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Determination of halogens in organic compounds by high resolution inductively coupled plasma mass spectrometry (HR-ICP-MS)

Xiaodong Bu,*[a] Tiebang Wang*[a] and Gene Hall[b]

[a]*Analytical Research Department, Merck Research Laboratories, P.O. Box 2000, RY80L-115, Rahway, NJ 07065-0900, USA. E-mail: Xiaodong_Bu@merck.com; E-mail: Tiebang_Wang@merck.com*
[b]*Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08855-8087, USA*

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The feasibility of the determination of sub ppm to percentage levels of halogen elements (fluorine, chlorine, bromine, and iodine) in solid organic compounds and drug substances by double focusing sector field high-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) was investigated. Samples were dissolved in appropriate solvents and then diluted in either deionized water or 5% (v/v) ammonium hydroxide. By applying medium or high resolution, the background counts can be lowered by up to five orders of magnitude compared to conventional quadrupole ICP-MS systems. The signal sensitivities and memory effects of all four elements in different solvents were compared and assessed. The methods were applied to the determination of sub ppm to percentage levels of F, Cl, Br and I in a series of organic compounds and Merck drug substances. The results were found to be in excellent-to-reasonable agreement with the known or theoretical values of these compounds or drug substances. The limit of detection in solution for F was estimated to be 5 μg ml^{-1} (medium resolution), and for Cl, Br and I was 3 (high resolution), 0.08 (high resolution) and 0.03 (high resolution) ng ml^{-1}, respectively.

Introduction

Traditionally, the halogen elements (F, Cl, Br, and I) are analyzed by ion chromatography (IC);[1] it is not only very time-consuming but also offers no isotopic information.

It is well known that ICP-MS offers the analyst an almost unrivaled technique for the determination of metallic elements in a variety of complex matrices, but little attention has been paid to the determination of non-metals, such as halogen elements. Since only unit mass resolution is achievable for most commercial ICP-MS instruments equipped with a quadrupole mass analyzer, severe spectral interferences alone made their analysis extremely difficult or impossible. The majority of such interferences are caused by the presence of the plasma gas, water, acids used, and concomitant elements, from which a variety of molecules with overlapping nominal mass to charge ratios (m/z) are formed. The nominal mass to charge ratios (m/z) of these interfering polyatomic ions are mostly less than 80 amu (atomic mass unit), which can be identical to those of halogen elements[2] as well as to those of many other elements of interest.

In order to extend the multi-element capabilities of a quadrupole ICP-MS (ICP-QMS) system, cool plasma techniques have been developed and applied by manufacturers and ICP mass spectroscopists. The idea of cool plasma is to lower the excitation temperature thus leading to reduced formation of molecular species generated from the combination of Ar with O, N and H.[2–5] Although the cool plasma conditions can dramatically reduce the formation of interfering molecular species for these elements, the much lower ionization temperature would also suppress the ionization of the halogen elements which require significantly higher ionization energies to be ionized than those of K or Fe.[6] Overall this would result in unacceptable sensitivities for the halogen elements.

An effective solution to the spectral interference problems in ICP-MS is to use a high resolution instrument equipped with a double focusing mass analyzer consisting of a magnetic and electrostatic sector instead of a quadrupole filter.[2–5] Since the new generation sector-field ICP mass spectrometers can provide a resolution of as high as 14,000 ($m/\Delta m$), it provides the ICP mass spectrometrists new possibilities for interference-free, accurate determination of these elements. Besides high resolving power, another attractive feature of a magnetic sector instrument is its very high sensitivity combined with extremely low background levels. High ion transmission in low resolution mode translates into sensitivity specifications of typically 100–200 million counts per second (mcps) per ppm, while background levels resulting from extremely low dark current noise are typically 0.1–0.2 counts per second (cps). This compares with a typical sensitivity specification of 10–50 mcps per ppm and a typical background level of ~10 cps for a quadrupole instrument.[5] High ion transmission combined with extremely low background levels results in superior detection limits, typically orders of magnitude better than those achievable by a quadrupole-based instrument. Halogen elements have much higher ionization potentials than most other elements in the periodic table. This explains their relatively low sensitivities in ICP-MS. The most obvious example is fluorine (with an ionization potential of 17.42 eV); its estimated ionization efficiency (F^+/F) based on the *Saha equation* is only about 9×10^{-4}% at an ionization temperature of 7500 K, whereas under the same conditions sodium (with an ionization potential of 5.14 eV)[6] is estimated to be 100% ionized. This is the major reason why the sensitivity of fluorine is about 2 million times lower than that of fully ionized sodium.

The inherent nature of high sensitivity together with high resolving power of the sector-field ICP-MS makes accurate determination of these elements possible.

The goal of this study is to develop reliable, robust and accurate methods for the determination of these four halogen elements from sub ppm to major levels in various organic compounds, which include bulk drug substances in development at

Merck. These methods would open the way for rapid determination and confirmation of the stoichiometries of many halogenated organic compounds and drug substances as well as the detection of halogen impurities in them. This would help to ease the ever-increasing demands from organic chemists for efficient support of new drug discovery and development programs.

There have been few reports on the direct determination of these elements by various ICP methods.[7–14] This can be partially attributed to severe spectral interference, the high ionization potentials of these elements, and the memory effects of some of these elements, all of which have seemed too serious to be circumvented. Okamoto[10] reported the determination of fluorine in aqueous samples by electrothermal vaporization inductively coupled plasma mass spectrometry (ETV-ICP-MS). Bayón *et al.*[11] also reported an indirect method, which was based on the formation of an aluminium monofluoride complex and the sequential monitoring of the aluminium ions at mass 27. Several studies of the determination of fluorine and other halogen elements in geological samples have also been reported.[15–19] However, few comprehensive studies of all four halogen elements and their spectral interferences have been found in the literature.

Experimental

All the measurements were carried out with a Finnigan Element 2 (Finnigan, Bremen, Germany) high resolution inductively coupled plasma sector-field mass spectrometer. The instrument was equipped with a double focusing mass analyzer using reversed Nier-Johnson geometry. The system allows three pre-defined nominal mass resolutions ($m/\Delta m$) of 300, 4000, and 10,000 by means of selectable slits. The actual mass resolutions vary between 300–500 for low, 3500–4500 for medium, and 8000–14,000 for high-mass resolution mode depending on the optimization of the parameter settings.

Samples were introduced into the plasma through a PFA microconcentric nebulizer and a PFA spray chamber (Elemental Scientific, Omaha, NE). Passive aspiration was used to improve the stability of the ion beam and eliminate possible memory effects from the PVC tubing of the peristaltic pump.

