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Ion chromatography

USP-aligned ion chromatographic assay of magnesium sulfate using a next-generation electrolytic suppressor

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Keywords

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Abstract

This study presents a USP-aligned ion chromatographic method for the quantitative determination of magnesium sulfate, integrating the Thermo Scientific™ Dionex™ Cation Next Generation Electrolytic Suppressor (NGES-C) into the USP-defined assay framework. The NGES-C suppressor enhances conductivity detection by minimizing background noise and achieving faster baseline stabilization compared to earlier generations of suppressors. The method adheres to USP specifications for mobile phase composition, column configuration, and system suitability, while demonstrating improved reproducibility and robustness.

1. Introduction

Magnesium sulfate is an inorganic compound widely used in both pharmaceutical and industrial applications due to its versatile chemical properties and therapeutic efficacy. In pharmaceuticals, it is commonly employed as an electrolyte replenisher, anticonvulsant, and osmotic laxative, with formulations tailored for both parenteral and non-parenteral use. The compound exists in various hydrated forms—anhydrous, monohydrate, and heptahydrate—each with distinct physicochemical characteristics that influence its analytical evaluation and quality control parameters.[1] Owing to its broad pharmacological relevance, precise quality control standardization and assays of magnesium sulfate are vital to ensure consistent potency and safety across formulations.

Recent advancements, such as the modernization of magnesium oxide monographs using ion chromatography, have demonstrated the effectiveness of cation-exchange columns and suppressed conductivity detection for precise assay and impurity control in similar matrices.[2] Also, in Thermo Fisher Scientific AN120, we demonstrated an effective approach for quantifying trace levels of calcium and magnesium in complex matrices like brine using ion chromatography with matrix elimination techniques, highlighting the importance of selective retention and suppression technologies in achieving accurate results.[3]

Magnesium sulfate is used in various dosages. Its quantification is critical for ensuring compliance with pharmacopeial standards. A U.S. Pharmacopeia (USP) monograph outlines a conductivity-based ion chromatographic assay using methanesulfonic acid (MSA) as the eluent and suppression techniques to enhance detection specificity.[4] Here, we detail the integration of the NGES-C suppressor into the USP method, evaluating its impact on assay performance and reliability. The suppressor ensures accurate magnesium ion detection by minimizing background conductivity from the mobile phase, which consists of 48 mM MSA. The system suitability requirements include a resolution of no less than 3.0 between magnesium and calcium ions, a tailing factor of no more than 2.0, and a relative standard deviation of no more than 1.0% for the standard solution. These parameters confirm that the suppressor and overall system maintain precision and reliability during the assay, ensuring accurate quantification of magnesium sulfate.

2. Materials and methods

2.1 Chemicals, standards, samples, and reagents

- Deionized (DI) water, Type I reagent grade, 18 MΩ-cm resistance or better
- USP Magnesium Sulfate RS (reference standard)
- USP Calcium Carbonate RS (for system suitability)
- Hydrochloric acid 37%, Sigma Aldrich (Part No. 320331)
- Magnesium Sulfate Anhydrous, Thermo Scientific™ Chemicals (Part No. 033337, Lot No. 0000793642)
- Magnesium Sulfate Anhydrous, Thermo Scientific Chemicals (Part No. 033337, Lot No. W24L010)
- Magnesium Sulfate Anhydrous, Thermo Scientific Chemicals (Part No. 033337, Lot No. T25L002)
- Magnesium Sulfate Anhydrous, Thermo Scientific Chemicals (Part No. 033337, Lot No. Y08J022)

2.2 Instrumentation

- Thermo Scientific™ Dionex™ Integrion™ HPIC™ System* (Part No. 22153-60305), including:
  - Thermo Scientific™ Dionex™ EGC 500 MSA (Methanesulfonic Acid) (Part No. 075779)
  - CD detector
  - Thermostatted column oven
  - Thermo Scientific™ Dionex™ AS-AP Autosampler (Part No. 074926) with Thermo Scientific™ Dionex™ AS-AP Autosampler Tray, 1.5 mL (Part No. 074936)
  - Thermo Scientific™ Dionex™ AS-AP Autosampler Vial Kit, 1.5 mL polypropylene with caps and split septa (Part No. 079812)

*A Thermo Scientific™ Dionex™ Inuvion™ IC System with Thermo Scientific™ reagent-free ion chromatography (RFIC™) or a Thermo Scientific™ Dionex™ ICS-6000 HPIC™ System can also be used for this application.

