

# Accurate Determination of Selenium in the Serum by Inductively Coupled Plasma Tandem-Mass Spectrometry

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**ABSTRACT:** As the selenium (Se) levels in the serum are critical to human health, it is imperative to develop highly sensitive analytical methods for determining the content of Se in the serum. Although using O<sub>2</sub> as a reaction gas in the MS/MS mode can effectively eliminate spectral interference, the sensitivity for determining Se remains low with the use of inductively coupled plasma tandem-mass spectrometry (ICP-MS/MS). In this study, a new strategy of using ICP-MS/MS to determine the trace Se level in human serum containing gadolinium (Gd)-based magnetic resonance imaging (MRI) contrasting agents was proposed. In the MS/MS mode, N<sub>2</sub>O was used as the reaction gas, N atom transfer reaction between N<sub>2</sub>O and Se<sup>+</sup> was adopted, and SeN<sup>+</sup> was selected as the detection ion to eliminate all mass spectrometric interferences, including Gd<sup>++</sup>. The accuracy and precision of the analytical method were evaluated by using standard reference materials. The results obtained indicated that interference-free determination of the Se level can be achieved by using high abundance isotopes <sup>80</sup>Se and <sup>78</sup>Se in the N<sub>2</sub>O reaction mode. The sensitivity of Se was higher when compared to that of the case in the conventional O<sub>2</sub> reaction mode. The limit of detection (LOD) was set as low as 2.19 ng L<sup>-1</sup> (for the most-abundant Se isotope). The RSD was 2.5%–4.2%, and the spiking recovery was 94.8%–106%. The proposed method is simple and practical, with high sensitivity and good accuracy and precision. The present study offers not only a precise and dependable approach for the highly sensitive detection of Se level in human serum containing gadolinium (Gd)-based MRI contrast agents but also introduces a novel concept for designing an N<sub>2</sub>O-reaction mode to eliminate spectral interference, thereby enabling the wider application of Se detection across various fields.

## INTRODUCTION

Selenium (Se), an essential trace element for the human body, is a component of several enzymes and proteins in organisms, with a significant impact on human physiological health.<sup>1</sup> In the human body, 25 types of gene-encoded Se proteins have been discovered so far, all of which achieve physiological functions such as anti-oxidation activity, redox regulation, thyroid hormone synthesis, and calcium signals transmission through enzymatic action.<sup>2-4</sup> Numerous studies have demonstrated that Kashin-Beck disease

and Keshan disease are typical Se-deficient disorders.<sup>5</sup> With more studies conducted on the significance of Se in the human body, it is found that Se deficiency could induce metabolic disorders.<sup>6</sup> The concentration of Se in the human body can be categorized into three situations: a trace concentration of Se maintains normal body growth and development; a medium concentration of Se maintains function stability; and a concentration of Se slightly higher than the level required for human health induces toxic effects, such as abnormal nail shedding, skin lesions, and nervous system damage.<sup>7-10</sup> Dietary levels of the desired amount of Se fall in a very narrow range: the consumption of food containing >1 mg kg<sup>-1</sup> Se

can result in toxic manifestation, whereas  $<0.1 \text{ mg kg}^{-1}$  can cause deficiency, with the maximum recommended Se dietary intake per day of  $400 \mu\text{g L}^{-1}$ .<sup>11,12</sup> Monitoring the change in the Se concentration in human serum is an essential issue in clinical medical research since the safe range of Se concentration in the human body is tiny.

For the detection of Se in the serum, several atomic spectrometry techniques have been developed, including atomic fluorescence spectrometry (AFS),<sup>13-15</sup> atomic absorption spectrometry (AAS),<sup>16-18</sup> inductively coupled plasma optical emission spectrometry (ICP-OES),<sup>19,20</sup> and inductively coupled plasma mass spectrometry (ICP-MS).<sup>21-23</sup> AFS has a high sensitivity and a low limit of detection (LOD), which may be reduced by more than one order of magnitude when combined with hydride generation (HG) technology. However, the fluorescence-quenching effect and the inherent scattered light interference limit AFS' theoretical advantages. The resonance absorption line for determining Se by AAS is close to the vacuum ultraviolet region, whereas the high excitation potential for determining Se by ICP-OES results in low sensitivity and high LOD for determining Se by AAS and ICP-OES, making it difficult to fulfill the requirements for determining the trace Se level in the serum. Although ICP-MS has lower LOD and higher sensitivity than AFS, AAS, and ICP-OES,<sup>24-26</sup> and has become the most commonly used analytical technique for determining Se in the serum, it still faces many challenges. For instance, Se has a high first ionization potential (9.75 eV) and a low ionization efficiency even in high-temperature plasma, which affects its analytical sensitivity. All isotopes of Se are subject to spectral interference, with high abundance isotopes such as  $^{80}\text{Se}$  (49.6%) and  $^{78}\text{Se}$  (23.8%) being severely interfered by the argide ions and matrix Ca. Due to the lower second ionization energy (12.09 eV) of Gd, the generated doubly charged ion  $\text{Gd}^{++}$  would substantially interfere with the determination of  $^{80}\text{Se}$  and  $^{78}\text{Se}$  when the serum sample contains the gadolinium (Gd)-based magnetic resonance imaging (MRI) contrasting agents.<sup>27</sup> Traditional quadrupole ICP-MS (ICP-QMS) cannot eliminate these interferences, and the sector magnetic field ICP-MS (SF-ICP-MS) cannot separate all interferences either.<sup>28,29</sup>