The typical instrument conditions and measurement parameters used throughout the work are listed in Table 1. These conditions are optimized daily by using a 1.0 ng ml^{-1} multi-element standard tuning solution containing Li, B, Na, Al, Sc, Fe, Co, Ga, Y, In, Rh, Ba, Lu, Tl and U. An accurate mass calibration at the beginning of the measurement session was routinely performed for low resolution (LR), medium resolution (MR), and high resolution (HR) modes using the same tuning solution.

Table 1 HR-ICP-MS operating conditions and measurement parameters

RF Power/W	1150–1450
Sample uptake rate/μl min^{-1}	100–150
Plasma gas flow/l min^{-1}	17.0
Auxiliary gas flow/l min^{-1}	0.87
Nebulizer gas flow/l min^{-1}	0.6–1.2
Additional gas flow/l min^{-1}	0.05–0.15
Nebulizer	PFA microconcentric nebulizer
Spray chamber	PFA spray chamber (room temperature)
Sampler	Platinum 1.1 mm aperture diameter
Skimmer	Platinum 0.8 mm aperture diameter
Torch position	Optimized daily
Guard electrode	Yes
Acquisition mode	E-scan; electric scanning over small mass ranges
Number of scans	10
Number of acquisition points	20
Acquisition window (%)	100
Search window (%)	100
Integration window (%)	60
Dwell time per sample/ms	50

Reagents and standards

Deionized water was prepared by passing distilled water through a Milli-Q water system (Millipore Corporation, Bedford, MA) to a resistivity of 18 MΩ cm^{-1} and was used throughout for rinsing and solution preparations. Ultra-pure grade nitric acid (Optima, Fisher Scientific, Fair Lawn, NJ) was used throughout. A 5% (v/v) ammonium hydroxide solution was prepared by diluting 5 ml of concentrated ammonium hydroxide solution (Fisher Scientific, Fair Lawn, NJ) to 100 ml with deionized water.

A stock standard solution of fluorine (10,000 μg ml^{-1}) was prepared by dissolving an appropriate amount of NH_4F (Sigma-Aldrich, St. Louis, MO, USA) in 100 ml deionized water. Calibration standards of fluorine were prepared by serial dilutions of the 10,000 μg ml^{-1} stock standard in deionized water. The calibration standards of Br, Cl, and I were prepared by serial dilutions of 1000 μg ml^{-1} stock standard solutions purchased from Inorganic Venture (Lakewood, NJ) in 5% (v/v) ammonium hydroxide solution.

All the organic compounds used in this study were purchased from Sigma-Aldrich (St. Louis, MO). The drug substances used in the experiments were from Merck Research Laboratories (Merck and Co. Inc, Rahway, NJ). The structures of the compounds are not relevant to the study and therefore are not revealed.

Sample preparation

Fluorine analysis. Solid samples were prepared by weighing approximately 100 mg of sample into a 10 ml volumetric flask, and bringing to volume with either deionized water, concentrated nitric acid or acetonitrile depending on sample solubility. Further dilutions were always performed with deionized water as needed to bring the sample concentrations within the linear range of the calibration curve.

Chlorine, bromine, and iodine analysis. Solid samples were prepared by weighing approximately 100 mg of sample into a 10 ml volumetric flask, and bringing to volume with deionized water, concentrated nitric acid or acetonitrile depending on sample solubility. Further dilutions were always performed with 5% (v/v) ammonium hydroxide solution to bring the sample concentrations within the linear ranges of the calibration curves.

Results and discussion

Fluorine detection

Fluorine cannot be directly determined by conventional quadrupole ICP-MS because of intense water-derived spectral interference and extremely low sensitivity. High resolving power combined with high sensitivity of the sector-field ICP-MS affords us another chance to reliably and accurately determine the fluorine content in organic compounds and drug substances from sub-ppm to percentage levels.

In the experiments, the instrument was operated under hot plasma conditions as shown in Table 1 using the CD-1 guard electrode option. A low-flow (~100 μl min^{-1}) self-aspirating PFA capillary nebulizer and a PFA spray chamber were used to introduce the sample into the plasma. Fluorine is measured as the F^+ (m/z 18.998) ion. Medium resolution is required to resolve $^{19}F^+$ from interference species such as $^1H_3{}^{16}O^+$, $^1H_2{}^{17}O^+$, $^1H^{18}O^+$, and $^{38}Ar^{2+}$. The medium resolution ($m/\Delta m$ = ~4000) ICP-MS spectrum of the fluorine ion resolved from interferences at m/z 19 are given in Fig. 1. It is clearly shown that at a resolution

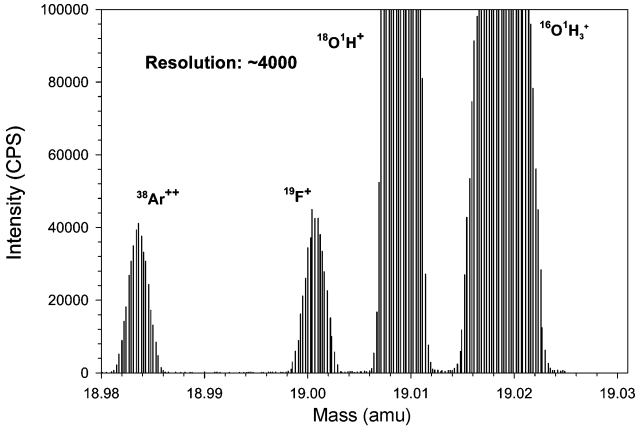

Fig. 1 HR-ICP-MS spectrum of the fluorine ion resolved from interfering species at *m*/*z* 19.

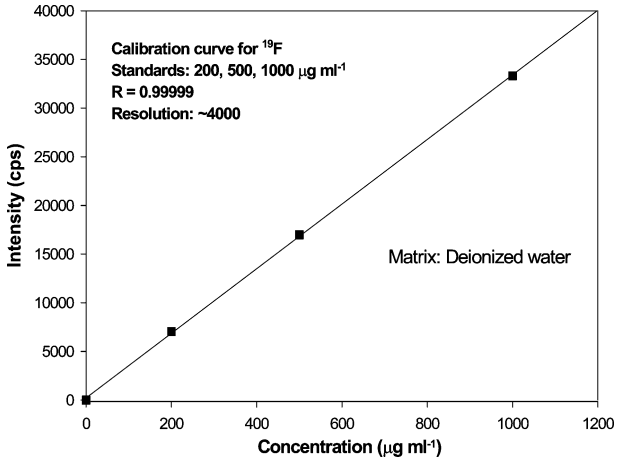

Fig. 2 Calibration curve of the fluorine ion in deionized water.

of about 4000, $^{19}F^{+}$ can be confidently baseline-resolved from all its interferences.