Software

- Thermo Scientific™ Dionex™ Chromeleon™ Chromatography Data System (CDS), software version 7.3.2.14225 MUe

Consumables

- Thermo Scientific™ Dionex™ IonPac™ CS16 Guard Column, 5 × 50 mm (Part No. 057574, USP L84 designated column)
- Thermo Scientific™ Dionex™ IonPac™ CS16 Analytical Column, 5 × 250 mm (Part No. 079805, USP L84 designated column)
- Thermo Scientific™ Dionex™ NGES-C suppressor, 4 mm (Part No. 060002)
- Dionex EGC 500 MSA (Part No. 075779)
- Thermo Scientific™ Dionex™ CR-CTC 600 Continuously Regenerated Cation Trap Column (Part No. 088663)
- Merck™ Millipore™ Millex™ nylon syringe filter, 0.2 µm x 25 mm (Part No. SLGNDZ5)

Instrument method

System	Dionex Integrion RFIC
Columns	IonPac CS16, analytical, 5 x 250 mm IonPac CG16, guard, 5 x 50 mm
Eluent source	RFIC-MSA cartridge
Eluent	48 mM MSA
Flow rate	1.0 mL/min
Injection volume	10 µL (full loop)
Temperature	40 °C (column oven) 20 °C (detector compartment)
Autosampler vial temperature	25 °C
Suppressor	NGES-C, 4 mm in Recycle Mode
Suppressor current	141 mA
Detection	Conductivity
System backpressure	~2300 psi
Background conductance	<0.5 µS
Typical noise	<0.50 nS
Run time	20 min

2.3 Diluent, standards, and sample preparation

Diluent: 0.02 N HCl in DI Water

- **5 mg/mL of USP Magnesium Sulfate RS (standard stock solution)**
  Transfer 50 mg of USP Magnesium Sulfate RS to a 10 mL polypropylene volumetric flask. Add 5 mL of diluent and sonicate to dissolve. Dilute with diluent to 10 mL final volume.

  Note: The standard stock solution can be used to prepare the system suitability solution.

- **100 µg/mL of USP Magnesium Sulfate RS (standard solution)**
  Prepare 100 µg/mL of standard solution by diluting 2.0 mL of standard stock solution to 100 mL of diluent.

- **1 mg/mL of USP Calcium Carbonate RS (calcium carbonate standard stock solution for the system suitability test [SST])**
  Transfer 10 mg of USP Calcium Carbonate RS to a 10 mL polypropylene volumetric flask. Add 8 mL of diluent and sonicate to dissolve. Dilute with diluent to a final volume of 10 mL.

- **100 µg/mL of USP Magnesium Sulfate RS and 5.0 µg/mL of USP Calcium Carbonate RS (SST standard solution)**
  Prepare SST standard solution by diluting 2.0 mL of standard stock solution and 0.5 mL of calcium carbonate standard stock solution to 100 mL of diluent.

- **Sample stock solution**
  Transfer 50 mg of magnesium sulfate sample to a 10 mL polypropylene volumetric flask. Add 5 mL of diluent and sonicate to dissolve. Dilute with diluent to a final volume of 10 mL.

- **Sample solution**
  Prepare 100 µg/mL of sample solution by diluting 2.0 mL of sample stock solution to 100 mL of diluent. Filter with 0.2 µm nylon membrane filter.

3. System conditions

- The IC system was configured as shown in Figure 1. To start conditioning the system, the pump was primed with eluent and system flow was set to 1.0 mL/min through the tubing leading to the column.
- Condition the guard column by flushing for at least 15 min with 100 mM MSA at 0.5 mL/min before connecting it to the Dionex IonPac CS16 analytical column. Flush the guard and analytical columns together for at least 60 min with 100 mM MSA at 0.5 mL/min before connecting them to the suppressor.
- Before installing the Thermo Scientific™ Dionex™ NGES-A suppressor, follow the NGES installation guide instructions to check the system, suppressor, and CD pressures and to hydrate the membranes properly.
- Connect the suppressor in Recycle Mode and equilibrate the system using the starting analytical conditions outlined in the instrument method above.

