex IonPac CS16, 3 x 250 mm, IonPac CG16, 3 x 50 mm
Eluent:	10 mM MSA for 0 to 11 min, 65 mM MSA 11 to 16 min, 10 mM MSA for 16 to 22 min
Eluent Source:	Dionex ICS-5000⁺ EG with Dionex CR-CTC II trap column
Temperature:	40 °C
Flow Rate:	0.45 mL/min
Inj.Volume:	10 µL
Detection:	Dionex CERS 500 suppressor, 2 mm, recycle mode
Peak:	1. Lithium 10 mg/L

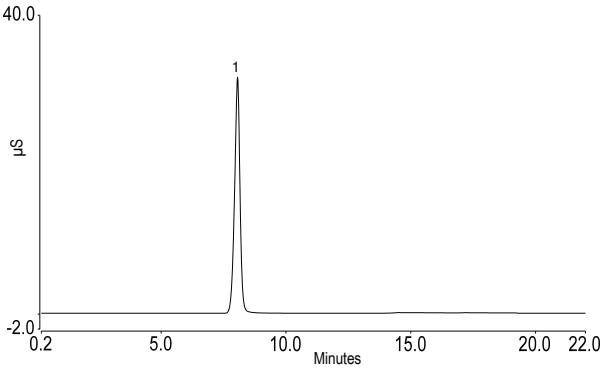

Figure 1A. Determination of 10 mg/L lithium in 10 mM acetic acid.

Columns:	Dionex IonPac CS16, 3 x 250 mm, IonPac CG16, 3 x 50 mm
Eluent:	10 mM MSA for 0 to 11 min, 65 mM MSA 11 to 16 min, 10 mM MSA for 16 to 22 min
Eluent Source:	Dionex ICS-5000⁺ EG with Dionex CR-CTC II trap column
Temperature:	40 °C
Flow Rate:	0.45 mL/min
Inj.Volume:	10 µL
Detection:	Dionex CERS 500 suppressor, 2 mm, recycle mode
Peaks:	1. Lithium 10 mg/L 2. Calcium 0.013 mg/L

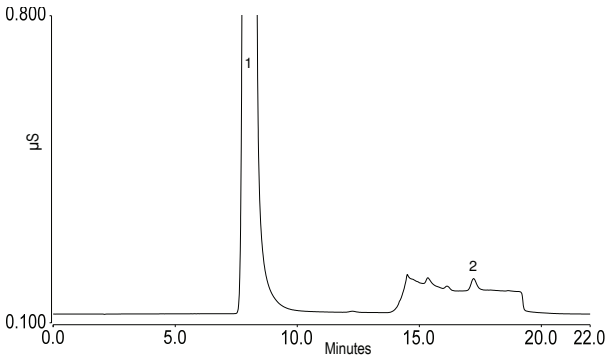

Figure 1B. Enlarged view of Figure 1A showing the calcium peak.

Columns:	Dionex IonPac CS16, 3 x 250 mm, IonPac CG16, 3 x 50 mm
Eluent:	10 mM MSA for 0 to 11 min, 65 mM MSA 11 to 16 min, 10 mM MSA for 16 to 22 min
Eluent Source:	Dionex ICS-5000⁺ EG with Dionex CR-CTC II trap column
Temperature:	40 °C
Flow Rate:	0.45 mL/min
Inj.Volume:	10 µL
Detection:	Dionex CERS 500 suppressor, 2 mm, recycle mode
Peaks:	1. Lithium 2. Sodium 3. Ammonium 4. Potassium 5. Magnesium 6. Calcium

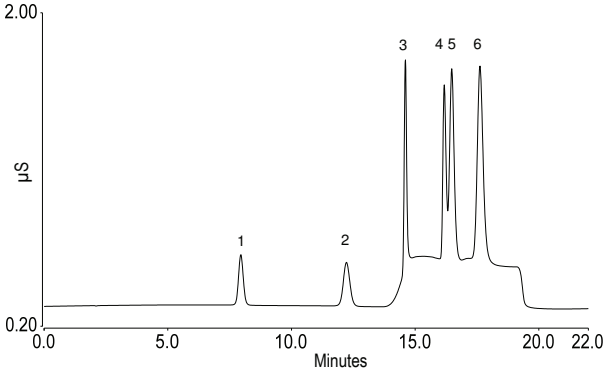

Figure 2. Separation of six common cations.

