Inductively coupled plasma with mass-spectrometry method development and validation for gadolinium in gadolinium-based contrast agents of pharmaceutical formulations

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KEYWORDS
Gadolinium
Method validation
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Gadolinium-based contrast agents (GBCAs)
Inductively coupled plasma mass-spectrometry

ABSTRACT

Gadolinium-based contrast agent interacts with the human body temporarily and improves the pictures of inside of the body produced by magnetic resonance imaging, computed tomography, X-rays and ultrasound and it also helps to distinguish the normal from abnormal conditions. In this study, the authors developed a simple, rapid, reliable and robust inductively coupled plasma mass-spectrometry method for estimation of gadolinium in gadolinium-based contrast agents to check the drug quality and ensure the patient safety. The samples were digested at 160°C using the microwave digestion system and the gadolinium was extracted in 0.4% (w/w) nitric acid. Interference of deposited gadolinium on sample cone and skimmer cone were investigated and evaluated. The developed method was validated as per ICH Q2 (R1) guideline and USP<730>. The precision was evaluated with six independent assays of gadolinium in each gadolinium-based contrast agent. The test method was found linear (r^2 > 0.999) with five different levels covered from 25~200%, and accurate, mean recoveries were 92.5~107.5% at three different levels covered from 50~150%. The robustness was performed by changing the nitric acid concentration (0.4±0.04%, w/w) in diluent system. This method is suitable to quantitatively determine the amount of gadolinium in gadolinium-based contrast agent of drug products in presence of excipients used in formulation and also in drug substance.

1. Introduction

Gadolinium (Gd^{3+}/Gd) is toxic metal and can pose severe health hazards, but the chelating gadolinium compounds are far less toxic as they can carry gadolinium through the kidneys and out of body before free ion can be released into tissue. The solutions of chelated gadolinium compounds (Gadolinium-based contrast agents, GBCA) are chemical substances which interact with the human body temporarily and improve the pictures obtained by tomography, X-rays and ultrasound methods. However, the amount of gadolinium must be estimated to check the quality and to ensure the safety of the patients who have undergone for medication. In this study, the authors aim to determine the amount of gadolinium in gadolinium-based contrast agent. The test method was validated as per ICH Q2 (R1) guideline and USP<730>. The precision was evaluated with six independent assays of gadolinium in each gadolinium-based contrast agent. The test method was found linear (r^2 > 0.999) with five different levels covered from 25~200%, and accurate, mean recoveries were 92.5~107.5% at three different levels covered from 50~150%. The robustness was performed by changing the nitric acid concentration (0.4±0.04%, w/w) in diluent system. This method is suitable to quantitatively determine the amount of gadolinium in gadolinium-based contrast agent of drug products in presence of excipients used in formulation and also in drug substance.

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1. Introduction

Gadolinium (Gd^{3+}/Gd) is toxic metal and can pose severe health hazards, but the chelating gadolinium compounds are far less toxic as they can carry gadolinium through the kidneys and out of body before free ion can be released into tissue. The solutions of chelated gadolinium compounds (Gadolinium-based contrast agents, GBCA) are chemical substances which interact with the human body temporarily and improve the pictures obtained by tomography, X-rays and ultrasound methods. However, the amount of gadolinium must be estimated to check the quality and to ensure the safety of the patients who have undergone for medication. In this study, the authors aim to determine the amount of gadolinium in gadolinium-based contrast agent. The test method was validated as per ICH Q2 (R1) guideline and USP<730>. The precision was evaluated with six independent assays of gadolinium in each gadolinium-based contrast agent. The test method was found linear (r^2 > 0.999) with five different levels covered from 25~200%, and accurate, mean recoveries were 92.5~107.5% at three different levels covered from 50~150%. The robustness was performed by changing the nitric acid concentration (0.4±0.04%, w/w) in diluent system. This method is suitable to quantitatively determine the amount of gadolinium in gadolinium-based contrast agent of drug products in presence of excipients used in formulation and also in drug substance.
It is composed of the organic acid DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) as a chelating agent, and gadolinium (Gd³⁺), and is used in form of the meglumine salt (Gadoterate meglumine). It is chemically 2-[4,7-bis(carboxylatomethyl)-10-(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetate:gadolinium(3⁺); (2R,3R,4R,5S)-6-(methylamino)hexane-1,2,3,4,5-pentol¹ with a molecular mass of 753.9 g/mol and molecular formula of C₃₂H₅₀O₁₃N₅Gd (anhydrous basis) [3].

