A novel ICP-MS/MS approach for the analysis of vanadium in glucose magnesium sulfate injection to meet the requirement of USP<232>/<233>

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USP232/233 has become official since January 1st, 2018 and the final version completely aligned with ICH-Q3D, including impurities test of 24 elements. Elemental impurities include catalysts and environmental contaminants that may be present in drug substances, excipients, or drug products. ICP-MS is the most widely used atomic spectrometry technique for the measurement of trace elements. Typically, for the analysis of drug products, single-quad ICP-MS could achieve excellent performance, even though for the large volume injection products. Hydrochloric acid is used for stabilizing mercury during the sample preparation. However, measurement of vanadium in glucose magnesium sulfate that seems extremely difficult, due to the serious poly-atomic interferences from Cl and Mg matrix. In comparison with ICP-SQ-MS, extremely low DL of vanadium, at 0.002 µg/L and outstanding stability could be achieved by ICP-MS/MS. ICP-MS/MS as an inorganic tandem mass spectrometry, operated with both Q1 and Q2 at 1 amu resolution, could easily control the reaction process in the cell. Vanadium reacts with ammonium in the reaction cell and forms the product ion, $^{51}V^{14}N^{1}H_2$, which could completely remove the Mg and Cl related interferences.

In this study, we investigated three different collision/reaction gas with ICP single-quadrupole and tandem MS modes.

Instrumentation

An Agilent 8900 ICP-MS/MS was used. The standard configuration instrument includes HMI and single-quadrupole (SQ) and tandem MS (MS/MS) mode. Oxygen, helium and ammonium as collision/reaction gas were used to remove the poly-atomic interferences.

The ICP-MS MassHunter software provides a pre-configured method and report template which matches the USP<232/233> requirements, including the calculation of J value, spike recovery, and precision, etc.

Sample preparation

Vanadium standards, dedicated for USP<232/233> parenteral route, were prepared in trace-level of hydrochloric acid (TAMA-Pure-AA-100, Kanagawa, Japan). Weigh the samples to the nearest 2.50g, and dilute the samples with 2% HCl (v/v) at 4 times. Agitate the mixture for couples of minutes for sample well distribution. Before introducing to ICP-MS, make filtration through a membrane filter to remove visible material.
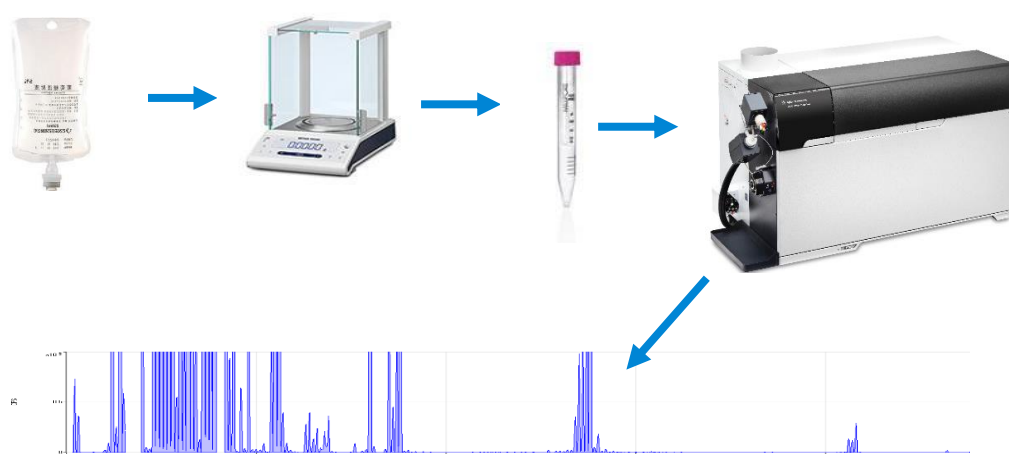
ICP-MS/MS Operating Parameters

Agilent 8900 Triple Quadrupole ICP-MS #100 with 2.5 mm injector torch. RF = 1550W, SD = 8.0mm, CRGS = 0.9L/min, MUGS = 0.2L/min, Spray Chamber Temp. = 2 ℃

Three modes were used in this study, for investigating the different interference removal capability. Meanwhile, evaluating the single-quadrupole (SQ) and tandem MS (MS/MS) mode, 8900 ICP-MS/MS could easily achieve the free-interference results for this kind of samples under the Q1 and Q2 operating simultaneously.