Inductively coupled plasma tandem-mass spectrometry (ICP-MS/MS) utilizes two quadrupole mass filters ( $Q_1$ ,  $Q_2$ ) located before and behind the octopole reaction system (ORS) to accurately control the types of ions entering the ORS, thereby improving the ability to eliminate spectral interference.<sup>30-33</sup> In the MS/MS mode,  $\text{Se}^+$  is transferred to  $\text{SeO}^+$  for determination through an O-atom transfer reaction with  $\text{O}_2$  as the reaction gas, allowing a high abundance of Se isotopes to be determined.<sup>34</sup> However, some studies have demonstrated that adding a small amount of  $\text{H}_2$  can further reduce the background equivalent concentration (BEC) of Se in the  $\text{O}_2$  reaction mode,<sup>35</sup> indicating that the interference is still not eliminated incompletely in the  $\text{O}_2$

reaction mode. When  $\text{N}_2\text{O}$  is utilized as the reaction gas in ICP-MS/MS, its lower affinity for the O atom makes  $\text{N}_2\text{O}$  more prone to an O-atom transfer reaction.<sup>36</sup> In the  $\text{N}_2\text{O}$  reaction mode, several endothermic reactions that occur in the  $\text{O}_2$  reaction mode become exothermic.<sup>37</sup> Simultaneously,  $\text{N}_2\text{O}$  can conduct an N-atom transfer reaction with a small number of ions.<sup>38</sup> Therefore,  $\text{N}_2\text{O}$  is a more effective mass shift reaction gas than  $\text{O}_2$ .<sup>39</sup> To accurately determine the Se level in serum-containing gadolinium-based MRI contrasting agents, we selected  $\text{N}_2\text{O}$  as the reaction gas, and the N-atom transfer reaction between  $\text{Se}^+$  and  $\text{N}_2\text{O}$  was used to eliminate spectral interference in the MS/MS mode by ICP-MS/MS. The aim of the study was to develop a high-throughput analysis method for interference-free determination of Se level in serum-containing gadolinium-based MRI contrasting agents.

## EXPERIMENTAL

**Instrumentation.** All measurements were performed using an ICP-MS/MS (Agilent 8800, USA) equipped with a MicroMid nebulizer, Peltier-cooled double-pass Scott-type spray chambers, and octopole impact reaction cell (ORS) located between the two quadrupole analyzers. Milli-Q water purification system was purchased from Millipore (USA). The Element XR SF-ICP-MS instrument (Thermo Fisher Scientific, USA) was used to obtain the reference values of the analytes. The optimized operating conditions of ICP-MS/MS and SF-ICP-MS are given in Table 1.

**Reagents and standard solutions.** The standard solution of Se ( $1000 \text{ mg L}^{-1}$ );  $1000 \text{ mg L}^{-1}$  of the standard solution of the internal standard element Y (Merck, Germany); 65% (w/w) suprapur  $\text{HNO}_3$ , 30% (w/w)  $\text{H}_2\text{O}_2$ , EDTA, Triton X-100,  $\text{NH}_4\text{OH}$ , and isopropanol were purchased from Sigma Aldrich (Merck KGaA); bovine serum (SRM 1598a) standard reference material was

**Table 1.** ICP-MS/MS and SF-ICP-MS operating conditions

ICP-MS/MS		SF-ICP-MS	
Parameters	Setting	Parameters	Setting
RF power	1550 W	RF power	1250 W
Carrier gas flow rate	0.80 L $\text{min}^{-1}$	Carrier gas flow rate	1.05 L $\text{min}^{-1}$
Sampling depth	8.0 mm	Plasma gas flow rate	16.0 L $\text{min}^{-1}$
Makeup gas flow rate	0.40 L $\text{min}^{-1}$	Auxiliary gas flow rate	0.95 L $\text{min}^{-1}$
Integration time	3.0 s	Resolution	HR
Extract 1	0 V	Mass window	125%
Extract 2	- 180 V	Integration window	60%
Reaction gas	$\text{N}_2\text{O}$	Detection mode	Triple
Reaction gas flow rate	0.30 mL $\text{min}^{-1}$	Sample dwell time	0.2 s
Octopole bias	- 18 V	Samples/peak	20
Energy discrimination	- 10 V	Isotope selected	$^{77}\text{Se}$

**Fig. 1** Product ions scan for (a)  $^{78}\text{Se}$  and (b)  $^{80}\text{Se}$  using  $\text{N}_2\text{O}$  as the reaction gas in the MS/MS mode. The Se standard ( $10\ \mu\text{g L}^{-1}$ ) solution, and deliberately added  $10\ \text{mg L}^{-1}$  Ca,  $20\ \text{mg L}^{-1}$  K,  $1\ \text{mg L}^{-1}$  S, and  $1\ \text{mg L}^{-1}$  Gd as the interfering elements.