Gadopentetate dimeglumine injection is GBCA (each mL of solution for injection contains 469.01 mg gadopentetate dimeglumine, equivalent to 0.5 mmol gadopentetate dimeglumine containing 157.25 mg gadolinium) used in magnetic resonance imaging for intravenous administration. It is chemically 1-deoxy-1-(methylamino)-D-glucitol dihydrogen [N, N-bis[2-{bis(carboxymethyl)amino}ethyl]glycinato(5⁻)]gadolinate(2⁻) (2: 1) with a molecular mass of 938 g/mol and molecular formula of C₳₂H₄₀O₁₃N₅GdO₂ [4].

Literature survey reveals that a variety of analytical techniques such as spectrophotometric methods, including atomic absorption spectroscopy (AAS) and UV-Visible spectrophotometer (UV-Vis), and traditional methods, such as titration methods and colorimetric determinations, were used for the estimation of gadolinium in drug substances and drug products of GBCAs [5-7], but no sophisticated and robust analytical technique like ICP-MS method was used for the gadolinium determination either in the pharmaceutical formulations or pure drug substances, except some of the analyses of biological samples [8-11]. Thus, the authors used the sophisticated technique ICP-MS, and a simple, rapid and reliable method was developed for estimation of gadolinium with combination of microwave assisted digestion procedure. It is a new method for the analysis of gadolinium in the pharmaceutical formulations according to GBCAs requirements.

Inductively coupled plasma is a high-temperature excitation source that desolvates, vaporizes, and atomizes aerosol samples and ionizes the resulting atoms. The excited or ground state ions are to be determined using the inductively coupled plasma with mass-spectrometry. This technique is utilized for analyses of either single element or multi-elements, and is also used for either sequential or simultaneous analyses with good sensitivity over an extended linear range. The key advantages of ICP-MS over the traditional methods is its ability to quantitatively determine the trace amount of elemental impurities and assays with accurately and precisely, rapidly, relative lack of interference, and definitive multiple isotope capability [12]. This hyphenated technique requires only small amount of sample and reduced turnaround time. It provides more reliable and robust results without any interference as compare to traditional and spectroscopic methods. High throughput and sensitivity are major criterion for selecting and using the ICP-MS for gadolinium analysis in GBCAs. The microwave assisted digestion procedure was applied in this study and a suitable digestion procedure was designed for the sample digestion of formulated GBCAs. Microwave digestion instrument is a microwave assisted closed vessel digestion technique used for the reliable sample preparation process in the elemental impurities and assay analyses. It is a most convenient and rapid technique for dissolving the organic moiety in solid samples and parental samples with help of acids [13].

This study proposes a new ICP-MS method for the analysis of gadolinium in the pharmaceutical formulations of GBCAs. The developed ICP-MS method was validated as per the U.S. Pharmacopoeia (USP<730> , UP<233>), ICH Q2 (R1) and Eurachem Guidance [12,14,15] for specificity, linearity, accuracy, precision, robustness, and solution stability.