An external calibration curve of $^{19}F^{+}$ is shown in Fig. 2. Standards used were 200, 500, and 1000 μg ml^{-1} prepared by serial dilution of a 10,000 μg ml^{-1} stock standard solution. The measured signal intensity of $^{19}F^{+}$ under the current experiment conditions is approximately 30 cps ppm^{-1} (or 30 cps per μg ml^{-1}), whereas the signal intensity of $^{23}Na^{+}$ under similar conditions (m/z = 23, $m/\Delta m$ = ~4000, hot plasma conditions) is roughly 6 × 10^{7} cps ppm^{-1}, approximately 2 million times higher than that of $^{19}F^{+}$.

Chlorine, bromine and iodine detection

Compared to fluorine, sensitivities are less of an issue than spectral interferences for these three elements. Table 2 lists all of the major spectral interferences and the resolution required to resolve them for all the isotopes of fluorine, chlorine, and bromine. Iodine is not listed since it does not suffer major

Table 2 Resolution required to separate analyte ions from interfering ions

Isotope	Mass (amu)	Main Interference	Mass (amu)	Resolution required
^{19}F	18.9984	$^{38}Ar^{2+}$	18.98137	1116
^{19}F	18.9984	$^{1}H^{18}O$	19.00699	2212
^{19}F	18.9984	$^{1}H_{2}{}^{16}O^{1}H$	19.0184	950
^{35}Cl	34.96885	$^{18}O^{16}O^{1}H$	35.0019	1058
^{37}Cl	36.9659	$^{1}H^{36}Ar$	36.97538	3899
^{79}Br	78.91834	$^{40}Ar^{38}Ar^{1}H$	78.93294	5405
^{81}Br	80.91629	$^{40}Ar^{40}Ar^{1}H$	80.93259	4964

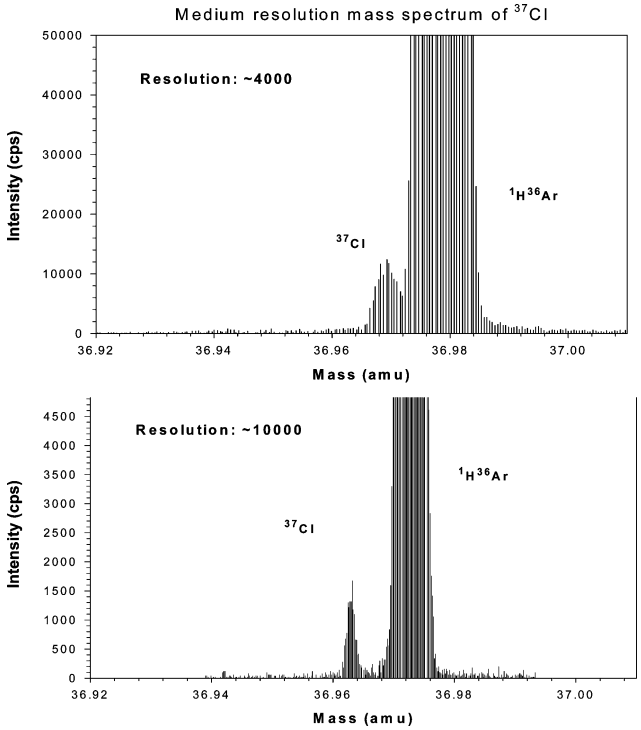

Fig. 3 HR-ICP-MS spectral comparison of ^{37}Cl at medium and high resolutions.

interferences from plasma-derived species like the other halogen elements. $^{37}Cl^{+}$ determination is very important to the isotope ratio measurement. However, the accurate ICP-MS determination of $^{37}Cl^{+}$ is difficult with quadrupole ICP-MS because of the interference from $^{36}Ar^{1}H^{+}$. Fig. 3 allows the comparison of the $^{37}Cl^{+}$ spectra at medium resolution and at high resolution. Clearly, at medium resolution the $^{37}Cl^{+}$ analyte and $^{36}Ar^{1}H^{+}$ interference cannot be totally baseline separated, while high resolution is adequate to avoid the overlap. However, unless zinc ($^{70}Zn^{2+}$) and germanium ($^{70}Ge^{2+}$) are present at significant levels, medium resolution is more than adequate to ensure an interference-free determination of $^{35}Cl^{+}$ as shown in Fig. 4. For comparison, the high resolution spectrum of $^{35}Cl^{+}$ is also given in Fig. 4. Similarly, high resolution is required to fully resolve $^{81}Br^{+}$ from the interference of $^{40}Ar^{40}Ar^{1}H^{+}$ as shown in Fig. 5. Theoretically speaking, ^{79}Br suffers interference from $^{40}Ar^{38}Ar^{1}H^{+}$. Upon close examination of the medium and high resolution spectra of ^{79}Br in Fig. 6 and Fig. 7, it is clear that the formation of $^{40}Ar^{38}Ar^{1}H^{+}$ under the current experimental conditions is extremely minimal. From the close-ups of the $^{79}Br^{+}$ spectra at both medium and high resolutions, the intensities of $^{40}Ar^{38}Ar^{1}H^{+}$ are only about less than 0.3% of that of $^{79}Br^{+}$. Since the spectra in Fig. 6 and Fig. 7 were obtained from 100 ng ml^{-1} bromine solution, the contribution of $^{40}Ar^{38}Ar^{1}H^{+}$ to $^{79}Br^{+}$ is only about less than 0.3 ng ml^{-1}, which is the detection limit of $^{79}Br^{+}$ at medium resolution, as will be shown later in this paper. Therefore, it is safe to say that the use of medium resolution for the determination of $^{79}Br^{+}$ is acceptable under the current operating conditions. As for $^{127}I^{+}$, it is monoisotopic and the spectral interferences are not a big concern unless $^{89}Y^{+}$ ($^{89}Y^{38}Ar$), $^{87}Sr^{+}$ ($^{87}Sr^{40}Ar$), $^{87}Rb^{+}$ ($^{87}Rb^{40}Ar$), $^{91}Zr^{+}$ ($^{91}Zr^{36}Ar$), $^{111}Cd^{+}$ ($^{111}Cd^{16}O$), and $^{109}Ag^{+}$ ($^{109}Ag^{18}O$) are present at significant levels in the samples.

The calibration curves for chlorine, bromine, and iodine are given in Figs. 8, 9 and 10, respectively.