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purchased from the National Institute of Standards and Technology (NIST); bovine serum (GBW09131) and bovine blood (GBW09141) standard reference materials were supplied by the National Standard Reference Material Research Center (Beijing, China).  $\text{H}_2$ ,  $\text{O}_2$ , and  $\text{N}_2\text{O}$  were obtained from Hubei Wuhan Newradargas Co., Ltd. (Wuhan, China). Milli-Q water purification system produced ultra-pure water (resistance  $>18.2\ \text{M}\Omega\ \text{cm}$ ).

**Source, collection, and treatment of samples.** A total of 76 patients (35 men, 41 women) were selected from the Affiliated Hospital of Hunan Academy of Chinese Medicine. All subjects had not undergone any imaging examinations using gadolinium-contrasting agents over the past 6 months. This study has been approved by the Ethics Committee of the Affiliated Hospital of Hunan Academy of Chinese Medicine (No. [2023] 66). All subjects were informed in advance that their serum samples would be collected for research and they provided their signed informed consent.

The serum samples of the patients within 1 h before and after injection of the same gadolinium contrasting agent were collected as control and sample groups, respectively. The patients' fasting peripheral venous blood samples were collected and centrifuged at  $4^\circ\text{C}$  for 5 min with a low-temperature centrifuge at a speed of  $1200\ \text{r min}^{-1}$ . The upper serum level was transferred to a low-temperature tube for refrigerator storage at  $-20^\circ\text{C}$ , and, subsequently, to a refrigerator for long-term storage at  $-80^\circ\text{C}$ .

**Experimental methods.** Serum samples ( $0.1\ \text{mL}$ ) were accurately transferred into an Eppendorf tube, and  $10\ \text{mL}$  of the diluent containing 4% isopropanol, 0.1% EDTA, 0.1% Triton X-100, and 2%  $\text{NH}_4\text{OH}$  were added. The sample solution was obtained after fully mixing them.

The whole blood sample (standard reference material) was

digested by the microwave digestion (CEM Mars 5, USA) and  $0.5\ \text{mL}$  of it was accurately transferred into a digestion vessel. Then,  $2\ \text{mL}$  of 65% (w/w)  $\text{HNO}_3$  and  $1\ \text{mL}$  of 30% (w/w)  $\text{H}_2\text{O}_2$  were successively added to the sample and allowed to rest for 10 min, followed by heating as per a three-stage digestion program at 100% power (maximum power  $1600\ \text{W}$ ): (1) ramp 5 min, control temperature  $120^\circ\text{C}$ ; (2) ramp 3 min, control temperature  $150^\circ\text{C}$ , hold for 5 min; (3) ramp 5 min, control temperature  $180^\circ\text{C}$ , hold for 10 min. Next, the digestion vessel was cooled and the transparent solution obtained was transferred to a  $50\ \text{mL}$  polypropylene volumetric flask containing ultra-pure water. The digestion vessel was washed repeatedly and the resultant solutions obtained were collected in volumetric flasks of a constant volume.

A series of standard solutions of Se with varying concentration gradients were then analyzed by ICP-MS/MS together with the sample and blank solutions. The reaction gas in the MS/MS mode was  $\text{N}_2\text{O}$ , and the spectral interference was eliminated by the N-atom transfer reaction (Fig. 1). Then,  $100\ \mu\text{g L}^{-1}$  of Y internal standard solution was introduced online to all test solutions using the standard T-type internal standard mixing connector, and the determination was completed within 12 h.

## RESULTS AND DISCUSSION

**Selection of the reaction mode.** The six Se isotopes displayed varying degrees of spectral interference, with  $^{80}\text{Se}$  and  $^{78}\text{Se}$  showing a high abundance, while the other isotopes showed  $<10\%$  abundance. As a result,  $^{78}\text{Se}$  and  $^{80}\text{Se}$  were selected as analytical isotopes in this experiment.  $^{78}\text{Se}$  and  $^{80}\text{Se}$  were subjected to interference from Gd, Ca, S, Cl, Zn, and Ar in the human serum samples containing gadolinium-based MRI contrasting agents (Table S1). In the MS/MS mode,  $\text{H}_2$ ,  $\text{O}_2$ ,  $\text{O}_2/\text{H}_2$ ,  $\text{N}_2\text{O}$ , and  $\text{N}_2\text{O}/\text{H}_2$  were selected as the reaction gas to investigate the changes in sensitivity (defined as the slope of analytical calibration curves)

**Table 2.** Sensitivity and BEC of Se in the different reaction modes by ICP-MS/MS

Mode	Determined ion	Sensitivity (cps/ $\mu\text{g L}^{-1}$ )	BEC (ng L <sup>-1</sup> )
No-gas	<sup>82</sup> Se	752	1280
H <sub>2</sub> on-mass	<sup>78</sup> Se	988	164
	<sup>80</sup> Se	2120	173
O <sub>2</sub> (O-atom transfer)	<sup>78</sup> Se	691	60.2
O <sub>2</sub> /H <sub>2</sub> (O-atom transfer)	<sup>80</sup> Se	1480	71.5
	<sup>78</sup> Se	676	3.61
N <sub>2</sub> O (O-atom transfer)	<sup>80</sup> Se	1430	3.52
	<sup>78</sup> Se	1430	23.4
N <sub>2</sub> O/H <sub>2</sub> (O-atom transfer)	<sup>80</sup> Se	2950	29.8
	<sup>78</sup> Se	1450	3.46
N <sub>2</sub> O (N-atom transfer)	<sup>80</sup> Se	2930	3.27
	<sup>78</sup> Se	780	3.58
N <sub>2</sub> O/H <sub>2</sub> (N-atom transfer)	<sup>80</sup> Se	1600	3.34
	<sup>78</sup> Se	796	3.40
	<sup>80</sup> Se	1580	3.29

and BEC (calculated by the intercept on the Y-axis of the calibration curve divided by the slope of analytical calibration curves) of <sup>78</sup>Se and <sup>80</sup>Se. Although <sup>82</sup>Se is not a high-abundant isotope, it can avoid the interferences from the carrier gas, while <sup>82</sup>Se is selected as the analytical isotope in the no-gas mode, as well as in the elimination of spectral interference.

