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Ion Chromatography Method Development and Validation for Assay of Sodium Thiosulfate

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Abstract: ***A new ion chromatography method was developed, validated and adapted for the assay of Sodium Thiosulfate Pentahydrate as active pharmaceutical ingredient. In this method, separation of Thiosulfate was done using IonPac AS19 column with eluent of 45mM Potassium Hydroxide using suppressed conductivity detection. Thiosulfate was eluted at around 5.3 minutes. Linearity rangeis 1.0 – 100.0mg/L with regression coefficient value of 0.9999 for Thiosulfate. The Limit of Detection (LOD) value found was 0.15mg/L, and the Limit of Quantification (LOQ) value of 0.06mg/L. Validation parameters examined following suggestions of ICH are accurate ample for the supposed assay. The approach is confirmed as splendid method for assay of Sodium Thiosulfate as active pharmaceutical ingredient with excellent assay percentage values.***

Keywords: Ion Chromatography, Suppressor, Conductivity, IonPac AS19, Chromeleon, Sodium Thiosulfate

1. Introduction

Sodium Thiosulfate is an ionic compound containing two sodium ions (Na^{+1}) and one thiosulfate polyatomic ion ($S_2O_3^{-2}$). Chemical formula for Sodium Thiosulfate is $Na_2S_2O_3$. Sodium Thiosulfate has its medicinal usage from quite long time. It is also used as food preservative and most of population is exposed to this non-toxic compound [1]. Its early medicinal usage was to treat mercury, arsenic, lead and bismuth poisoning. It is also approved for treatment for some rare medical conditions like Calciphylaxis. Its another use to protect against cisplatin toxicity. It is also used for the treatment of cyanide poisoning. It had demonstrated to be used as anti-inflammatory agent [1].

Thiosulfate analysis has been mostly executed using various instrumentation techniques such as flame-containing molecular emission cavity analysis (MECA), kinetic spectrophotometry, gas chromatography–mass spectrometry (GC–MS), flame atomic absorption spectrometry (FAAS), high-performance liquid chromatography (HPLC), ion-pair chromatography with ultraviolet absorbance, ion chromatography (IC) based on isocratic elution with fluorescence detectionand inductively coupled plasma mass spectrometry (ICP– MS). These methods are expensive, tedious and time-consuming as well as poor precision at low concentrations and requires expertise in that field[2]. Iodometry titration method is another well-known method for the estimation of sodium thiosulfate, end point of which is based on visual inspection which is error prone. This method is still mentioned in many regulatory bodies likes USP monograph [3].

Thus, present study, involves developing a method which is convenient, rapid, accurate and precise for determining the assay of Sodium Thiosulfate using Ion Chromatography with suppressed conductivity detection. Column utilized is high capacity IonPac AS19 which is a anion exchange column that allows determination most of anions in single run.

2. Experimental

2.1 Materials and Reagents

All chemicals usedfor preparation of reagents, standards and mobile phase were of analytical grade. Ultrapure deionized water (18.2 MΩ cm, <10ppb TOC) was used for the preparation of mobile phase, standards and samples. Sodium ThiosulfatePentahydrate (AR grade, Merck) was used for the preparation of Thiosulfate standard, Reagent Free Ion Chromatography (RFIC) Potassium Hydroxide (KOH) Cartridge is used to generate 45mM Potassium Hydroxide (KOH) eluent.

2.2 Instrument

Thermo Fisher Scientific Dionex Aquion Ion Chromatography system was used in the present study, Chromeleon 7.2 software used for data interpretation, IonPac AS19, 4mm and its guard was used as separation column, ADRS600, 4mm suppressor and Conductivity detector was used inIon Chromatography System.45mM KOH eluent was generated through RFIC cartridge. Sample injections were done using Dionex AS-DV autosampler.

2.3 Ion Chromatography Conditions

Column: IonPacAS19 column (4 x 250mm) and its guard (4 x 50mm)
Eluent:45mM Potassium Hydroxide (KOH)
Flow rate:1.0 mL/min
Injection volume:25 µl
Detector: Conductivity
Suppressor:ADRS600, 4mm (Recycle Mode)
Suppressor Current:112mA
Run time:15minutes

2.4 Standard Preparation

Certified Sodium Thiosulfate Pentahydrate was procured from Merck. From this salt, a 1000mg/L standard Thiosulfate solution was prepared. From this 1000mg/L

standard solution, 1.0, 10.0, 25.0, 50.0 and 100.0mg/L of Thiosulfatewas prepared for the Linearity study, and 25.0mg/L of Thiosulfate was prepared for the precision study. 0.015mg/L of Thiosulfate solution was prepared for Limit of Detection (LOD) and 0.06mg/L of Thiosulfate was prepared for Limit of Quantification (LOQ).