Solvent selection

Since halogen elements are known for their severe memory effects if nebulizer-based sample introduction systems are

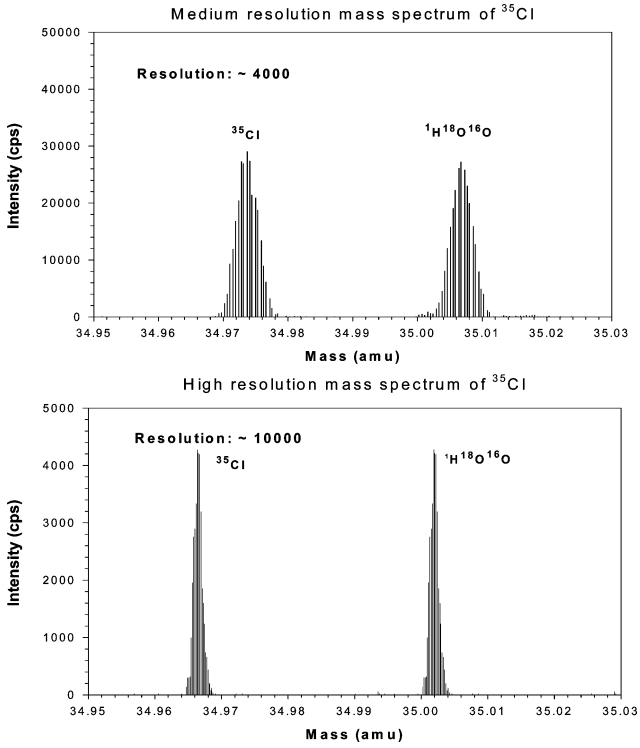

Fig. 4 HR-ICP-MS spectral comparison of ^{35}Cl at medium and high resolutions.

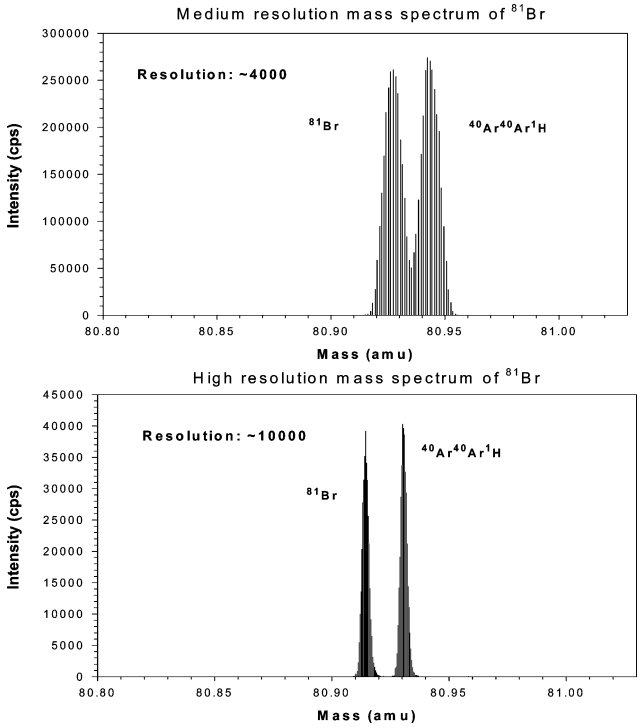

Fig. 5 HR-ICP-MS spectral comparison of ^{81}Br at medium and high resolutions.

used,[20,21] more attention should be paid to this aspect in the selection of solvents. The memory effects of these four elements in 20% and 5% nitric acid solutions, deionized water, and in 5% ammonium hydroxide solution were evaluated by studying their wash-out behaviors. The wash-out experiments were carried out by continuously measuring and monitoring the signal intensity variations with time for these four halogen ions while aspirating appropriate blank solutions immediately after various halogen element standard solutions were aspirated.

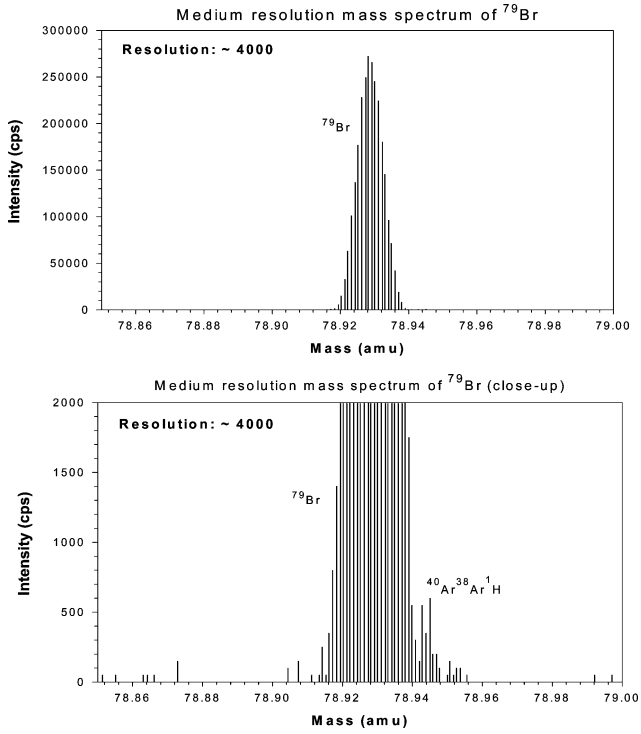

Fig. 6 HR-ICP-MS spectrum of ^{79}Br at medium resolution.

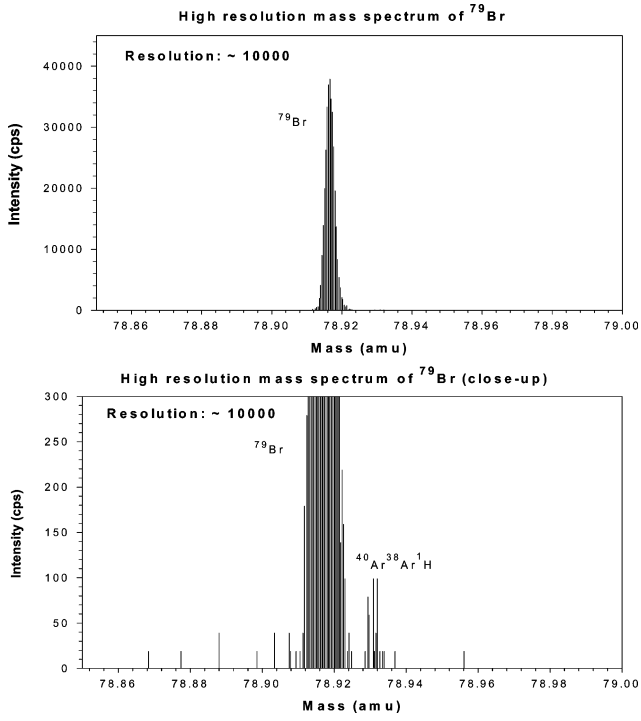

Fig. 7 HR-ICP-MS spectrum of ^{79}Br at high resolution.