In the no-gas mode, the main interferences to <sup>82</sup>Se<sup>+</sup> are by <sup>42</sup>Ca<sup>40</sup>Ar<sup>+</sup>, <sup>66</sup>Zn<sup>16</sup>O<sup>+</sup>, <sup>81</sup>BrH<sup>+</sup>, <sup>45</sup>Sc<sup>37</sup>Cl<sup>+</sup>, and <sup>82</sup>Kr<sup>+</sup>. Due to the low abundance of <sup>82</sup>Kr, the interference from isobaric ion <sup>82</sup>Kr can be ignored.<sup>40</sup> Moreover, there is no interference from Gd<sup>++</sup>, albeit the presence of polyatomic ion interferences can result in a higher BEC of <sup>82</sup>Se. As the sensitivity obtained is partially contributed by polyatomic ion interferences, it does not represent the true sensitivity of <sup>82</sup>Se. Therefore, in the no-gas mode, even when the <sup>82</sup>Se isotope is used for analysis, spectral interferences remain.

Using H<sub>2</sub> as the reaction gas can quickly react with Ar-based ions and undergo mass shift reactions with some polyatomic ions, making it the most effective method for eliminating interference in the ICP-QMS determination of Se. However, it can be seen from Table S1 that, in the H<sub>2</sub> reaction mode, when compared with that in the other modes, the BECs of <sup>78</sup>Se and <sup>80</sup>Se were only lower than those of the no-gas mode, indicating that <sup>78</sup>Se and <sup>80</sup>Se can still be subject to serious interference from Gd<sup>++</sup> and have not been eliminated. Therefore, using H<sub>2</sub> as the reaction gas in the MS/MS mode is not suitable for the determination of Se in a serum containing gadolinium-based MRI contrasting agents.

The reaction between Se<sup>+</sup> and O<sub>2</sub> to form SeO<sup>+</sup> in the O<sub>2</sub> reaction mode was an endothermic process (Se<sup>+</sup> + O<sub>2</sub> → SeO<sup>+</sup> + O) with a reaction enthalpy ( $\Delta H_r$ ) > 0. Since the reaction between Se<sup>+</sup> and O<sub>2</sub> cannot occur spontaneously, the reaction was promoted by increasing the negative octopole bias voltage ( $V_{oct}$ ). To determine the BEC of Se, the product SeO<sup>+</sup> of O-atom transfer was adopted. Although the sensitivity of Se presented almost no change when a

small amount of H<sub>2</sub> was added to O<sub>2</sub> as the reaction gas, the BEC of Se was further reduced (Table 2).

In the N<sub>2</sub>O reaction mode, Se<sup>+</sup> and N<sub>2</sub>O can undergo not only the O-atom transfer reaction (Se<sup>+</sup> + N<sub>2</sub>O → SeO<sup>+</sup> + N<sub>2</sub>,  $\Delta H_r < 0$ ) but also the N-atom transfer reaction (Se<sup>+</sup> + N<sub>2</sub>O → SeN<sup>+</sup> + NO,  $\Delta H_r > 0$ ),<sup>37</sup> providing more possibilities for eliminating the spectral interference of Se. The mode of eliminating interference via the O-atom transfer reaction is similar to the O<sub>2</sub> reaction mode. Since the reaction generating SeO<sup>+</sup> was exothermic, but the reaction that generated SeN<sup>+</sup> was endothermic, the abundance of the resultant ion SeN<sup>+</sup> was lower than that of SeO<sup>+</sup>. Fig. 1 shows the mass spectrum scanning diagram of Se in the N<sub>2</sub>O reaction mode. According to Fig. 1(a), <sup>78</sup>Se<sup>+</sup> was strongly interfered with mainly by the argide ions of <sup>38</sup>Ar<sup>40</sup>Ar<sup>+</sup> and <sup>40</sup>Ca<sup>38</sup>Ar<sup>+</sup>, as well as by the doubly charged ions <sup>156</sup>Gd<sup>++</sup> and dimer ions <sup>39</sup>K<sup>39</sup>K<sup>+</sup>. There was a charge transfer reaction between <sup>38</sup>Ar<sup>40</sup>Ar<sup>+</sup> and N<sub>2</sub>O (<sup>38</sup>Ar<sup>40</sup>Ar<sup>+</sup> + N<sub>2</sub>O → <sup>38</sup>Ar + <sup>40</sup>Ar + N<sub>2</sub>O<sup>+</sup>) that did not interfere with the determination. None of the other interfering ions underwent O-atom and N-atom transfer reactions with N<sub>2</sub>O. Thus, <sup>78</sup>Se<sup>16</sup>O<sup>+</sup> or <sup>78</sup>Se<sup>14</sup>N<sup>+</sup> may be selected to provide interference-free Se determination. The mass spectrum behavior of <sup>80</sup>Se in the N<sub>2</sub>O reaction mode was consistent with that of <sup>78</sup>Se, with the resultant ions <sup>80</sup>Se<sup>16</sup>O<sup>+</sup> and <sup>80</sup>Se<sup>14</sup>N<sup>+</sup> (Fig. 1(b)). <sup>80</sup>Se<sup>+</sup> was strongly interfered with by Ar and Ca, as well as the oxides generated from S and doubly charged <sup>160</sup>Gd<sup>++</sup>. Except for <sup>40</sup>Ar<sub>2</sub><sup>+</sup>, which may conduct a charge transfer reaction with N<sub>2</sub>O (<sup>40</sup>Ar<sub>2</sub><sup>+</sup> + N<sub>2</sub>O → <sup>40</sup>Ar<sub>2</sub> + N<sub>2</sub>O<sup>+</sup>), no other interfering ions can undergo O-atom and N-atom transfer reactions with N<sub>2</sub>O. Therefore, the <sup>80</sup>Se<sup>16</sup>O<sup>+</sup> and <sup>80</sup>Se<sup>14</sup>N<sup>+</sup> produced by mass shift reaction between <sup>80</sup>Se<sup>+</sup> and N<sub>2</sub>O could achieve interference-free Se determination.