Figure 1. Chemical structure of GBCAs: (a) Gadobutrol, (b) Gadodiamide, (c) Gadoterate meglumine and (d) Gadopentetate dimeglumine.
2. Experimental

2.1. Chemicals and materials

The suprapur® grade nitric acid (HNO₃, 69%, w/w) and hydrochloric acid (HCl, 30%, w/w) were purchased from Merck, Germany. National Institute of Standards and Technology (NIST), TraceCERT® grade commercial gadolinium standard with a concentration of 1002±5 mg/L was purchased from Sigma-Aldrich, Switzerland. Samples of commercially available gadolinium solution (conc. 1000 mg/L) were prepared in diluent (0.4% nitric acid, HNO₃, 69%, w/w) using the MassHunter 4.4 Work Station. The samples for digestion treatment was done in fume hood (Citizen Industries, India) and followed by the microwave assisted digestion procedure was used for the formulated GBCAs which were carried out on Multiwave GO (Anton-Paar) with the microwave digestion system, and the sample solutions were digested using the Multiwave GO (Anton-Paar) with the digestion program as specified in Table 2 and Figure 2. After sample digestion process, the digestion vessels were taken out and were cooled to the room temperature. Carefully, the vessels were unlocked and the digested sample solutions were transfer into suitable volumetric flasks (Note: The digestion vessel lids were rinsed with water and the resulting solution was transferred into the same volumetric flask), and were made up to the volume with water as given in Table 3, and then mixed well.

![Figure 2. Profiles of temperature and pressure of digestion carried out using 0.4% HNO₃ and 100 mg of GBCA samples in Microwave assisted digestion program.](image)

2.2. Instruments

Gadolinium experiments were carried out on Agilent 7800 inductively coupled plasma with mass-spectrometry (Agilent, Singapore). The output signal was monitored and processed using the MassHunter 4.4 Work Station. The samples were introduced to the microwave digestion system, and the sample solutions were digested using the Multiwave GO (Anton-Paar) with the digestion program as specified in Table 2 and Figure 2. After sample digestion process, the digestion vessels were taken out and were cooled to the room temperature. Carefully, the vessels were unlocked and the digested sample solutions were transfer into suitable volumetric flasks (Note: The digestion vessel lids were rinsed with water and the resulting solution was transferred into the same volumetric flask), and were made up to the volume with water as given in Table 3, and then mixed well.

Table 1. Acquisition parameters of ICP-MS instrument.

| ICP-MS parameter | Set value | ICP-MS parameter | Set value |
|------------------|-----------|------------------|-----------|
| Analyte / Isotope | Gd / 157  | Spectrum mode option | Spectrum mode option |
| RF power         | 1550 Watt | Peak Pattern      | 3 point   |
| Plasma mode      | Low Matrix| Replicates        | 3         |
| Sampling cone and skimmer cone | Nickel | Sweeps | 100 |
| Sampling depth   | 8.0 mm    | Sample Acquisition: Pre-Run | Sample Acquisition: Pre-Run |
| Tune mode        | He gas    | Sample uptake     | 60 sec    |
| Acquisition mode | Spectrum  | Stabilization     | 50 sec    |
| Plasma gas flow rate | 15.0 L/min | Nebulizer pump speed | 0.30 L/min |
| Auxiliary gas flow rate | 1.0 L/min | Probe rinse       | 10 sec    |
| Nebulisation gas flow rate | 1.0 L/min | Rinse            | 60 sec    |
| He flow rate (collision gas) | 4.3 mL/min |                |           |

2.3. ICP-MS acquisition parameters

The ICP-MS acquisition parameters used for the entire analysis of gadolinium in pharmaceutical formulation samples of GBCA are listed in Table 1.

2.4. Standard solution

A standard stock solution (conc. 2 μg/mL) of gadolinium was prepared in diluent (0.4% nitric acid, w/w) using the commercially available gadolinium solution (conc. 1000 mg/L). Using this stock solution, the final working standard solution was prepared in diluent to obtain the concentration 0.12 μg/mL, and was subjected to the ICP-MS analysis of gadolinium content in pharmaceutical formulation samples of GBCA.