The wash-out curves of ^{19}F (200 μg ml^{-1}), ^{35}Cl (200 ng ml^{-1}), ^{79}Br (50 ng ml^{-1}), and ^{127}I (50 ng ml^{-1}) are given in Figs. 11, 12, 13, and 14, respectively. It is demonstrated clearly in the four figures that the memory effects of all four elements can be eliminated effectively by rinsing the system with 5% ammonium hydroxide solution. It only takes about 120 seconds wash time to bring the intensities of the four elements down to as low as 0.1% of their original levels. It is also conclusive that the less acidic the solution is, the more effective the wash-out of the four elements will be. Unlike the other three elements, deionized water is almost as effective as 5% ammonium hydroxide for ^{19}F. This is the reason why if only fluorine was to

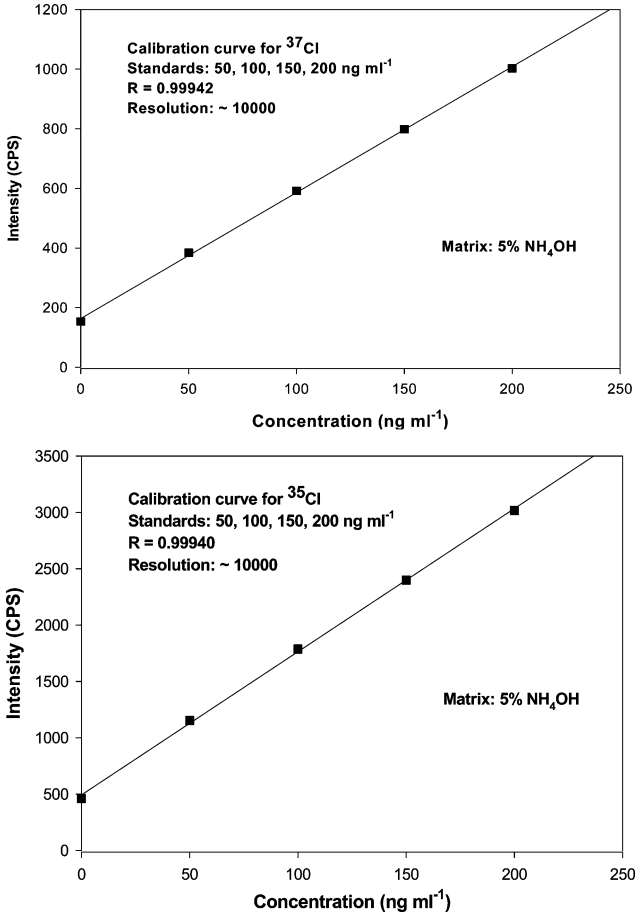

Fig. 8 Calibration curve of Cl in 5% NH_4OH.

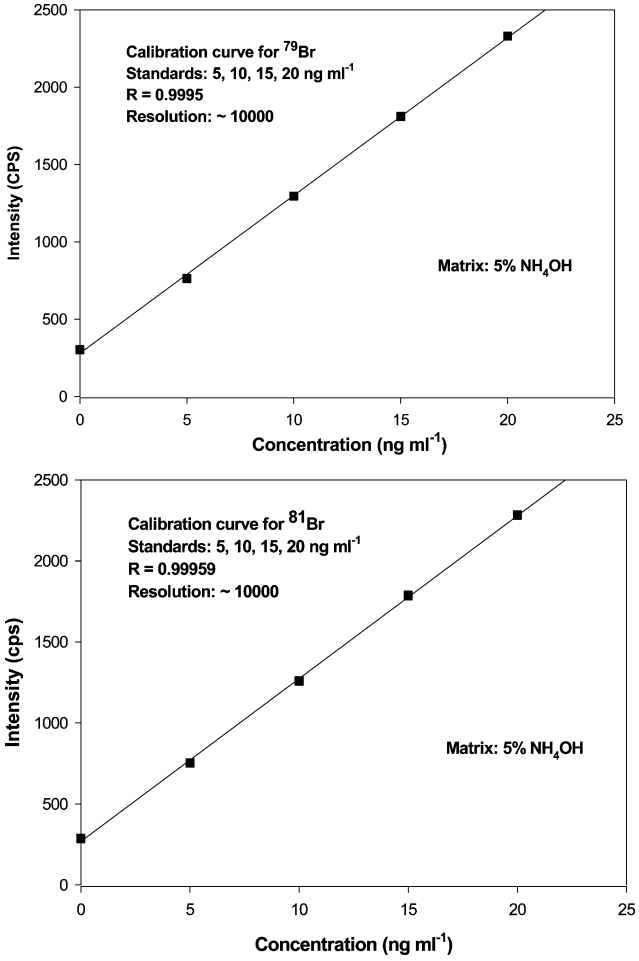

Fig. 9 Calibration curve of Br in 5% NH_4OH.

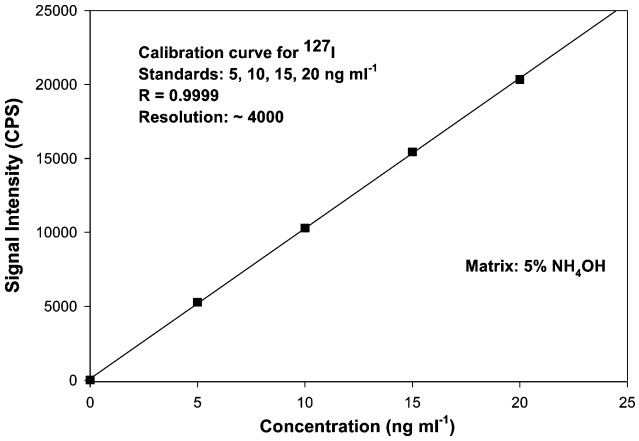

Fig. 10 Calibration curve of I in 5% NH_4OH.

be determined, deionized water was used in both sample and standard preparations for convenience and simplicity. If one or more of the other three elements are to be determined together with fluorine, the use of 5% ammonium hydroxide makes more sense. From Fig. 12, it is shown that chlorine has the most severe memory effect in 20% nitric acid. Even after a 10 minute wash, as much as 30% of the counts of the original 200 ng ml^{-1} ^{35}Cl remains, whereas only about 0.1% of the counts of the original standard solution remains after only about 2 minutes if 5% ammonium hydroxide solution is used as the wash solution. Although not as effective as for ^{19}F, it takes less than 3 minutes to wash down to about 1% of their original signal intensities of the other 3 elements with deionized water as shown in Figs. 12–14.

The effects of the same four solvents on the relative sensitivities of these four ions are shown in Fig. 15. All the signal intensities in the various solvents were obtained under optimized operating conditions, *i.e.* after each solvent-switching the system was always re-optimized before the next measurement was taken. Since the signal intensities were normalized, the inclusion of ^{37}Cl and ^{81}Br is redundant. It is also obvious that in deionized water all four elements exhibit their highest intensities under optimized operating conditions.

Taking into account both the sensitivity and memory effects, it is obvious that deionized water is the most appropriate solvent for the determination of F if the solubilities of the compounds permit. However, for the determinations of Cl, Br, and I, 5% ammonium hydroxide solution is a better choice than deionized water due to the superior wash-out behaviors of 5% ammonium hydroxide solution for these three elements, although all three elements have slightly better sensitivities in deionized water. For simplicity and matrix matching, in addition to sample preparations, 5% ammonium hydroxide solution was also used to prepare calibration blanks, working calibration standards, and it also served as the rinsing solution whenever the determination of any or all of these three elements was required.