Table 2 depicts that the BEC obtained with SeO<sup>+</sup> as the detection ion in the N<sub>2</sub>O reaction mode was significantly lower than that in the O<sub>2</sub> reaction mode, while the sensitivity was significantly higher than that in the O<sub>2</sub> reaction mode, indicating that N<sub>2</sub>O was a more effective O-atom transfer reaction gas than O<sub>2</sub>. When SeN<sup>+</sup> was taken as the detecting ion, the obtained BEC in the N<sub>2</sub>O reaction mode was significantly lower than in the O<sub>2</sub> reaction mode, while the sensitivity was slightly higher. When N<sub>2</sub>O with a trace of H<sub>2</sub> added was employed as the reaction gas, the sensitivity of Se remained the same, but the BEC obtained with SeO<sup>+</sup> as the detection ion could be decreased further. However, no change was observed in the BEC obtained with SeN<sup>+</sup> as the detection ion. Therefore, whether SeO<sup>+</sup> was selected as the detecting ion or O<sub>2</sub> or N<sub>2</sub>O was utilized as the reaction gas, a small amount of H<sub>2</sub> was required to further reduce BEC via synergistic action. This effect may be because the small amount of Ar-based ions that interfered with the determination of Se could also undergo O-atom transfer reactions with O<sub>2</sub> or N<sub>2</sub>O and the small amount of Ar-based oxide ions generated interfered with SeO<sup>+</sup>. However, the small amount of H<sub>2</sub> added could quickly react with these Ar-based oxide ions to eliminate the interference of these Ar-

based oxide ions on  $\text{SeO}^+$ , thereby further reducing the BEC. Interestingly, the BEC of Se obtained in  $\text{O}_2/\text{H}_2$  and  $\text{N}_2\text{O}/\text{H}_2$  reaction modes was extremely close to that obtained in the  $\text{N}_2\text{O}$  reaction mode with  $\text{SeN}^+$  as the detection ion, indicating that the interference to Se was effectively eliminated to the background level. The sensitivity of the O-atom transfer product of  $\text{SeO}^+$  obtained with  $\text{N}_2\text{O}+\text{H}_2$  as the reaction gas mixture was higher than that of the N-atom transfer product of  $\text{SeN}^+$  obtained with  $\text{N}_2\text{O}$  as the reaction gas. However, the sensitivity of  $\text{SeN}^+$  could fully satisfy analytical requirements, and it was preferable to employ a single reaction gas ( $\text{N}_2\text{O}$  only) than a reaction gas mixture ( $\text{N}_2\text{O}/\text{H}_2$ ) in the operation. To minimize interference,  $\text{N}_2\text{O}$  was employed as the reaction gas in this research, and the N-atom transfer product of  $\text{SeN}^+$  was utilized as the detecting ion using  $\text{N}_2\text{O}$  mass shift reaction (Table S1).

**N atom transfer reaction mechanism between  $\text{Se}^+$  and  $\text{N}_2\text{O}$ .** In ORS, the N-atom transfer reaction between  $\text{Se}^+$  and  $\text{N}_2\text{O}$  was endothermic. To promote the reaction, the  $V_{\text{oct}}$  in the experiment was set to negative, and the centroid collision energy ( $E_{\text{cm}(\text{N}_2\text{O})}$ ) was provided for  $\text{Se}^+$  and  $\text{N}_2\text{O}$  before the reaction. The relationship between  $E_{\text{cm}(\text{N}_2\text{O})}$  and  $V_{\text{oct}}$  was described as follows:<sup>41</sup>

$$E_{\text{cm}(\text{N}_2\text{O})} = (m_{(\text{N}_2\text{O})}/(m_{(\text{N}_2\text{O})} + m_{(\text{Se})})(V_p + 2.5(m_{(\text{Se})}/m_{(\text{Ar})})kT_0 - V_{\text{oct}}) \quad (1)$$

Where,  $m_{(\text{N}_2\text{O})}$ ,  $m_{(\text{Se})}$ , and  $m_{(\text{Ar})}$  are the masses of  $\text{N}_2\text{O}$ ,  $\text{Se}^+$ , and Ar atoms, respectively;  $V_p$  is the plasma potential energy (about 2 eV);  $k$  is the Boltzmann constant, and  $T_0$  is the plasma gas temperature (about 5000 K).