2.5 Sample Preparation

About 0.11g of Sodium Thiosulfate Pentahydrate Samples was dissolved in 100mL of diluent (Deionized Water). It was then sonicated to dissolve. 0.1mL of this solution was diluted to 10mL of diluent. Filtered through 0.2µ nylon membrane filter and used for analysis.

3. Results and Discussions

3.1 Method Development

Method Development was tried with IonPac AS11HC, IonPac AS23 and IonPac AS19 columns. To which IonPac AS19 provides fast analysis, good resolution between sulfate and thiosulfate and good symmetry with excellent theoretical plates. IonPac AS19 had been chosen because of mentioned benefits but other columns can also be used for assay analysis with modified analytical mentioned conditions.

Changes in Column Oven Temperature was studied from 25, 30 and 35°C. There are no significant changes observed in retention time and results. Therefore, this method was developed at room temperature conditions which can be applicable for any state of art laboratories.

3.2 Validation

Limit of Detection (LOD) for Thiosulfate was 0.015mg/L and it was injected (n) six times and observed average signal to noise ratio (S/N) was 15.0. Limit of Quantification (LOQ) for Thiosulfate was 0.06mg/L, it was injected (n) six times and observed signal to noise ratio (S/N) was 40.0. Table 1 shows results for LOD and LOQ of Thiosulfate.

Table 1: LOD and LOQ data for Thiosulfate

Iodate	*Amount, mg/L*	*S/N*	*% RSD (n=6)*
LOD	0.015	15.0	0.78
LOQ	0.060	40.0	0.27

The response was linear over the range of 1.0 to 100.0mg/l of Thiosulfate. Calibration curve fits well and that is significantly linear having correlation coefficient 0.9999 (figure 2). Each standard injection was repeated thrice. Therefore, number of calibration points (n) for linearity study was 15. Its data had been shown in table 2.

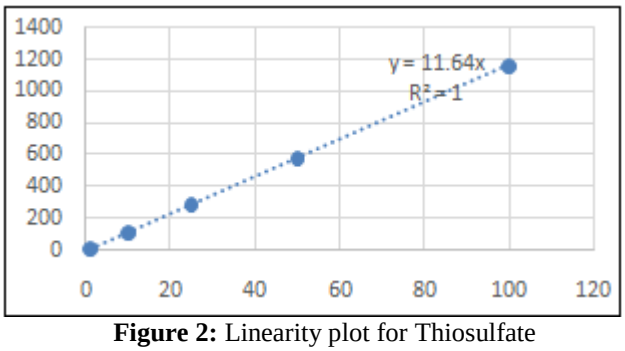

Figure 2: Linearity plot for Thiosulfate

Table 2: Linearity data for Thiosulfate

Analyte	*Points*	*Corr. Coeff.*	*Offset*	*Slope*
Thiosulfate	15	0.9999	0	11.643

Method specificity was also done with separation of Thiosulfate (25.0mg/L) and Sulfate (5.0mg/L. Its chromatogram was shown in figure 3.

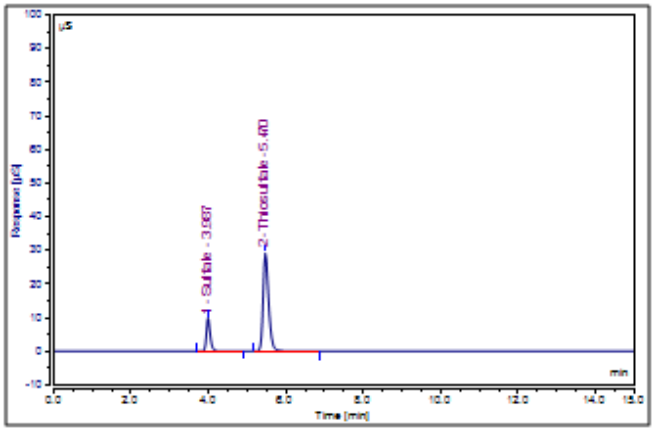

Figure 3: Specificity chromatogram separation of Thiosulfate (25.0mg/L) and Sulfate (5.0mg/L)

Replicate injections of Thiosulfate were done and their percent relative standard deviation for peak area was 0.14%. Table 3 shows results for its precision study.