The effects of nebulizer gas flow rate and ICP RF power

Nebulizer gas flow rate is one of the key plasma operating parameters affecting analyte ion signal intensities in ICP-MS. In the present work, the effect of nebulizer gas flow rate on the signal intensities of these elements was evaluated. The results are given in Fig. 16. For easy viewing and comparison, all ion intensities are normalized in the figure. Nebulizer gas flow rate was varied in steps of 0.025 l min^{-1}, and a 30 second delay was included in the running sequence after each flow rate change in order for the plasma to stabilize. As shown in the

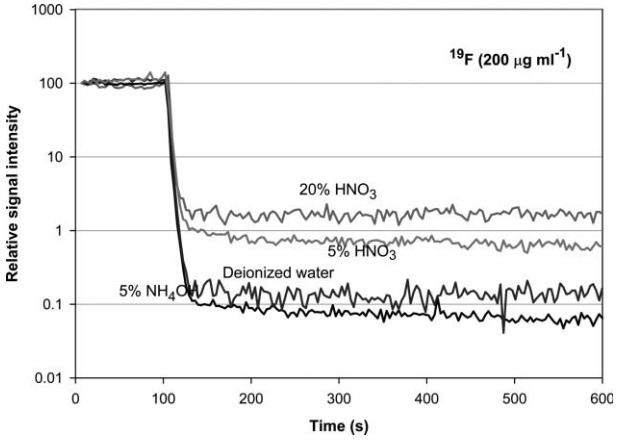

Fig. 11 Wash-out curve for ^{19}F in various matrices (200 μg ml^{-1}).

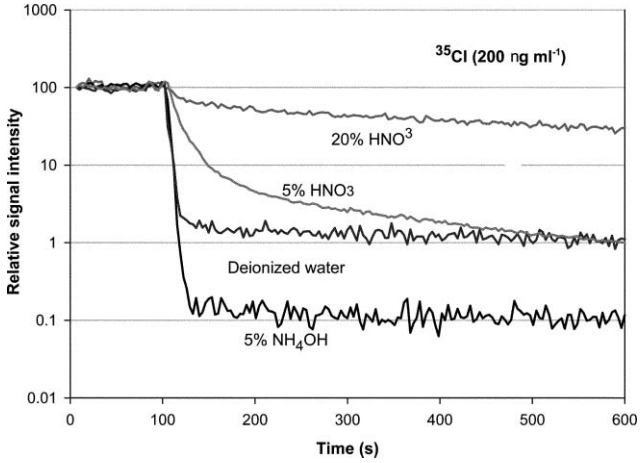

Fig. 12 Wash-out curve for ^{35}Cl in various matrices (200 ng ml^{-1}).

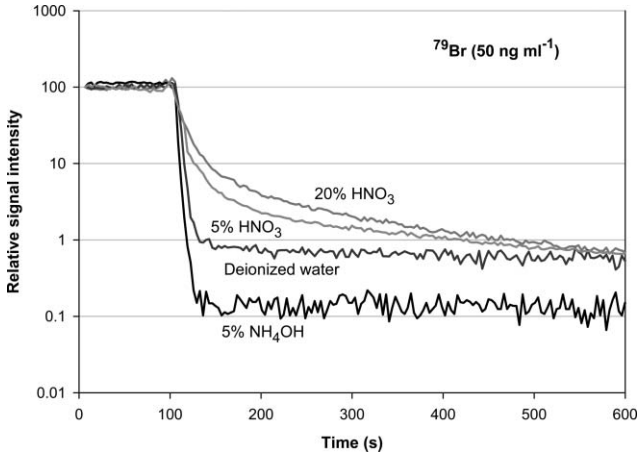

Fig. 13 Wash-out curve for ^{79}Br in various matrices (50 ng ml^{-1}).

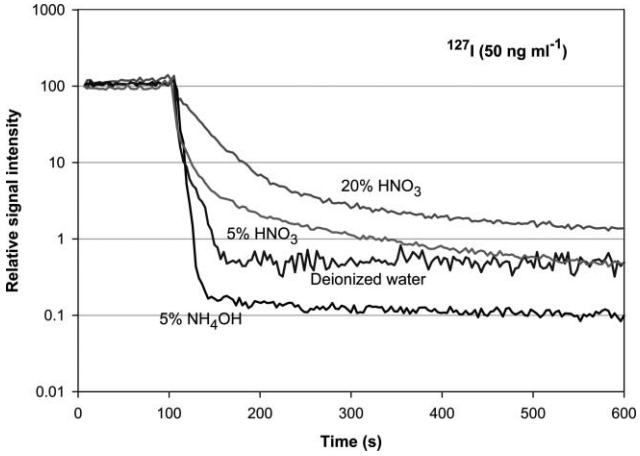

Fig. 14 Wash-out curve for ^{127}I in various matrices (50 ng ml^{-1}).

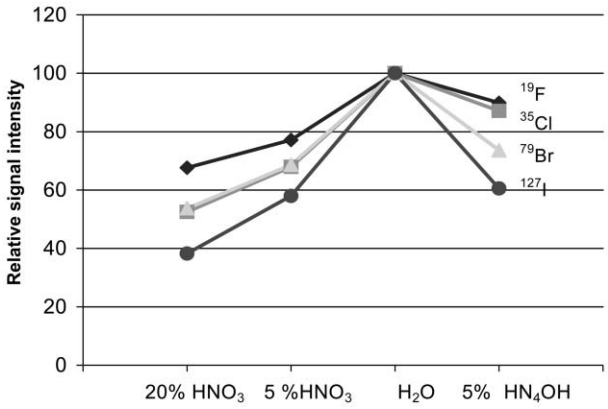

Fig. 15 The effects of solvents on the sensitivities of the halogen elements (F, Cl, Br, and I).

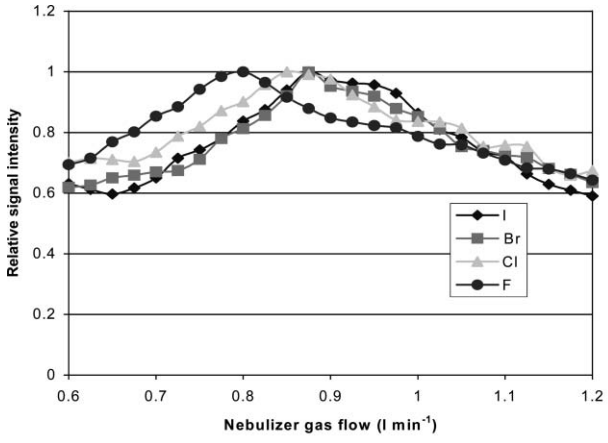

Fig. 16 Effect of nebulizer gas flow rate on the intensities of different halogen elements.

figure, at a fixed RF power of 1250 watts, the optimum nebulizer gas flow rates for F and Cl, were achieved at 0.8 and 0.85 l min^{-1}, respectively, and for Br and I at 0.875 l min^{-1}. This correlates well with the ionization potentials of these elements since higher nebulizer gas flow rate leads to "cooler" plasma, and fluorine possesses the highest ionization potentials of these elements thus needing the "hottest" plasma at relatively low nebulizer gas flow rate.