Parameter	Value		Parameter	Value
RF (W)	1550		Spray chamber temp. (℃)	2
Sampling depth (mm)	8.0		O_2 flow rate (mL/min)	0.25
Carrier gas (L/min)	0.9		He flow rate (mL/min)	4.5
Makeup gas (L/min)	0.2		NH_3 flow rate (mL/min)	0.15
Integration time (s)	0.3-0.6			

Parenteral drug: Measurement of vanadium in glucose magnesium sulfate with ICP-SQ and ICP-MS/MS

Following microwave digestion, all 24 elements were measured in the oral drug sample digests using ICP-MS. The digests were spiked according to the PDE limits. All results are given in Table 2.

Table 2. Precision of vanadium in sequential sample running by ICP-MS and ICP-MS/MS (µg/L)

	ICP-SQ	ICP-MS/MS	
	51 V	51-->51 V	51-->67 VNH$_2$
Sample1-rep1	2.12	0.175	0.166
Sample1-rep2	2.45	0.179	0.161
Sample1-rep3	2.75	0.201	0.163
Sample1-rep4	2.90	0.182	0.158
Sample1-rep5	3.00	0.178	0.155
Sample1-rep6	3.05	0.168	0.156

According to the data generated by ICP-SQ-MS, it seems that magnesium and chloride ions could accumulate in the sample introduction system. Therefore, sequential 6 samples running, the results of V in the sample gradually increased using ICP-SQ-MS, ranging from 2.1 to 3.0 µg/L. Quick different from ICP-SQ, the precision of the 6 replicates achieved by ICP-MS/MS is 2.6%, even at extremely low concentration of 0.15 µg/L. Here, we demonstrate the effect of tandem MS coupled with ammonium as reaction gas in achieving interference-free measurement, as shown in Fig.1.

- Analyte $^{51}V^+$ $V^+ + NH_3 \longrightarrow$ nearly no reaction

- Interference $^{35}Cl^{16}O^+$, $^{34}S^{16}OH$ $ClO^+ + NH_3 \longrightarrow NH_3^+ + ClO$

        $^{34}S^{16}OH + NH_3 \longrightarrow NH_3^+ + SOH$

- Unwanted precursor ion $35Cl^+$

        $Cl^+ + NH_3 \longrightarrow Cl\,NH_2^+ + H$
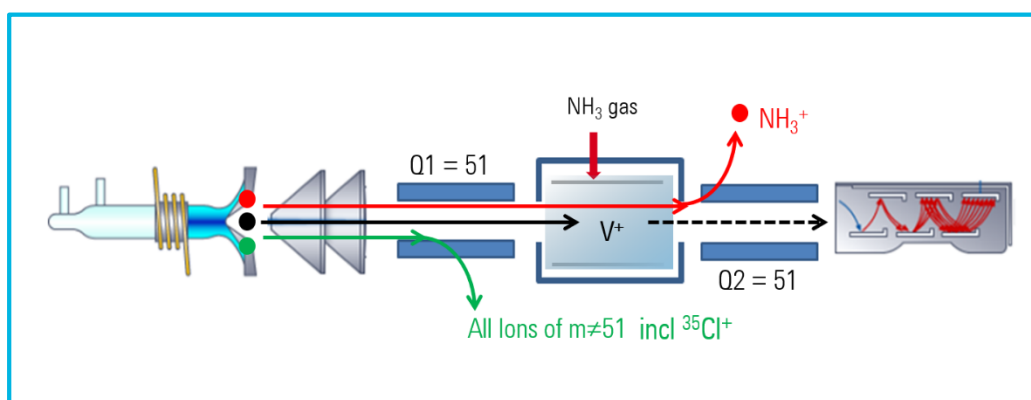

Figure 1. Mechanism of MS/MS mass-shift, using NH$_3$ for the measurement of V in high-sulfur and chloride matrix

The ClO$^+$ interference on 51V was removed by NH$_3$ on-mass mode. Meanwhile, $^{14}NH_2{}^{35}Cl^+$ could form in the cell and overlap at m/z 51, interference on V. However, the mass resolution of Q1 on the 8900 ICP-QQQ ensures that ions at m/z 51 could enter the cell. All other matrix and analyte ions, e.g. 35Cl$^+$, are removed by the mass filter and cannot, therefore, contribute to the signal at the analyte ion.