As can be seen from Formula (1), the greater the negative voltage of  $V_{\text{oct}}$ , the greater the  $E_{\text{cm}}$  obtained by  $\text{Se}^+$  before the reaction, and the more conducive it is to the occurrence of the reaction, thereby improving the yield of  $\text{SeN}^+$  with higher sensitivity. However, an excessively high negative voltage of  $V_{\text{oct}}$  can increase the BEC of  $\text{SeN}^+$ , which would be detrimental to the determination of Se.

The influence of changing the negative voltage of  $V_{\text{oct}}$  on the BEC of  $\text{SeN}^+$  was investigated. According to Fig. 2(a), the changing trends of BEC of  $^{78}\text{SeN}^+$  and  $^{80}\text{SeN}^+$  with  $V_{\text{oct}}$  were consistent. The BEC of  $\text{SeN}^+$  gradually decreased as the negative voltage of  $V_{\text{oct}}$  increased. When the values of  $V_{\text{oct}}$  were -16 V and -18 V, respectively, the BEC of  $^{78}\text{SeN}^+$  and  $^{80}\text{SeN}^+$  were the smallest, and when the negative voltage of  $V_{\text{oct}}$  increased, the BEC of  $^{78}\text{SeN}^+$  and  $^{80}\text{SeN}^+$  began to grow. In this experiment, the  $V_{\text{oct}}$  value was adjusted to -18 V, and the  $E_{\text{cm}(\text{N}_2\text{O})}$  of  $\text{Se}^+$  was estimated as 7.92 eV using Formula (1), which was much greater than  $\Delta H_r$  of the reaction between  $\text{Se}^+$  and  $\text{N}_2\text{O}$  to generate  $\text{SeN}^+$ , thereby promoting the occurrence of N-atom transfer reaction. As a result, of the consistency between the experimental and theoretical data, it was concluded that  $\text{Se}^+$  underwent an N-atom transfer reaction

with  $\text{N}_2\text{O}$  in the  $\text{N}_2\text{O}$  reaction mode.

The Se standard ( $10 \mu\text{g L}^{-1}$ ) solution was employed to optimize the flow rate of  $\text{N}_2\text{O}$ , and the effect of different  $\text{N}_2\text{O}$  flow rates on the signal intensity of  $\text{SeN}^+$  was investigated (Fig. 2(b)). As a compromise, the flow rate of  $\text{N}_2\text{O}$  corresponding to a high signal intensity of  $\text{SeN}^+$  was adopted. The variations in signal intensity of  $^{78}\text{Se}^{14}\text{N}^+$  and  $^{80}\text{Se}^{14}\text{N}^+$  were almost the same. The signal intensity of  $\text{SeN}^+$  increased rapidly as the flow rates of  $\text{N}_2\text{O}$  reached  $0.25 \text{ mL min}^{-1}$  and  $0.30 \text{ mL min}^{-1}$ , respectively,  $^{78}\text{Se}^{14}\text{N}^+$  and  $^{80}\text{Se}^{14}\text{N}^+$  achieved the highest signal intensity. The signal intensity of  $^{78}\text{Se}^{14}\text{N}^+$  and  $^{80}\text{Se}^{14}\text{N}^+$  then steadily decreased as the flow rate of  $\text{N}_2\text{O}$  increased. As a result, the flow rate of  $\text{N}_2\text{O}$  in this study was set as  $0.30 \text{ mL/min}$  to ensure the optimum analytical performance of  $^{80}\text{Se}^{14}\text{N}^+$  with high abundance.

