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Method Development and Validation of Lanthanum Content from Lanthanum Carbonate Chewable Tablets by Ion Chromatography

Chanakya Thaker[1], Chetan Chavan[2]

[1, 2]Application Laboratory, Thermo Fisher Scientific India Pvt. Ltd., Powai, Mumbai 400076, India

Abstract: ***An accurate, simple, reproducible, and sensitive method for the estimation of Lanthanum was developed and validated. Lanthanum was separated using a weak cation exchange guard column by isocratic elution with a flow rate of 1.2mL/min. The mobile phase composition was 6mM Methanesulfonic acid and Ion chroamtographic Non Suppressed conductivity detection technique was carried out. The linearlity of method has been tested in the range of 1.0mg/L to 20mg/L and correlation cofficient (R^2) was 0.99996. The method was shown excellent reproducible, linear, specific, sensitivity, rugged. The Limits of Detection and Quantification have been also established for lanthanum as 0.4mg/L and 1.0mg/L respectively. Hence, the validated method is easy to adapt for regular analysis.***

Keywords: Chewable tablets, Lanthanum Carbonate, Methanesulfonic Acid, Non Suppressed Conductivity detector, Ion Chromatography

1. Introduction

Lanthanum carbonate chewable tablets are used in the treatment of hyperphosphatemia associated with end stage renal disease (ESRD). Lanthanum Carbonate is a third-generation phosphate binder that avoids the toxicities associated with use of aluminum carbonate, and increased serum calcium levels linked with the use of calcium carbonate. It is also shown to have a higher binding affinity to phosphate as compared to Sevelamer hydrochloride, an ion exchange resin, the first binder in this class.

Lanthanum is administered as its carbonate salt, and reduces absorption of phosphate by forming insoluble lanthanum phosphate complexes that pass unabsorbed through the gastrointestinal (GI) tract [2].

It is found to have a very low absolute bioavailability (0.00127% ± 0.000800%) on oral administration [4]. Thus, there is a need to evaluate the concentration of lanthanum in lanthanum carbonate chewable tablets so that an appropriate level is achieved in plasma to observe the desired therapeutic effect. Also, it has been reported that it crosses the blood brain barrier and a decline in neurobehavioral performance in male Wistar rats was observed on long term exposure to lanthanum. Thus, it is necessary to ensure that the concentration of lanthanum does not exceed the maximum required levels [5].

So far, no chromatographic method has been reported to estimate the amount of lanthanum in lanthanum carbonate chewable tablets. Thus, there was a need to develop a simple, accurate, precise and robust method to determine the amount of lanthanum in the above formulation.

Ion exchange chromatography is a liquid chromatographic technique, in which ionic and strongly polar species can be well separated and detected. It can be used to detect the presence of lanthanum ions in Lanthanum carbonate chewable tablets and will give a better estimate of Lanthanum ions compared to other conventional methods since it allows detection of ions at low mg/L(ppm) level. The developed methodology has been validated and it is highly effective to estimate the Lanthanum from Lanthanum Carbonate Chewable Tablets.

2. Experimental

2.1 Reagents and Chemicals

All chemicals used for preparation of reagents, standards and mobile phase were of analytical grade. Ultrapure deionized water (18.2 MΩ cm, Milli-Q system) was used for the preparation of mobile phase, standards and samples. Lanthanum Carbonate (AR grade) was used for the preparation of Lanthanum standard, Methanesulfonic Acid (HPLC grade) and Acetonitrile (HPLC grade) was used for the preparation of mobile phase.

2.2 Apparatus

The equipment used was Thermo Fisher Dionex Ion Chromatograph ICS 1100 having AS-AP Autosampler with a 10µL loop, IonPac SCG1 guard column (4 x 50mm inner diameter), with IonPac Mixer. The experiment was conducted using a pre-degassed eluent 6mM Methanesulfonic Acid and 10% Acetonitrile at a flow rate of 1.2ml/min with Non-Suppressed conductivity detection technique. It was connected serially with Ion Chromatography system and Software used for data acquisition was Thermo Fisher Dionex Chromeleon (version: 6.80 SP2). Chromatograms were monitored simultaneously during analysis.

2.3 Procedure

Preparation of 6mM Methanesulfonic Acid: - 0.4mL of Methanesulfonic Acid solution was taken in 1000ml volumetric flask containing 500ml of ultrapure deionized water. It was sonicated for 2 minutes and made up to the

mark with ultrapure deionized water. It was then filtered through 0.2µ nylon membrane filter.

Preparation of Eluent: 900mL of above prepared 6mM Methanesulfonic Acid and 100mL of Acetonitrile mixed thoroughly and sonicated for 2mins.

Preparation of standard solutions
Certified Lanthanum Carbonate Salt was procured from sigma Aldrich. From this salt, a 1000mg/L standard solution was prepared. From this 1000mg/L standard solution, 1.0, 2.5, 5.0, 10.0 15.0, 20.0mg/L of Lanthanum was prepared for the Linearity study, and 10.0mg/L of Lanthanum was prepared for the precision study. 0.4 and 1.0mg/L of Lanthanum were prepared from 1000mg/L standard solution for limit of detection and limit of quantification respectively.