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.[7,9] 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 with eight concentration levels ranging from 0. 3 to 20 mg/L. The results yielded a linear relationship of peak area to concentration with a coefficient of determination (r^2) of 0.9999. Calcium was calibrated from 0.03 to 2 mg/L with an r^2 of 0.9999 (Table 1).

The limits of detection (LODs) and limits of quantitation (LOQs) were determined using a method described in ICH guidelines.[9] The method uses slope of the calibration curve and standard deviation of the lowest calibration standard response as described below.

$$LOD = 3.3\ \sigma / S$$

$$LOQ = 10\ \sigma / S$$

Where σ is the standard deviation of the response and S is the slope of the calibration curve.

The calculated LOD and LOQ for lithium were 2.0 and 6.1 µg/L, respectively. The LOD and LOQ values for calcium were 8.5 µg/L and 26 µg/L, respectively (Table 1).

Table 1. Method calibration, LOD, and LOQ data for lithium.

Parameter	Li	Ca
Linearity (r^2)	0.9999	0.999
LOD (µg/L)	2.0	8.5
LOQ (µg/L)	6.1	26.0

Sample Analysis

The USP monograph requires that lithium hydroxide contain not less than 98.0% and not more than 102% lithium calculated on the dried basis.[2] In this study, commercially available lithium hydroxide (≥ 99.995%) was used to prepare the test solution of 10 mg/L lithium. The calculated concentration of the test solution was 9.86 mg/L, equivalent to 98.6 % lithium content (Table 2), thus verifying the label claim. This indicates that the method is capable of determining lithium concentration within the USP specification. The USP requires that the lithium hydroxide be dried prior to assay for 1 h at 135 °C; this should result in weight loss of between 41.0 to 43.5% of its weight. In our hands, the 1 h drying process resulted in weight loss of 42.2%, as compared to a maximum 42.89% possible water loss, indicating residual water in the lithium hydroxide.

Table 2. Recovery data for lithium and calcium spiked in 10 mg/L lithium solution prepared using lithium hydroxide.

Cation (Concentration, mg/L)	Spike (mg/L)	Total Recovered (mg/L)	Recovery (%)	RT RSD (N=3)	Peak Area RSD (N=3)
Li (9.92)	1	0.99	99.6	0.01	0.03
	5	4.94	98.9	0.03	0.03
	10	9.86	98.6	0.03	0.06
Ca (0.013)	0.06	0.056	94.1	0.02	3.14
	0.12	0.11	94.7	0.01	4.19
	0.18	0.16	93.4	0.006	3.89

Note- values in parenthesis represent base concentrations determined in the 10 mg/L lithium solution before spiking.

Because we were uncertain that the drying process was successful, we used the water content provided by the manufacturer for making all lithium hydroxide solutions.

Sample Accuracy and Precision

To test sample accuracy, recovery studies were performed after spiking lithium samples prepared using lithium hydroxide 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 each spike level. The results of the lithium spike recovery experiment are 98.6 to 99.6% recovery of the spiked lithium amount. The USP monograph limits the amount of calcium in lithium hydroxide at 0.2%.[2] This corresponds to 1.2 mg/L calcium in 100 mg/L lithium. The 10 mg/L lithium solution was spiked with three calcium concentrations 0.06, 0.12, and 0.18 mg/L calcium, which correspond to 50, 100, and 150% of the prescribed limit. The calcium spike recoveries were 93.4 to 94.1%. The recovery results for lithium as well as calcium are summarized in Table 2. A chromatogram of the lithium hydroxide sample spiked with calcium at the concentration level prescribed in the USP monograph (0.2%) is shown in Figure 3.