2.5. Sample solutions

The sample solution (100 mg) of the formulated drug product of each GBCA was taken into the microwave digestion vessel and nitric acid (6 mL, HNO₃, 69%, w/w) was added each vessel, and then the samples were kept in fume hood for pre-digestion (Note: Pre-digestion was carried out for 15~30 minutes till the bubbles and fumes got disappeared). After that the digestion vessels were closed with a cap and were introduced to the microwave digestion system, and the sample solutions were digested using the Multiwave GO (Anton-Paar) with the digestion program as specified in Table 2 and Figure 2. After sample digestion process, the digestion vessels were taken out and were cooled to the room temperature. Carefully, the vessels were unlocked and the digested sample solutions were transfer into suitable volumetric flasks (Note: The digestion vessel lids were rinsed with water and the resulting solution was transferred into the same volumetric flask), and were made up to the volume with water as given in Table 3, and then mixed well.
not en-suited for the gadolinium analysis using the ICP-MS technique as the methodology and detection technique used are different. So, the authors conducted the method development trials using a variety of microwave digestion programs along with different sample quantities and acids.

### 3.1.1. Challenges-faced in ICP-MS method development

The major and critical challenges faced during the method development and optimization experiments were gadolinium matrix interference. Owing to that an auto-tune of ICP-MS (which has to perform as part of daily performance verification check) was failed to meet the pre-defined criteria (Oxide ratio, CeO+/Ce++, 156/140: ≤ 1.8%; doubly charged, Ce2+/Ce++, 70/140: ≤ 3.0%). After evaluating the ICP-MS parameters and chemical properties of gadolinium, it was noticed that the observed interference was due to the deposits of Gd on the nickel cones (sample cone and skimmer cone) and ICP-MS spare parts, and it was also related to the gadolinium isotope 156 which was significantly interfered with the oxide ratio of cerium and doubly charged ratio used in no gas mode of the ICP-MS auto-tune [16,17]. However, the deposited matrix did not show interference on the accuracy (recoveries) results of gadolinium as, thus, the ICP-MS analysis was performed using an isotope 157 and appropriate cleaning procedures were adopted to remove the sample matrix on nickel cones and to avoid the deposits of sample matrix on the ICP-MS parts.

### 3.1.2. Optimization of ICP-MS parameters

The ICP-MS parameters were optimized in presence of the sample matrix as there is a chance to get the interference from matrix and can affect seriously on that the sensitivity and throughout of gadolinium. Isotope 157 was selected and the amount of gadolinium was estimated without any matrix interference. The major and critical parameters of ICP-MS such as radio frequency (rf) power and flow rate of argon gas (plasma, auxiliary, nebulizer and collision) were chosen and optimized using the digested sample matrix rather than the standard solution. The radio frequency power was studied ranged from 1500~1600 Watt and the optimized rf was chosen as it effects on the plasma temperature and improves performance of ion excitation. The results of optimized rf1550 Watt proved that the sensitivity, reproducibility and linearity of gadolinium were better and more reliable. The effect of argon gas flow such as nebulizer gas and auxiliary gas (0.8~1.2 L/min), plasma gas (13.5~16.5 L/min), and collision gas [4.0~5.0 L/min] were studied, and the optimum sensitivity was achieved with 1.0 L/min of nebulizer and auxiliary gases, 15.0 L/min of plasma gas and 4.3 L/min of collision gas. The sample acquisition and spectrum parameters were setup based on the good sensitivity and response of gadolinium (counts per second). The optimized ICP-MS parameters were summarized in Table 1.