**Optimal selection of internal standard ion.** The use of internal standards in ICP-MS analysis can effectively correct the potential matrix effects and instrument facility. Ge, Y, Rh, In, and Te are commonly used as internal standard selection elements of Se in ICP-MS analysis based on the internal standard selection principle that the mass number and ionization potential are close to the analytes. However, since  $\text{SeN}^+$ , the mass shift product of  $\text{Se}^+$  was used as the detection ion in ICP-MS/MS analysis, the selection of internal standard elements became complicated.<sup>42</sup> The internal standard elements of Ge, Y, and Te can undergo mass shift reactions (O-atom transfer) with  $\text{N}_2\text{O}$  in the  $\text{N}_2\text{O}$  reaction mode, while Rh and In seldom react with  $\text{N}_2\text{O}$ . Therefore,  $^{72}\text{Ge}^{16}\text{O}^+$ ,  $^{89}\text{Y}^{16}\text{O}^+$ ,  $^{103}\text{Rh}^+$ ,  $^{115}\text{In}^+$ , and  $^{125}\text{Te}^{16}\text{O}^+$  were adopted as the internal standard ions in this study, and the sensitivity of  $^{72}\text{Ge}^{16}\text{O}^+$ ,  $^{89}\text{Y}^{16}\text{O}^+$ ,  $^{103}\text{Rh}^+$ ,  $^{115}\text{In}^+$ , and  $^{125}\text{Te}^{16}\text{O}^+$  is 11500, 97300, 41600, 127000, 368 cps  $\text{L } \mu\text{g}^{-1}$ , respectively. The  $10\text{-}\mu\text{g L}^{-1}$  spiked Se sample solution was repeatedly detected within 60 min (the time interval was 10 min, and the test was repeated 6 times in total) to investigate the influence of different internal standard ions on the determination results of  $^{78}\text{Se}$  and  $^{80}\text{Se}$  (Fig. 2(c)). No significant difference was noted in the spike recovery rates obtained by the five internal standard ions; however, in the ICP-MS/MS analysis, ions with the same mass spectrometry behavior as the analyte ions, such as  $^{72}\text{Ge}^{16}\text{O}^+$ ,  $^{89}\text{Y}^{16}\text{O}^+$ , and  $^{125}\text{Te}^{16}\text{O}^+$ , were found to be more suitable as internal standard ions. Since  $^{89}\text{Y}^{16}\text{O}^+$  has a substantially better sensitivity than  $^{72}\text{Ge}^{16}\text{O}^+$  and  $^{125}\text{Te}^{16}\text{O}^+$ ,  $^{89}\text{Y}^{16}\text{O}^+$  was selected as the internal standard ion in this experiment.

**Sensitization effect of organic solvent.** Se has a poor analytical sensitivity due to its low ionization efficiency in inductively coupled plasma (ICP). A small amount of organic reagent dissolved in the sample or mixed with ICP can significantly increase the signal intensity of Se. Although there is no clear consensus on the mechanism of organic reagent sensitization, this sensitization effect has been widely applied.<sup>43</sup> In polar and non-polar solvents, low-carbon alcohols (MeOH) containing small molecules can be dissolved. Isopropanol was selected as the

**Fig. 2** Effect of ORS bias potential ( $V_{oct}$ ) on BEC of  $\text{SeN}^+$ ; (b) Effect of the  $\text{N}_2\text{O}$  flow rate on the signal intensity of  $\text{SeN}^+$ ; (c) Effect of different internal standard ions on the spike recovery of  $10 \mu\text{g L}^{-1}$  Se; (d) Effect of isopropanol on the signal intensity of Se.

**Table 3.** Linear relationship, the limit of detection (LOD), and the limits of quantification (LOQ) obtained for Se by ICP-MS/MS.

Isotope	$Q_1 \rightarrow Q_2$	Product ion	Linearity range ( $\mu\text{g L}^{-1}$ )	Correlation coefficients ( $R^2$ )	LOD ( $\text{ng L}^{-1}$ )	LOQ ( $\text{ng L}^{-1}$ )
$^{78}\text{Se}$	78→92	$^{78}\text{Se}^{14}\text{N}^+$	0.010-100	0.9997	3.05	10.2
$^{80}\text{Se}$	80→94	$^{80}\text{Se}^{14}\text{N}^+$	0.007-100	0.9998	2.19	7.30

sensitizer in this experiment, and the ionization efficiency of Se in ICP was improved by adding isopropanol to the sample solution. The analytical isotopes  $^{78}\text{Se}$  and  $^{80}\text{Se}$  were selected to study the effect of isopropanol concentrations on the signal intensity of  $10 \mu\text{g L}^{-1}$  Se standard solution, and the results are shown in Fig. 2(d). The signal intensity of Se steadily rose as the concentration of isopropanol increased. The signal intensity of Se was greatest when the isopropanol concentration was 3–5%. The signal strength of Se began to decline as the concentration of isopropanol increased. The high concentration of isopropanol entering the ICP torch tube increased the load on ICP and decreased Se ionization. In this experiment, the isopropanol concentration was set to 4%,

which significantly improved the Se signal intensity.

**Linearity of the method and LOD.** The linear relationship and LOD (calculated as 3 times the standard deviation of 10 consecutive measurements with a blank solution, divided by the slope of the calibration curve) of Se in the  $\text{N}_2\text{O}$  reaction mode were explored to assess the analytical performance of employing  $\text{N}_2\text{O}$  as a reaction gas to eliminate spectral interference in the MS/MS mode. The linear correlation coefficient of Se was  $\geq 0.9997$ , as shown in Table 3, and the developed method exhibited a good linear relationship. The LODs of  $^{78}\text{Se}$  and  $^{80}\text{Se}$  were 3.05 and 2.19  $\text{ng L}^{-1}$ , respectively. The LOD of Se declined by nearly an order of

**Table 4.** Analytical results for the determination of Se in the standard reference materials by ICP-MS/MS (mean  $\pm$  standard deviation, n = 6)