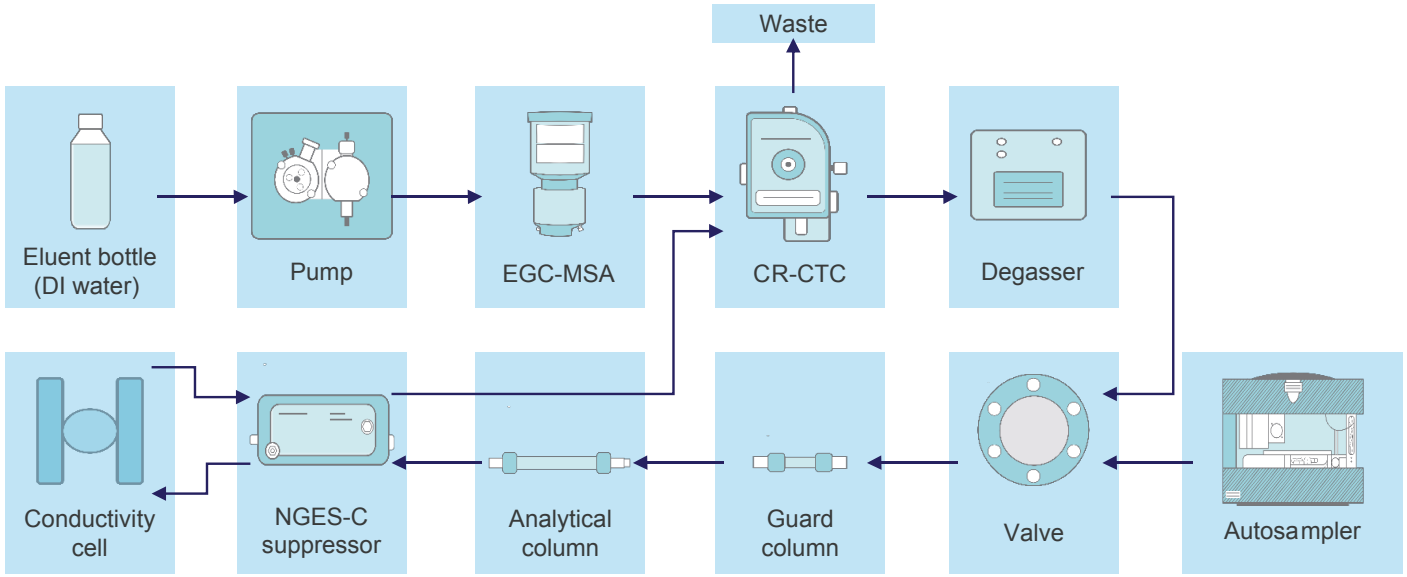

Figure 1. System configuration and flow diagram.

4. System suitability criteria

In addition to providing general methodology, USP monographs outline specific criteria that must be met to qualify a system's performance before subsequent use. Below is a list of the criteria required before proceeding further for the analysis of magnesium sulfate samples.

- Resolution between magnesium and calcium must be ≥3.0 in the system suitability solution injection.
- Tailing factor for the magnesium peak must be ≤2.0.
- Percentage relative standard deviation (%RSD) must be ≤1.0% for the standard solution.
- The relative retention times for the magnesium and calcium ions are 1.0 and 1.3, respectively, in the system suitability solution. Although it should not be present in the standard solution, if calcium is observed in the standard solution, it should also be present at a relative retention time of 1.3.

5. Assay calculation

Calculate the percentage of magnesium sulfate in the sample solution using the USP-defined formula:

$$\% MgSO_4 = (Ru/Rs) \times (Cs/Cu) \times 100$$

where:

Ru = Peak area of magnesium from sample solution

Rs = Peak area of magnesium from standard solution, averaged across the 6 replicates

Cs = Concentration of USP Magnesium Sulfate RS in the standard solution (µg/mL)

Cu = Concentration of magnesium sulfate in the sample solution (µg/mL)

Acceptance range: 98.0–102.0% for magnesium sulfate anhydrous.

6. Results and discussions

The Dionex IonPac CS16 column (USP L84) is a high-capacity, strong cation-exchange column specifically designed for the separation of alkali and alkaline-earth metal cations.[2,3,5] The column features a sulfonated polymer substrate that provides excellent ion-exchange capacity, allowing for the simultaneous quantification of multivalent and monovalent cations within a single run. One of its major advantages lies in its broad pH compatibility and high efficiency, which enable robust separations even in complex sample matrices such as pharmaceutical formulations, biological fluids, and environmental samples.[3] The column's optimized particle size and resin chemistry ensure sharp peak shapes, minimal tailing, and high resolution between closely eluting species such as magnesium and calcium—an essential requirement for USP SST criteria in this method.[2] Moreover, the Dionex IonPac CS16 column's ability to maintain stable retention times and reproducible peak areas across varying concentrations of MSA mobile phases enhances method precision and reproducibility.[3] When coupled with an NGES-C suppressor, which further reduces background noise, maintains peak efficiency, and provides quick baseline equilibration compared to earlier generation of suppressors, the Dionex IonPac CS16 is particularly

well suited for the analysis of inorganic cations in pharmaceutical quality control applications.