Columns:	Dionex IonPac CS16, 3 x 250 mm, IonPac CG16, 3 x 50 mm
Eluent:	10 mM MSA for 0 to 11 min, 65 mM MSA 11 to 16 min, 10 mM MSA for 16 to 22 min
Eluent Source:	Dionex ICS-5000$^+$ EG with Dionex CR-CTC II trap column
Temperature:	40 °C
Flow Rate:	0.45 mL/min
Inj.Volume:	10 µL
Detection:	Dionex CERS 500 suppressor, 2 mm, recycle mode
Peaks:	1. Lithium 10 mg/L 2. Calcium 0.12 mg/L

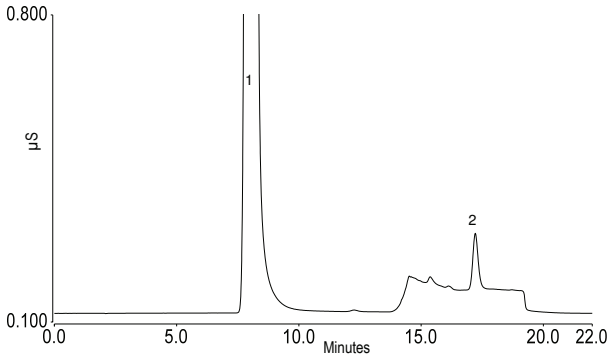

Figure 3. A 10 mg/L lithium sample spiked with calcium at the limit prescribed in the lithium hydroxide USP monograph.

Assay precision was evaluated by injecting seven replicates of 10 mg/L lithium spiked with 0.12 mg/L calcium and expressed as the RSDs of RT and peak area from the series of measurements. The RT RSDs were ≤0.03% and the peak area RSDs were ≤4.19% (Table 3).

Table 3. Retention time and peak area precision of 10 mg/L lithium sample spiked with 0.12 mg/L calcium.

Cation	Conc (mg/L)	RT RSD (N=7)	Peak Area RSD (N=7)
Li	9.99	0.03	0.04
Ca	0.11	0.01	4.19

Robustness

Assay robustness was evaluated by measuring the influence of small variations in procedural parameters (e.g., flow rate, eluent concentration during gradient, and column temperature) on the RT, peak asymmetry, and resolution of lithium from sodium, as well as calcium from magnesium on two columns from different lots. The peak asymmetry was measured using the USP formula.[8] A standard injection (10 mg/L lithium spiked with 0.12 mg/L sodium, 0.06 mg/L magnesium, and 0.12 mg/L calcium) was injected seven times (N=7) at each chromatographic condition. Tables 4 and 5 summarize the results for lithium and calcium robustness studies, respectively. These results indicate that the method is robust and suitable for lithium as well as calcium determination.

Table 4. Robustness of the IC-based assay for lithium determination performed using a 10 mg/L lithium sample spiked with 0.12 mg/L sodium, 0.06 mg/L magnesium, and 0.12 mg/L calcium.