Sample	Isotope	Found ( $\mu\text{g L}^{-1}$ )	RSD (%)	Certified ( $\mu\text{g L}^{-1}$ )	<i>t</i> test	Added ( $\mu\text{g L}^{-1}$ )	Total found ( $\mu\text{g L}^{-1}$ )	Recovery (%)
SRM 1598a (Bovine serum)	$^{78}\text{Se}$	129.7 $\pm$ 4.1	3.2	134.4 $\pm$ 5.8	$p = 0.07$	100	227.6	98.5
	$^{80}\text{Se}$	136.8 $\pm$ 5.0	3.7		$p = 0.23$		233.4	96.6
GBW09131 (Bovine serum)	$^{78}\text{Se}$	38.1 $\pm$ 1.6	4.2	38.9 $\pm$ 2.3	$p = 0.13$	50.0	91.3	106
	$^{80}\text{Se}$	37.9 $\pm$ 1.3	3.4		$p = 0.19$		85.8	95.8
GBW09141 (Bovine blood)	$^{78}\text{Se}$	102.5 $\pm$ 2.6	2.5	99.0 $\pm$ 6.9	$p = 0.14$	100	197.3	94.8
	$^{80}\text{Se}$	96.0 $\pm$ 3.4	3.5		$p = 0.18$		199.2	103

**Table 5.** Analytical results for the determination of Se in human serum samples by ICP-MS/MS

Sample	Male <sup>a</sup>			Female <sup>b</sup>		
	ICP-MS/MS ( $\mu\text{g L}^{-1}$ )	SF-ICP-MS ( $\mu\text{g L}^{-1}$ )	<i>t</i> test	ICP-MS/MS ( $\mu\text{g L}^{-1}$ )	SF-ICP-MS ( $\mu\text{g L}^{-1}$ )	<i>t</i> test
Control group	95.2 $\pm$ 3.6	94.8 $\pm$ 4.0	$p = 0.33$	91.0 $\pm$ 2.3	92.5 $\pm$ 2.8	$p = 0.12$
Sample group	96.1 $\pm$ 2.9	95.7 $\pm$ 2.6	$p = 0.27$	90.3 $\pm$ 3.1	91.2 $\pm$ 3.4	$p = 0.11$

<sup>a</sup> Mean  $\pm$  standard deviation, n = 35. <sup>b</sup> Mean  $\pm$  standard deviation, n = 41.

magnitude when compared to the O<sub>2</sub> reaction mode, and significantly lower than that previously reported for similar studies (Table S2).

The accuracy and precision of the analytical method were evaluated by using standard reference materials (SRM 1598a, GBW09131, and GBW09141).  $^{78}\text{Se}$  and  $^{80}\text{Se}$  were selected as analytical isotopes to conduct the determination six times, and the relative standard deviation (RSD) of Se was computed. Meanwhile, the Se standard solution was added to the standard reference materials' sample solution, and the spiking recovery of Se was computed (Table 4). The results indicated that at a 95% confidence level, there was no significant difference between the measurement results of all standard reference materials and the certified values ( $p > 0.05$ ). The RSD was 2.5%–4.2% and the spiking recovery was 94.8%–106%, indicating that the method was accurate and precise.

To further evaluate the effect of different concentrations of Gd on the determination of Se level, standard solutions of Gd at 250, 500, and 1000  $\mu\text{g/L}$ , respectively, were added to the standard reference materials, and the  $^{78}\text{Se}$  and  $^{80}\text{Se}$  were selected as analytical isotopes and the measurements were repeated six times. The recovery rate of Se was calculated (Table S3). It was found that the determination values for Se at all concentrations of the Gd matrix were basically consistent with the certified values, with the recovery rates ranging from 97.5% to 104.9%. This finding indicated that the determination of Se content using the N-atom transfer reaction in the MS/MS mode was not affected by the concentration of Gd, which further verified the high applicability of the method.

**Sample analysis.** The developed method was utilized to analyze the serum samples from 76 patients (35 men, 41 women) within 1 h of receiving the same gadolinium contrasting agent (control

group before injection and sample group after injection). Meanwhile, the SF-ICP-MS method was employed for comparative analyses. Each sample was measured six times, and the *t*-test method was employed to statistically analyze the findings of the method (ICP-MS/MS) and SF-ICP-MS (Table 5). The results of the measured values for the control groups agreed with those of the sample groups. For both genders, at the 95% confidence level, no significant difference was noted between the measured values of ICP-MS/MS and SF-ICP-MS ( $p > 0.05$ ), indicating that the presence of a high concentration of Gd in the serum sample did not interfere with the determination of Se, which further verifies the accuracy and reliability of the proposed method.

## CONCLUSION

The present findings clearly demonstrate the ability of ICP-MS/MS with N<sub>2</sub>O as the reaction gas to detect Se in a serum-containing gadolinium-based MRI-contrasting agents. In ORS, Se<sup>+</sup> can undergo mass shift reactions with N<sub>2</sub>O and O<sub>2</sub>, respectively. The effect of using the N<sub>2</sub>O mass shift method to determine Se was significantly better than that of using the O<sub>2</sub> mass shift method. In the N<sub>2</sub>O reaction mode, Se<sup>+</sup> and N<sub>2</sub>O can undergo the O-atom transfer reaction and the N-atom transfer reaction, respectively. Although the sensitivity obtained through the N-atom transfer reaction to determine Se was lower than that with the O-atom transfer reaction, the LOD obtained was lower than that for the O-atom transfer reaction. This study's findings provide technical support for the determination of Se in the serum-containing gadolinium-based MRI-contrasting agents and recommend the application of the developed analytical method to determine Se in more numbers of fields.

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### Notes

The authors declare no competing financial interest.

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