Sample preparation: Lanthanum carbonate tablets were crushed in to powder with the help of motor and pestle. Weighed accurately 950mg of powder sample in 200mL of volumetric flask, added 100mL of water, and 3mL of Methanesulfonic acid and finally made up to the mark with water. Samples were filtered through 0.2µ nylon membrane filter and collected in auto sampler vial. This procedure was repeated for each sample along with recovery samples and diluent. An Autosampler (Dionex AS-AP) was used to inject standard solution containing Lanthanum into the ion chromatography system. Subsequently, the standard solution in the sample loop was transferred onto the separator column, on which Lanthanum was separated. After separation on the column, the Lanthanum was detected by Non Suppressed Conductivity detector. A sequence containing the blank, standards, samples and recovery samples were run and results were then interpreted.

3. Results and Discussions

Limit of Detection (LOD) for Lanthanum was 0.4mg/L and it was injected (n) six times and observed average signal to noise ratio (S/N) was 3.5. Limit of Quantification (LOQ) for Lanthanum was 1.0mg/L, it was injected (n) six times and observed signal to noise ratio (S/N) was 12.3. It's percent relative standard deviation for peak area was 0.90% and 0.50% respectively. Table 1 shows results for LOD and LOQ of Lanthanum.

Table 1: LOD and LOQ data for Lanthanum

Lanthanum	Amount, mg/L	S/N	% RSD (n=6)
LOD	0.40	3.5	0.90
LOQ	1.00	12.3	0.50

The response of the analyte was linear over the range of 1.0 to 20.0mg/L. Calibration curve fits well and that is significantly linear having correlation coefficient of 0.99996, slope 0.0796 and offset 0.00 (figure 1). This linearity study was performed for the concentration range of 1.0, 2.5, 5.0, 10.0, 15.0, 20.0mg/L Lanthanum. Each standard injection was repeated thrice. Therefore, number of calibration points (n) for linearity study was 18. Its data had been shown in table 2.

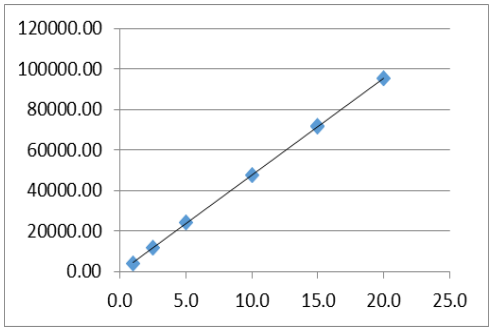

Figure 1: Linearity plot for Lanthanum

Table 2: Linearity data for Lanthanum

Analyte	*Points*	*Corr. Coeff.*	*Offset*	*Slope*
Lanthanum	18	0.99996	0	0.0796

Replicate injections of Lanthanum standard was done and its percent relative standard deviation for peak area was 0.51%. Table 3 shows results for its precision study.

Table 3: Precision data for Lanthanum

Analyte	*Amount, mg/L*	*% RSD (n=6)*
Lanthanum	10.0	0.51

Chromatogram for Lanthanum standard is shown in figure 2.

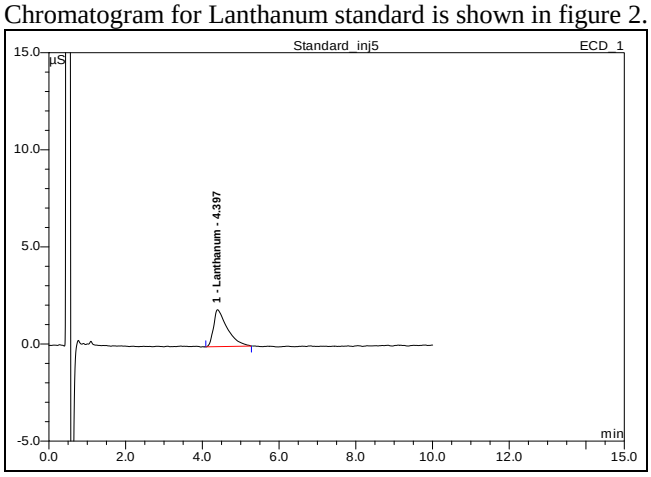

Figure 2: Standard chromatogram for Lanthanum (10mg/L)

Sample results: Samples were analysed using the linearity calibration method. Replicate injections of same sample was also done. Its results and routine analysis sample results were shown in table 4 and table 5.

Table 4: Sample precision

Analyte	*B. No.*	*Number of injections*	*% RSD*
Lanthanum	LCT1406	10.0	0.79

Table 5: Routine sample analysis results

Analyte	*B. No.*	*Results mg/tab*	*Label Claim*
Lanthanum	LCT1406	999.99	1000
	LCT1401	990.98	1000
	LCT1428	990.25	1000
	LCT2406	742.10	750
	LCT2410	748.16	750
	LCT3406	486.93	500
	LCT3408	500.92	500

Samples limit was set to 90 to 110% of its label claim. For which all samples were passing for its lanthanum content. Intraday analysis of Samples was done for seven consecutive days for which they are passing its label claim limit. Sample Chromatogram was shown is figure 3.