Parameter	Value	Column 1						Column 2					
		Lithium RT (min)	Difference (%)	Asymmetry	Peak Asymmetry Difference (%)	Resolution (From Na)	Resolution (From Na) Difference (%)	Lithium RT (min)	Difference (%)	Asymmetry	Peak Asymmetry Difference (%)	Resolution (From Na)	Resolution (From Na) Difference (%)
Flow Rate (mL/min)	0.405	8.98	11.04	0.92	-0.36	9.58	3.19	9.81	11.12	0.84	0	15.51	50.70
	0.45	8.09	-	0.92	-	9.29	-	8.83	-	0.84	-	10.29	-
	0.495	7.36	-8.96	0.93	0.72	9.09	-2.21	8.08	-8.85	0.985	1.19	10.15	-1.33
Column Temp (°C)	36	8.09	0.04	0.93	0.72	9.50	2.30	8.84	0.11	0.85	1.19	11.49	11.63
	40	8.09	-	0.92	-	9.58	-	8.83	-	0.84	-	10.29	-
	44	8.08	-0.10	0.92	-0.72	9.01	-2.94	8.83	0.02	0.84	0.0	9.94	-3.43
MSA Eluent Initial Concentration (mM)	9	8.76	8.38	0.91	-1.44	9.76	5.10	9.57	8.43	0.82	-1.98	15.96	55.1
	10	8.09	-	0.92	-	9.29	-	8.83	-	0.84	-	10.29	-
	11	7.53	-6.85	0.93	1.08	9.04	-2.66	8.22	-6.85	0.85	1.19	9.96	-3.21
MSA Eluent Final Concentration (mM)	58.5	8.09	0.02	0.93	0.36	9.23	-0.57	8.83	0.08	0.84	0	10.31	0.29
	65	8.09	-	0.92	-	9.29	-	8.83	-	0.84	-	10.29	-
	71.5	8.08	-0.03	0.92	0.0	9.26	-0.32	8.84	0.06	0.84	0.4	10.33	0.39

Table 5. Robustness of the IC-based assay for calcium determination performed using a 10 mg/L lithium sample spiked with 0.12 mg/L sodium, 0.06 mg/L magnesium, and 0.12 mg/L calcium.

Parameter	Value	Column 1						Column 2					
		Calcium RT (min)	Difference (%)	Asymmetry	Peak Asymmetry Difference (%)	Resolution (From Mg)	Resolution (From Mg) Difference (%)	Calcium RT (min)	Difference (%)	Asymmetry	Peak Asymmetry Difference (%)	Resolution (From Mg)	Resolution (From Mg) Difference (%)
Flow Rate (mL/min)	0.405	17.92	3.99	1.16	-0.29	2.91	-0.11	17.97	1.82	1.08	-7.14	3.46	4.53
	0.45	17.23	-	1.16	-	2.91	-	17.65	-	1.17	-	3.31	-
	0.495	16.71	-3.02	1.11	-4.87	2.82	-2.98	17.11	-3.06	1.14	-2.57	3.26	-1.61
Column Temp (°C)	36	17.29	0.35	1.12	-3.72	2.91	-0.11	17.71	0.36	1.12	-4.29	3.32	0.10
	40	17.23	-	1.16	-	2.91	-	17.65	-	1.17	-	3.31	-
	44	17.18	-0.31	1.12	-3.72	2.89	-0.69	17.59	-0.30	1.13	-2.86	3.32	0.10
MSA Eluent Initial Concentration (mM)	9	17.28	0.27	1.14	-2.29	2.85	-2.18	17.69	0.27	1.18	0.86	3.31	-0.20
	10	17.23	-	1.16	-	2.91	-	17.65	-	1.17	-	3.31	-
	11	17.18	-0.29	1.13	-2.87	2.91	0.00	17.59	-0.30	1.20	2.86	3.34	0.70
MSA Eluent Final Concentration (mM)	58.5	17.96	4.22	1.22	4.58	3.09	6.07	18.42	4.38	1.09	-6.29	3.65	10.16
	65	17.23	-	1.16	-	2.91	-	17.65	-	1.17	-	3.31	-
	71.5	17.23	0.02	1.20	2.87	2.92	0.23	17.65	0.01	1.14	-2.29	3.30	-0.50

Conclusion

This study describes an IC-based assay for determination of lithium in lithium hydroxide. Lithium was separated on a cation-exchange column and detected by suppressed conductivity in 22 min. This method allows the concentration of lithium to be determined in an automated way and thus eliminates the need to perform the cumbersome titration-based assay. This assay for lithium 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 hydroxide as per limits set in the USP monograph. Compared to the assay described in the USP lithium hydroxide monograph, this assay offers a simple, accurate, and robust measurement without handling hazardous reagents. Therefore, this method is a candidate to replace the existing assay for lithium hydroxide in the USP monograph, and thereby modernize the monograph.

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