The Dionex NGES-C suppressor enhances baseline stability and reduces noise primarily through its advanced electrolytic regeneration technology, which eliminates the need for chemical regenerants and minimizes contamination risks. By continuously regenerating the suppressor membrane during operation, the NGES-C suppressor maintains a consistent ionic environment, reducing fluctuations that often lead to baseline drift. Its design also minimizes void volume and optimizes flow paths, which helps in achieving sharper peaks and lower background conductivity. These improvements are beneficial for USP monograph compliance, where precision and reproducibility of ion chromatography assays are essential for accurate quantitation of analytes.[6]

In terms of robustness, the NGES-C suppressor offers superior backpressure tolerance (up to 500 psi) and reinforced membrane construction, making it highly reliable for demanding applications in the pharmaceutical industry.[6] This durability ensures stable performance even under variable conditions, reducing downtime and maintenance compared to older suppressor models. These features collectively improve system reliability, extend suppressor life, and ensure consistent alignment with this USP Magnesium Sulfate monograph.

Figure 2 illustrates the chromatogram obtained from a standard solution of mixed cations. The magnesium peak was well separated from other cations without any coelution of peaks.

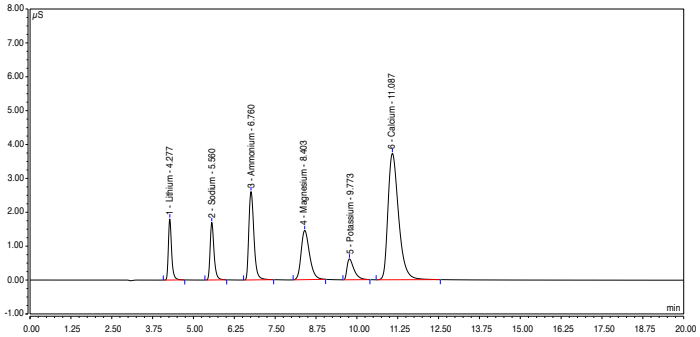

Figure 2. Chromatogram of a standard mixture of cations detected using suppressed conductivity detection.

A linearity study was performed for USP Magnesium Sulfate RS concentrations from 10.0, 25.0, 50.0, 100.0, 200.0, and 300.0 µg/mL. Three consecutive injections of each concentration were completed for a total of 18 injections. The correlation coefficient for magnesium was 0.9999 with a slope of 0.0217 and 0 intercept. Figure 3 shows the linearity profile of USP Magnesium Sulfate RS over the given range of concentrations. The linearity signifies that the analytical method can be used to quantify magnesium sulfate within this concentration range accurately and reliably because the instrument response is directly proportional to the analyte concentration. This linear range defines the method's working range, ensuring that any sample with magnesium sulfate concentration between 10 and 300 µg/mL will produce predictable and consistent results without significant deviation.

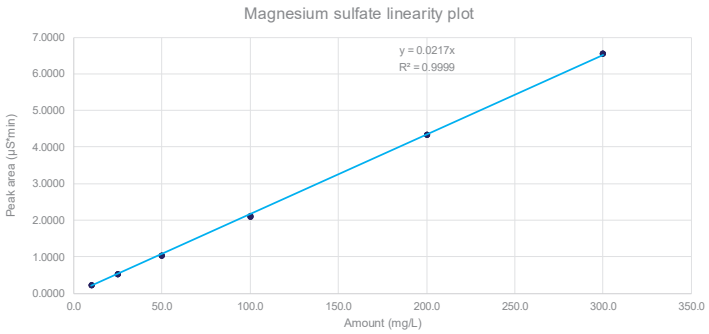

Figure 3. Calibration plot for USP Magnesium Sulfate RS from 10.0 to 300 µg/mL concentrations using suppressed conductivity detection.

An SST is required in pharmaceutical analytical analysis to ensure that the entire analytical system—including the instrument, reagents, column, and method—functions correctly and consistently before analyzing actual samples. It verifies critical performance parameters such as relative retention time (RRT), resolution, tailing factor, and standard solution %RSD, thereby confirming that the system can produce accurate, precise, and reliable results.

To ensure that our system was working correctly, the SST solution as per the USP monograph was injected, and observed results are shown in Table 1. Required criteria were successfully passed using the reported chromatographic conditions.

Table 1. Results obtained for magnesium and calcium compared to SST criteria.