Evaluation of the origin of interference ions with precursor ions scan

In order to make the mechanism of interference removing clearly, the function of product ion scan was applied in this study, as Fig.2 shows.
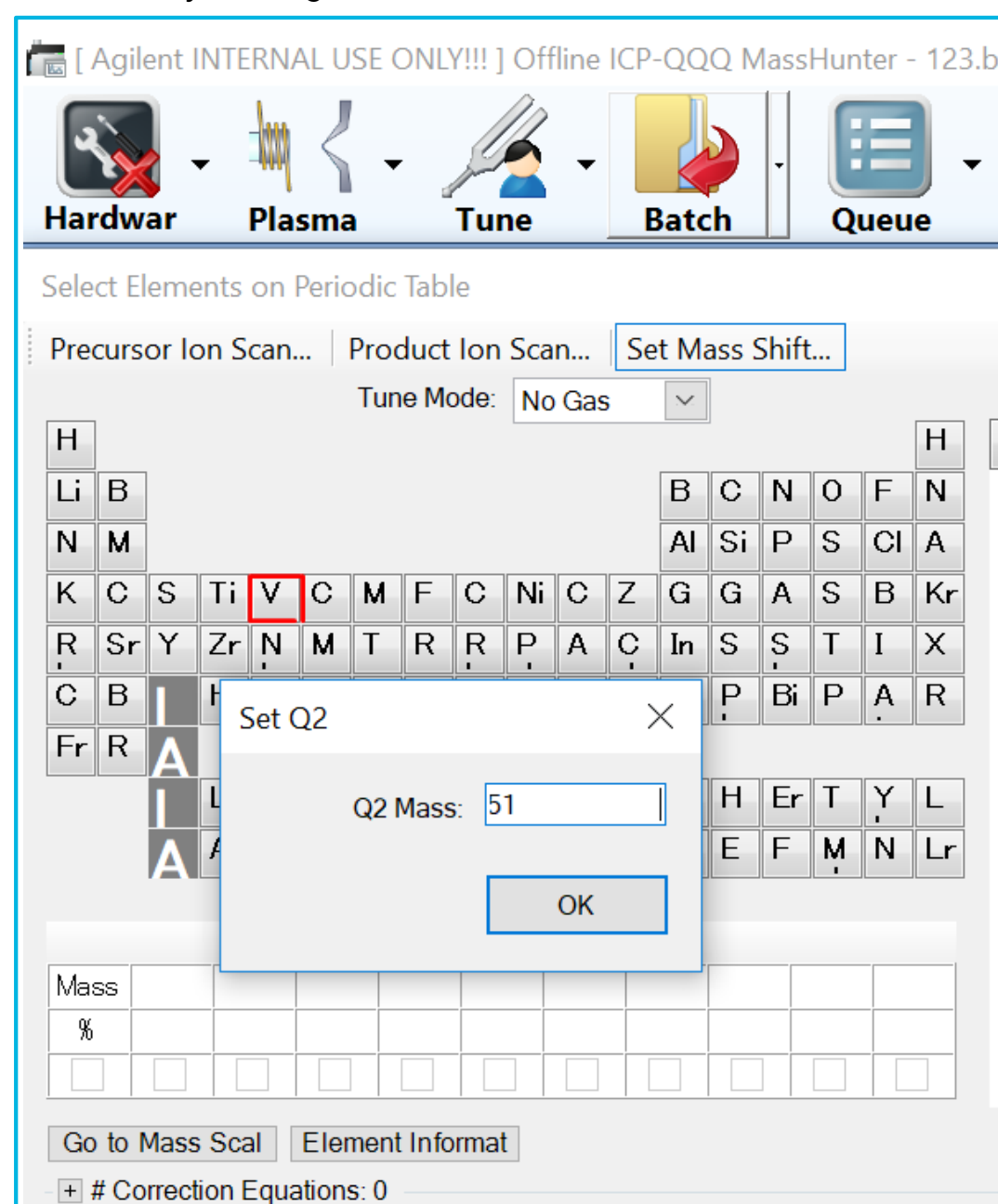

Figure 2. Precursor ions scan

As shown in Fig.2, the Q2 could be operated as filter at m/z 51, and Q1 scanned across the mass range from 2 to 275 amu. As discussed in the Fig.1, the sample solution contains high level concentration of sulfur and chloride ion, that should potentially overlap at vanadium of m/z 51. Therefore, we evaluated the original ions or any poly-atomic ions formed before entering the Q1, which could indicate that things happen in the plasma.