### 3.1.3. Selection of sample size, diluent and digestion procedure

The sample quantities between 100 to 200 mg were taken and different experiments were conducted, and finally the sample quantity 100 mg was chosen as final condition for the estimation of gadolinium as the proposed ICP-MS method showed good sensitivity and throughout. Different diluent systems were tried to get the good extraction and recovery of gadolinium in selected four GBCAs. Initial experiments were done using the ultrapure water. (Neat method: Sample solution was prepared directly by adding water) but the extraction was not good as expected. So, the hydrochloric acid (0.1~0.5%, w/w), nitric acid (0.1~0.6%, w/w) and aqua-regia (HCl+HNO3, 3:1, v/v) were selected as diluent systems and the sample solutions were made in neat method, open digestion method (digestion was carried-out at 80 °C by adding certain volume of acid to open vessels in a fume hood) and microwave digestion method (digestion was carried out using the closed vessels microwave assisted digestion system with combination of acids) were tried, however the sample digestions with different concentrations of nitric acid (0.1~0.6%, w/w) were effectively worked for determination of gadolinium as compared to neat method and open digestion method. A good extraction and recoveries were achieved in 0.4% (w/w) nitric acid. Thus, it was chosen as optimized diluent for sample and standard solutions. Different temperatures / ramps (150 °C / 20 min, 160 °C / 15 min and 170 °C / 5 min), and temperature / holding times (160 °C / 15 min, 160 °C / 20 min and 160 °C / 25 min) were tried using the microwave digestion system. Finally, a fully digested and neat sample solution with good extraction was achieved with the digestion program as shown in Table 2.
developed ICP-MS method to ensure safety, quality and efficacy of the drug.

### 3.2.1. Linearity

System suitability of the developed ICP-MS method for Gd (0.12 μg/mL) was measured from the six replicate aspirations of Gd response. Linearity of the test method was evaluated by aspirating the standard solutions of Gd with 5 different concentrations used were 0.03, 0.06, 0.12, 0.18 and 0.24 μg/mL which were covered 25, 50, 100, 150 and 200% of target concentration (0.12 μg/mL). The regression analysis was determined using linear regression: y = ax + b, where 'y' is the response of Gd obtained from the aspirations of standard solutions, 'a' is the slope of the regression line, 'x' is the concentration of Gd. The regression parameters such as the correlation coefficient, slope and y-intercept of the calibration curve are given in Table 5.

### 3.2.2. Specificity

Specificity of the developed test method was proven by determining the percent interference of diluents (as such and digested) and placebo matrix. The observed interference was found well within the pre-defined criteria, less than 1.0%, of the target concentration (0.12 μg/mL). The specificity results are given in Table 5. Nevertheless, the Gd response obtained from the blank aspiration was subtracted from the Gd response of samples and the amount of Gd was calculated from each formulated GBCA.

### 3.2.3. Accuracy

Accuracy of the developed ICP-MS method was evaluated by aspirating the spiked sample solutions of each formulated GBCA at the concentration levels of 50, 100 and 150%. Percent recoveries were calculated by comparing with the standard responses and the results were given in Table 6. The mean recoveries of three spiking levels were ranged from 92.5 to 105.4%. Each relative standard deviation was below 5.0%.

### 3.2.4. Precision

Repeatability of the proposed ICP-MS method was performed by preparing and aspirating six individual sample solutions of each formulated GBCA at the target concentration (about 0.12 μg/mL). Percent content of Gd in each formulated GBCA was calculated against the Gd standard solution. The mean content of Gd for each GBCA was found within the predefined limits. Each relative standard deviation was below 5.0%. Intermediate precision (ruggedness) of the proposed ICP-MS method was performed by a second analyst using the same instrument in the same laboratory on different day by preparing the six replicate sample solutions of each formulated GBCA at the target concentration using the same preparation of accuracy (i.e. 3 preparation at each level accuracy level, 50%, 100% and 150%).

### 3.2.5. Solution stability

The prepared standard solution and sample solutions of each GBCA which was stored at room temperature (25 °C) in the analytical laboratory and were found to be stable for 24 hours. Thus, all studies are preferred to run within 24 hours of storing at about 25 °C in an analytical laboratory.

### 3.2.6. Robustness

To validate the robustness of the proposed method, deliberate variations are made in testing conditions of ICP-MS like changing the diluent concentration (0.4% nitric acid, w/w, ± absolute 10%). The results from the robustness process are 95.5 to 101.8% (Limit: 95.0 to 105.0%), by observing there is no change in the relative standard deviation from six replicate aspirates of standard at each modified condition. For all the modified conditions (0.36% nitric acid and 0.44% nitric acid, w/w), a small variability was observed in the content of Gd in digested blank (%).