	Observed results	USP SST requirements		
Criteria	Magnesium	Calcium	Magnesium	Calcium
RRT	1.0	1.33	1.0	1.3
Resolution	Not applicable	5.33	Not applicable	≥3.0
Tailing factor	1.34	1.29	≤2.0	Not applicable
Standard solution %RSD (including bracketing standard) (n=7)	0.13%	Not applicable	≤1.0%	Not applicable

A chromatogram obtained from the SST is shown in Figure 4. Peaks of magnesium and calcium were baseline resolved with all SST conditions passed.

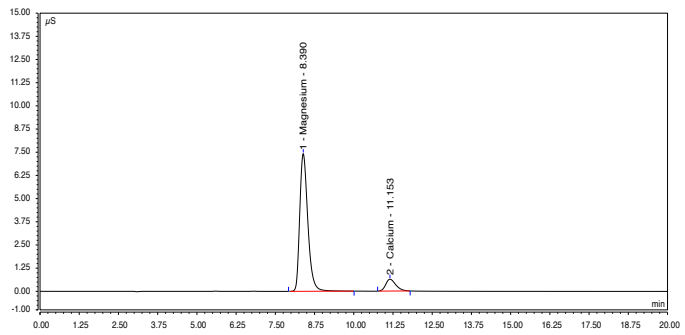

Figure 4. SST chromatogram with 100 µg/mL of USP Magnesium Sulfate RS and 5.0 µg/mL of USP Calcium Carbonate RS.

Figure 5 shows the overlaid chromatograms of a standard and a sample solution (with scale offset), which are notably free of interference from other cations.

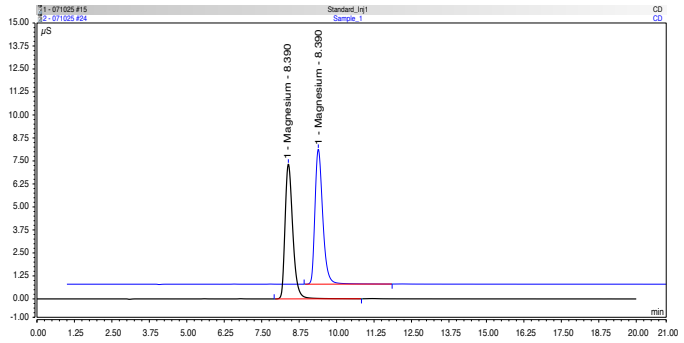

Figure 5. Overlaid chromatograms of a standard solution and a sample solution with signal and time offset of 5% each.

Four different magnesium sulfate samples were analyzed and the results obtained are shown in Table 2. Six consecutive injections were done for each sample. Samples assay results were all within the required range of 98.0% to 102.0% with RSDs all well below 1%.

Table 2. NGES-C method results for four different samples of magnesium sulfate.

Sample	Lot No.	Average quantity (%; n=6)	%RSD, n=6
Magnesium sulfate anhydrous	0000793642	100.02	0.06
Magnesium sulfate anhydrous	W24L010	98.69	0.09
Magnesium sulfate anhydrous	T25L002	99.54	0.06
Magnesium sulfate anhydrous	Y08J022	99.78	0.05

To check for system ruggedness and to ensure statistical robustness, we performed 200 consecutive injections of magnesium sulfate anhydrous Lot No. 0000793642 and 100 consecutive injections of magnesium sulfate anhydrous Lot No. Y08J022. The results from these injections are tabulated in Table 3. Averaged results were within the USP required limits of 98.0% to 102.0%, and RSDs were below 1.0%. This shows that the system, column, and NGES-C suppressor are working well, and that the method can be applied to long sequences for varieties of magnesium sulfate samples.

Table 3. Results for magnesium sulfate in samples for a series of consecutive injections (n ≥100).

Sample	Lot No.	Average quantity (%; n=6)	%RSD, n=6
Magnesium sulfate anhydrous	0000793642	100.16 (n=200)	0.87
Magnesium sulfate anhydrous	Y08J022	99.56 (n=100)	0.87

7. Conclusion

Here, we showed that an ion chromatography method incorporating the NGES-C suppressor can provide precise and accurate quantification of magnesium sulfate. The approach aligns with USP requirements while leveraging advanced suppression technology to enhance analytical performance.

The integration of NGES-C suppression significantly improves key parameters such as baseline stability, noise reduction, and overall robustness of the assay. These enhancements contribute to greater reliability and efficiency, making the method well-suited for high-throughput environments.

Given its accuracy, consistency, and alignment with regulatory standards, this method is highly applicable for routine quality control and regulatory testing of pharmaceutical-grade magnesium sulfate. Its adoption can streamline workflows and ensure dependable results across diverse pharmaceutical and regulatory laboratories.

8. References

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