Evaluation of the origin of interference ions with precursor ions scan

The data was generated by precursor ion scan mode, as shown in table 3. And the sample was diluted by 2% HCl.

Table 3. The precursor ion scan by ICP-MS/MS in no gas mode (cps)

	ICP-MS/MS (Precursor ion scan)		
	34-->51 V	35-->51 V	51-->51 V
Sample1-rep1	66	47	229457
Sample1-rep2	73	44	308369
Sample1-rep3	80	50	313158

From the data presented in Table 3, it seems that the sulfur and chloride ions contribute small amounts of signal at m/z 51. However, the mass pair of 51/51, takes great contribution on the signal. It could be considered that SOH^+ or ClO^+ formed before the Q1. In addition to that, the data indicates the chloride ion almost transfer to the oxide, which plays as the dominant product ions. ICP-QQQ with MS/MS and ammonium gas could removes this serious interference effectively. It could be illustrated by the low BEC of V at 8 ppt (Fig.3), even though for the measurement of 51/51. The low BEC also proves that the matrix derived interference can not react with NH_3. A further benefit of ammonium gas mode is that it could provide much higher sensitivity than He mode.

Table 4. The polyatomic ions evaluated by ICP-MS/MS in no gas mode (cps)

	ICP-MS/MS (Precursor ion scan)		
	24-->51 V	34-->51 V	35-->51 V
Sample-2% HCl dilu	0	66	47
Sample-DIW dilu	0	70	0

There was no signal observed at 24/51, we can conclude that magnesium would not form any kind of polyatomic ions at m/z 51, as shown in table 4. From the results, it is clear that chloride-based product ions could be formed using the 2% HCl as the diluent, comparing with DIW, which is demonstrated by the signal from mass pair of 35/51.

A major interference on V should be sulfur and chloride-based ions, that have already shown in table 3. These indicate that MS/MS mode ensures that the reaction process could be monitored and controlled in the cell. And the two mass filters combined with reactive gas could successfully eliminate the matrix-based interference before Q2.
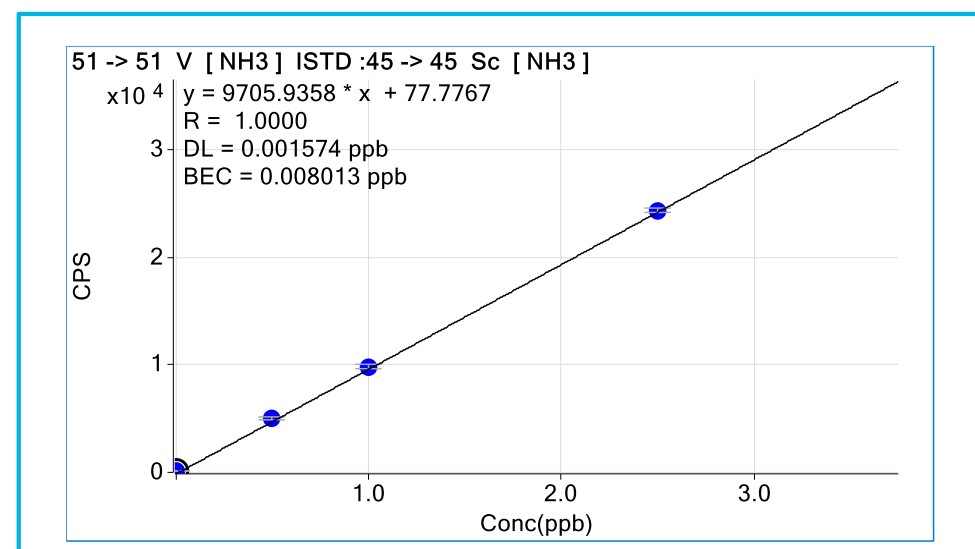

51 -> 51 V [NH3] ISTD :45 -> 45 Sc [NH3]
x10 4   y = 9705.9358 * x + 77.7767
        R = 1.0000
        DL = 0.001574 ppb
        BEC = 0.008013 ppb

Figure 3. Calibration of V with MS/MS mode

Conclusions

Couple of mass filters could easily control the reaction process and overcome the interference.

- ICP-MS/MS operated at tandem MS mode with NH3 as reaction gas, could prevent any unwanted ions from entering the cell and control the reaction process.

- One order of magnitude could be improved by ICP-MS/SM. More important, the results of vanadium would not suffer from the matrix from Cl and S, even though the accumulated matrix.

- The precursor ion scan approach makes the interference ions be easily evaluated.

References

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