The effects of RF power on the signal intensities of these elements are shown in Fig. 17. The power was varied in steps of 25 watts at a fixed nebulizer gas flow rate of 0.85 l min^{-1}. The highest signal intensities for F and Cl were achieved at about 1300 and 1225 watts, respectively, while for Br and I the highest signal intensities were obtained at around 1100 to 1125 watts. This is also consistent with the findings of the nebulizer gas flow rate experiments described above. Similar to a lower nebulizer gas flow rate at fixed RF power, higher RF power at a fixed nebulizer flow rate also leads to "hotter" plasma, thus favoring elements in the decreasing order of F (17.14 eV), Cl (13.01 eV), I (10.45 eV), and Br (11.84 eV), which is almost the exact order of decreasing ionization potentials for these elements.

The same solutions used for solvent selection/wash-out studies were used here for all four elements.

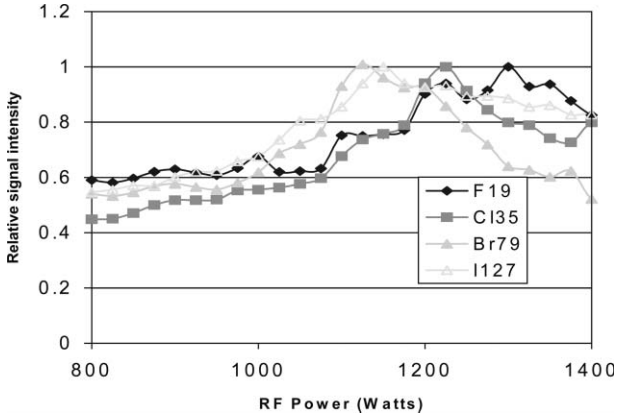

Fig. 17 Effect of RF generator power on the intensities of different halogen elements.

Instrumental limit of detection (LOD) and sensitivities

The instrumental limits of detection (LOD's) and sensitivities (counts per ng ml^{-1}) as well as background equivalent concentrations (BEC's) of all four halogen elements in medium (MR) and high (HR) resolution modes by HR-ICP-MS were evaluated and are listed in Table 3. The instrumental limits of detection (LOD's) for the four elements were estimated by analyzing ten replicate blank solutions as ten samples. The instrumental limit of detection (LOD) is defined as three times the standard deviation of the ten measurements. Sensitivities for the four elements were derived by analyzing a 100 μg ml^{-1} F standard solution, a 0.10 μg ml^{-1} Cl standard solution, and 0.01 μg ml^{-1} Br and I standard solutions. As shown in Table 3, the best limits of detection (LOD) for F, Cl, Br and I are 5067, 3, 0.08 and 0.03 ng ml^{-1}, respectively. These are parts per trillion (ppt) LOD's for Br, and I.

In Table 3, it is also interesting to note that although an increase in the mass resolution did lead to lower intensities for all four elements, this did not necessarily translate into higher limits of detection. This is because higher resolution not only reduced the ion transmission but also the background transmission as well. For ^{19}F and ^{127}I, higher resolution resulted in slightly deteriorated limits of detection and BEC's, whereas for ^{35}Cl and ^{79}Br, higher resolution yielded modestly improved limits of detection and BEC's.

Table 5 Spike recovery studies with actual Merck drug substances at both medium and high resolutions

Isotope	[Original sample]/ ng ml^{-1}	[Spiked sample]/ ng ml^{-1}	Recovery (%)
^{19}F (MR)	138 μg ml^{-1}	348 μg ml^{-1}	105
^{19}F (HR)	141 μg ml^{-1}	355 μg ml^{-1}	107
^{35}Cl (MR)	94	203	109
^{79}Br (MR)	120	219	99
^{127}I (MR)	119	216	97
^{35}Cl (HR)	92	203	111
^{37}Cl (HR)	91	200	109
^{79}Br (HR)	102	199	97
^{81}Br (HR)	101	203	102
^{127}I (HR)	115	216	101

Precision and accuracy

The precision of the methods used for the determination of F, Cl, Br, and I was estimated by analyzing a 100 μg ml^{-1} F solution at medium resolution, and 100 ng ml^{-1} Cl, Br, and I solutions at high resolution ten times as ten samples with rinsing in between. As described in the Experimental section,

Table 3 Detection limits and sensitivities in medium resolution (MR) and high resolution (HR) modes

	MR			HR		
Element	Detection limits/ng ml^{-1}	Sensitivity (counts per ng ml^{-1})	BEC/ng ml^{-1}	Detection limits/ ng ml^{-1}	Sensitivity (counts per ng ml^{-1})	BEC/ng ml^{-1}
^{19}F	5070	0.026	2050	8530	0.003	7270
^{35}Cl	7.01	222	0.17	3.25	34	0.08
^{37}Cl	N/A	N/A	N/A	4.18	13	0.08
^{79}Br	0.23	1390	0.08	0.08	193	0.05
^{81}Br	N/A	N/A	N/A	0.10	191	0.05
^{127}I	0.03	6970	0.02	0.05	1060	0.03

Table 4 Precision of the methods of determination of F, Cl, Br and I

Replicate number	Measured result					
	^{19}F (MR)/μg ml^{-1}	^{35}Cl (HR)/ng ml^{-1}	^{37}Cl (HR)/ng ml^{-1}	^{79}Br (HR)/ng ml^{-1}	^{81}Br (HR)/ng ml^{-1}	^{127}I (HR)/ng ml^{-1}
1	99.6	101.1	98.3	108.3	99.3	103.1
2	97.6	100.4	95.8	100.2	95.9	101.5
3	98.2	98.5	96.6	98.7	95.6	99.3
4	99.2	97.9	94.7	97.3	98.5	102.2
5	102.5	93.3	92.0	97.5	98.8	99.2
6	101.2	102.6	101.9	105.4	101.8	102.2
7	98.9	98.8	100.2	101.1	97.5	103.3
8	99.1	98.0	99.3	99.7	99.5	103.8
9	100.8	101.6	102.3	104.3	98.3	99.9
10	98.2	97.6	102.2	102.0	98.6	94.5
Mean	99.5	99.0	98.3	101.5	98.4	100.9
SD	1.53	2.7	3.5	3.6	1.8	2.8
RSD (%)	1.54	2.73	3.56	3.55	1.83	2.78

Table 6 Accuracy and precision of the determination of F, Cl, Br and I in organic compounds