Table 3: Precision data for Thiosulfate

Analyte	*Amount, mg/L*	*% RSD (n=6)*
Thiosulfate	25.00	0.14

Chromatogram of Thiosulfate standard injections is shown in figure 4.

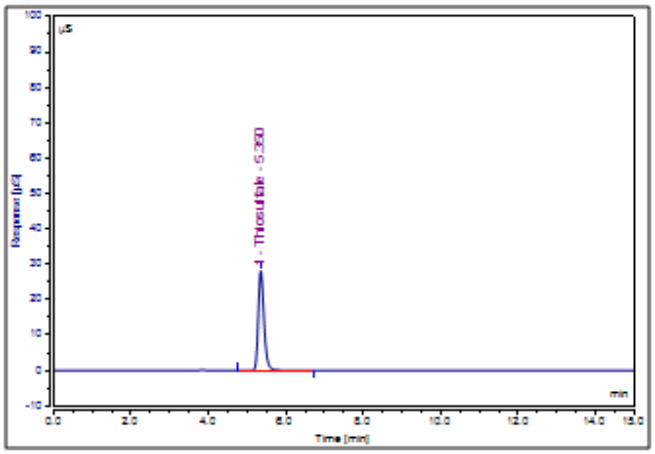

Figure 4: Standard chromatogram of Thiosulfate (25.0mg/l)

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

Table 4: Sample precision

Analyte	*Sample*	*Number of preparations*	*ASSAY %*
Thiosulfate	Sodium Thiosulfate Pentahydrate (S. I. No. STHP02)	10.0	99.91

Table 5: Routine sample analysis results

Sample.	*Sample Identification Number (S.I. No.)*	*ASSAY %*
Sodium Thiosulfate Pentahydrate	STHP03	99.99
Sodium Thiosulfate Pentahydrate	STHP04	99.85
Sodium Thiosulfate Pentahydrate	STHP05	100.1
Sodium Thiosulfate Pentahydrate	STHP06	99.95

Thiosulfate was observed in all samples and Sodium Thiosulfate assay results observed were within desired range of 99.0 – 100.5%.

Intraday analysis of Samples was done for seven consecutive days for which sample results were observed to be similar as given in table 5. Sample Chromatogram was shown is figure 5.

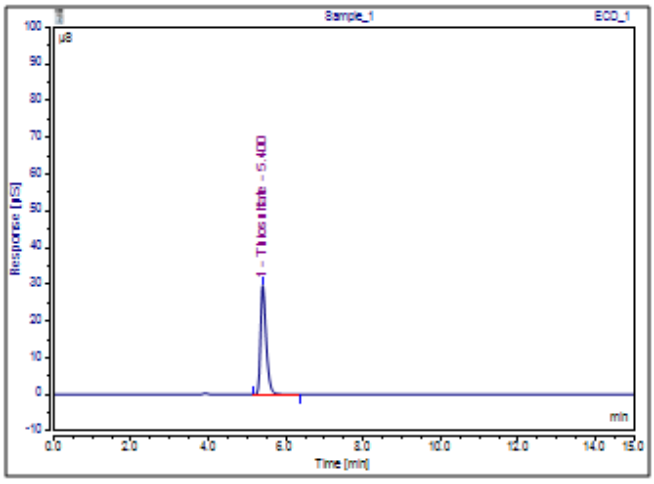

Figure 5: Sample chromatogram of Sodium Thiosulfate Pentahydrate (S. I. No. STPH02)

Recovery: - The sample used for recovery study was Sodium Thiosulfate Pentahydrate (S.I. No. STPH02) (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 (Thiosulfate) for sample Sodium Thiosulfate Pentahydrate (S.I. No. STPH02) (n = 3)

Analyte	*Level*	*Amount Added* mg/L	*Amount Recovered* mg/L	*% Recovery*
Thiosulfate	1	5.00	4.95	99.00
	2	12.50	12.43	99.44
	3	25.00	25.08	100.32
	4	37.50	37.61	100.29

The same method has been used on another Ion chromatography model like ICS 5000+ and ICS Integrion with different lot of IonPac AS19 column as a part of ruggedness study, for which there is no significant variations of sample results were observed.

4. Conclusions

A rapid and sensitive Ion Chromatography method was proposed and validated for assay of Sodium Thiosulfate as Active Pharmaceutical Ingredient.

This Ion Chromatography with suppressed conductivity detection gives specific and precise method for assay of Sodium Thiosulfate without any pretreatment. This technique is cost-effective with respect to analysis required for keeping a check on the limits as provided by USP and other regulatory bodies. This method can also be useful for analysis of sodium thiosulfate from various types of other samples.

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