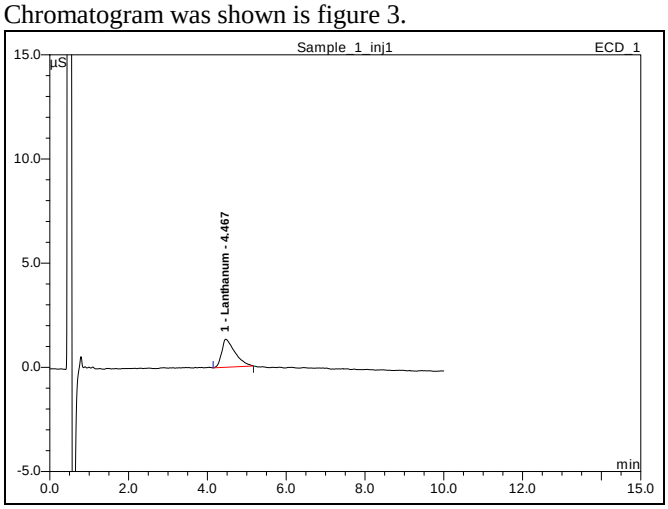

Figure 3: Sample chromatogram (B. No. LCT1406) for Lanthanum estimation

Recovery: The sample used for recovery study was B. No. LCT1406 (average concentration was taken for calculation). Recovery test solutions were injected in triplicate Also for recovery study, known concentrations of amount was added to sample at three different levels as shown in table 6.

Table 6: Recovery study (Lanthanum) for sample (B.No. LCT1406) (n = 3)

Recovery Level	Target Concentration	Amount Added mg/L	Amount Recovered mg/L	% Recovery
Lanthanum	50%	5.0	5.02	100.40
	100%	10.0	9.94	99.40
	150%	15.0	14.95	99.67

Method Ruggedness: - Method was tested with different flow rate like 1.0 and 1.5. Also, it was tested using different eluent concentrations. Sample shows negligible effect of these changes on its final results. Its results are shown in table 7.

Table 7: Routine sample analysis results

At 1.0ml/min flow rate			
Analyte	B. No.	Results mg/tab	Label Claim
Lanthanum	LCT1406	999.92	1000
	LCT1401	990.99	1000
	LCT1428	990.20	1000
	LCT2406	742.31	750
	LCT2410	748.35	750
	LCT3406	486.99	500
	LCT3408	500.19	500

At 1.5ml/min flow rate			
Analyte	B. No.	Results mg/tab	Label Claim
Lanthanum	LCT1406	998.96	1000
	LCT1401	991.03	1000
	LCT1428	995.55	1000
	LCT2406	745.20	750
	LCT2410	747.94	750
	LCT3406	487.88	500
	LCT3408	501.31	500

Using 6mM Methanesulfonic acid + 8% Acetonitrile as eluent			
Analyte	B. No.	Results mg/tab	Label Claim
Lanthanum	LCT1406	999.00	1000
	LCT1401	990.66	1000
	LCT1428	992.51	1000
	LCT2406	746.90	750
	LCT2410	746.68	750
	LCT3406	488.01	500
	LCT3408	498.91	500

Using 6mM Methanesulfonic acid + 12% Acetonitrile as eluent			
Analyte	*B. No.*	*Results mg/tab*	*Label Claim*
Lanthanum	LCT1406	999.93	1000
	LCT1401	992.49	1000
	LCT1428	991.62	1000
	LCT2406	744.22	750
	LCT2410	746.90	750
	LCT3406	486.84	500
	LCT3408	500.01	500

4. Conclusions

In the present work, an Ion chromatography-Non Suppressed conductivity method was validated and successfully used to provide qualitative and quantitative results of Lanthanum from Lanthanum Carbonate samples. This technique is cost effective with respect to analysis required for keeping check on its limit of lanthanum in lanthanum carbonate tablets.

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Author Profile

Chetan Chavan had completed the B.Sc (Chemistry). and M.Sc (Chemistry) degrees from Mumbai University and completed his ph.D in year, 2018., He had joined Dionex India Pvt. Limited, which is now Thermo Fisher Scientific Pvt. Ltd., as Applications Manger for Ion Chromatography (IC) and HPLC and currently working as Product Manager – IC/SP. His role is to provide technical support coordination with factory for India team requirements, provide guidance to sales, application and service team for IC and HPLC.

Chanakya Thaker received the B. Sc (Chemistry). and M.Sc (Analytical Chemistry) degrees from Mumbai University in 2006 and 2008, respectively. From 2009, he had joined Dionex India Pvt. Limited, which is now Thermo Fisher Scientific Pvt. Ltd., as Applications Specialist for Ion Chromatography (IC) and HPLC and currently working as Applications Manager – IC/SP. His role is to manage application team, provide customer training, sample analysis, technical presentations, method development and troubleshooting on IC and HPLC systems.