Table 4. Results of system suitability and linearity in the developed ICP-MS method.

| Aspiration | Gd (CPS) | Spike level | Concentration in percent (%) | Concentration of Gd, μg/mL | CPS of Gd |
|------------|----------|-------------|------------------------------|--------------------------|-----------|
| 1          | 1247285.95 | L1          | 0.0 (Blank)                  | 0.020                    | 128.35    |
| 2          | 1293397.38 | L2          | 25                           | 0.030                    | 304848.81 |
| 3          | 1290616.10 | L3          | 50                           | 0.050                    | 608372.97 |
| 4          | 1271499.11 | L4          | 100                          | 0.120                    | 1251209.45|
| 5          | 1266617.20 | L5          | 150                          | 0.180                    | 1234949.53|
| 6          | 1235385.66 | L6          | 200                          | 0.230                    | 2014931.99|

Mean               1270525.66     Correlation               200
RSD (%)             1.3     Slope                      10440029.33
Intercept           0.0     %RSD-Intercept             -0.74

* Counts per second (CPS) of Gd standard.
* RSD: Related standard deviation in percent is calculated from the CPS (counts per second) of six replicate measurements of gadolinium standard solution.

Table 5. Results of Specificity in the developed ICP-MS method.

| Name of dosage form | Blank (%) | Digested blank (%) | Placebo (%) |
|---------------------|-----------|--------------------|-------------|
| Gadobutrol solution for injection (1.0 mmol/mL) | 0.2       | 0.4                | 0.7         |
| Gadodiamide solution for injection (0.5 mmol/mL) | 0.1       | 0.0                | 0.0         |
| Gadopentetate dimeglumine solutions for injection (0.5 mmol/mL) | 0.0       | 0.0                | 0.0         |
| Gadobutrol solution for injection (1.0 mmol/mL) | 0.0       | 0.1                | 0.0         |

Table 6. Results of accuracy and precision of the developed ICP-MS method.

| Name of GBCA | %Recovery (90–110%) | Overall (n=9) |
|--------------|---------------------|---------------|
|              | R1 (n=3)            | R2 (n=3)      | R3 (n=3)      | Mean | %RSD |
| Gadobutrol   | 105.4%              | 100.5%        | 98.3%         | 101.4%| 3.6% |
| Gadodiamide  | 99.8%               | 95.7%         | 92.5%         | 96.0% | 3.8% |
| Gadopentetate dimeglumine | 98.5%   | 97.0%         | 97.7%         | 97.7% | 0.8% |
| Gadobutrol   | 101.5%              | 99.9%         | 97.9%         | 99.5% | 1.0% |

* Overall %RSD is calculated from 9 replicate preparation of accuracy (i.e. 3 preparation at each level accuracy level, 50%, 100% and 150%).

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limits in each GBCA. Apart from the variation in content of Gd, the developed method was found to be highly robust in nature for changing conditions.

4. Conclusion

Inductively coupled plasma mass-spectrometry method was developed and successfully validated to determine the amount of gadolinium ion in the gadolinium-based contrast agents of four pharmaceutical formulations that are important for the investigation of gadolinium retention in patients who have undergone the magnetic resonance imaging diagnostics. The problems faced related to the interference during the method optimization trials were resolved appropriately. The proposed method showed the linearity (over a range 25-200%), specificity, accuracy (over a range 50-150% of target concentration 0.12 µg/mL), precision (repeatability, n = 6, and intermediate precision, n = 6), robustness (change in diluent concentration 0.4±0.04% nitric acid, w/w), and solution stability. The proposed method is suitable for the estimation of gadolinium in active pharmaceutical ingredients and can be used in routine analysis for quality control in pharmaceutical industries.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.

Author contributions: All authors contributed equally to this work.

Ethical approval: All ethical guidelines have been adhered.

Sample availability: Samples of the compounds are available from the author.

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