	F (%)		Cl (%)		Br (%)		I (%)	
Compound name	Theoretical or known	Measured	Theoretical or known	Measured	Theoretical or known	Measured	Theoretical or known	Measured
Pentafluorobenzoic acid ($C_6F_5CO_2H$)	44.3	41.2 ± 0.52						
Tetrafluorohydroquinone (C_6F_4-1,4-$(OH)_2$)	40.9	40.9 ± 0.22						
2-Fluorocinnamic acid ($FC_6H_4CH{=}CHCCCO_2H$)	11.2	10.98 ± 0.27						
2-Fluoro-6-iodobenzoic acid ($FC_6H_3(I)CO_2H$)	6.92	6.61 ± 0.14					46.3	44.2 ± 0.52
3′,4′-Dichloroacetophenone ($Cl_2C_6H_3COCH_3$)			37.1	38.2 ± 0.45				
5-Bromo-2-chlorobenzoic acid ($BrC_6H_3(Cl)CO_2H$)			14.8	14.2 ± 0.11	33.2	32.5 ± 0.62		
1,4-Dibromobenzene ($C_6H_4Br_2$)					66.4	64.2 ± 1.30		
3-Bromo-5-iodobenzoic acid ($BrC_6H_3(I)CO_2H$)					24.0	24.6 ± 0.52	38.4	36.8 ± 0.75

Table 7 Accuracy and precision of the determination of F, Cl, Br and I in Merck drug compounds

	F (%)		Cl (%)		Br (%)		I (%)	
Compound Name	Theoretical or known	Measured	Theoretical or known	Measured	Theoretical or known	Measured	Theoretical or known	Measured
Merck compound #1	10.0	9.5 ± 0.12						
Merck compound #2	23.2	22.1 ± 0.19						
Merck compound #3	4.36	4.14 ± 0.08	8.13	7.85 ± 0.12				
Merck compound #4	4.13	3.67 ± 0.09	7.71	7.22 ± 0.21				
Merck compound #5			5.81	5.79 ± 0.09				
Merck compound #6	12.9	11.2 ± 0.017			27.2	26.2 ± 0.69		
Merck compound #7	17.7	15.4 ± 0.19						
Merck compound #8					35.7	33.9 ± 0.58		
Merck compound #9							31.2	33.2 ± 0.38

the fluorine solution was prepared in deionized water, whereas the Cl, Br, and I solutions were prepared in 5% ammonium hydroxide solution. The results are listed in Table 4. The relative standard deviations (RSD's) of the ten measurements varied from 1.5% to 3.6% for the four halogens.

In order to evaluate the accuracy and the extent of the matrix effect caused by an actual drug substance using these methods, three Merck compounds were chosen for this study. One of these compounds contained a percentage level of F, the second one percentage levels of Cl and Br, and the third one contained iodine also at a percentage level. These compounds were dissolved and diluted such that the concentration of each of the four elements was approximately 100 to 200 ng ml^{-1} (F, μg ml^{-1}). These solutions were then spiked with 200 μg ml^{-1} F, 100 ng ml^{-1} Cl, Br, and I, and both spiked and unspiked samples were analyzed at appropriate mass resolutions. The results are given in Table 5. The spike recoveries ranged from 97% to 111%.

To further validate the methods, eight commercially available organic compounds and nine Merck drug intermediates or active pharmaceutical ingredients containing one or more of the four elements were tested to determine the accuracy of the procedures. The results are given in Tables 6 and 7. As can be seen from these Tables, most of the results are in excellent to reasonable agreement with the theoretical or known values. It is obvious that most results that are not in perfect agreement with theoretical or known values have lower than 100% recoveries. This can be easily explained by the presence of other impurities in the compounds.

Conclusion

HR-ICP-MS proves to be a powerful and rapid tool for the determinations of sub ppm to percent levels of all four halogen elements in organic compounds and drug substances. The samples can be easily prepared by dissolving them in appropriate solvents and then diluting them in either deionized water or 5% ammonium hydroxide solution. By applying medium to high resolution, major spectral interferences can be easily isolated from the isotope of interest. In solution, the limits of detection were estimated to be 5 μg ml^{-1} for F, and 3.0, 0.08, and 0.03 ng ml^{-1} for Cl, Br, and I, respectively. Precise and accurate results have been obtained for eight commercially available compounds and nine Merck drug substances containing one or more of these four halogen elements. Undoubtedly, HR-ICP-MS has added one more arsenal to the development and discovery of new pharmaceutical products.

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References

1 L. E. Vanatta and D. E. Coleman, *J. Chromatogr. A*, 1997, **770**, 105–114.
2 N. Jakubowski, L. Moens and F. Vanhaecke, *Spectrochim. Acta, Part B*, 1998, **53**, 739–763.
3 D. Stuewer and N. Jakubowski, *J. Mass Spectrom.*, 1998, **33**, 579–590.
4 F. Vanhaecke, *Anal. Bioanal. Chem.*, 2002, **372**, 20–21.
5 F. Vanhaecke, *Spectrochim. Acta, Part B*, 1998, **53**, 1739–1763.
6 K. E. Jarvis, A. L. Gary and R. S. Houk, *Handbook of ICP-MS*, Blackie, Glasgow, 1999.

7 P. Evans, C. Wolff-Briche and B. Fairman, *J. Anal. At. Spectrom.*, 2001, **16**, 964–969.
8 T. Prohaska, C. Latkoczy and G. Stigeder, *J. Anal. At. Spectrom.*, 1999, **14**, 1501–1504.
9 M. Tran, Q. Sun, B. W. Smith and J. D. Winefordner, *Appl. Spectrosc.*, 2001, **55**, 739–744.
10 Y. Okamoto, *J. Anal. At. Spectrom.*, 2001, **16**, 539–541.
11 M. M. Bayón, A. R. Garcia, J. I. G. Alonso and A. Sanz-Medel, *Analyst*, 1998, **124**, 27–32.
12 B. Schnetger, Y. Muramatsu and S. Yoshida, *Geostand. Newsl.*, 1998, **22**, 181–187.
13 N. Lihareva, P. Kosturkova and Ts. Vakarelska, *Fresenius' J. Anal. Chem*, 2000, **367**, 84–92.
14 H. Wildner, *J. Anal. At. Spectrom.*, 1998, **13**, 573–578.
15 E. H. Larsen and M. B. Ludwigsen, *J. Anal. At. Spectrom.*, 1997, **12**, 435–442.
16 R. J. Cox and C. J. Pichford, *J. Anal. At. Spectrom.*, 1992, **7**, 635–641.
17 S. S. A. Buchert, *Fresenius' J. Anal. Chem.*, 1996, **354**, 323–330.
18 H. Baumann, *Fresenius' J. Anal. Chem.*, 1990, **338**, 809–817.
19 A. R. Date and M. E. Stuart, *J. Anal. At. Spectrom.*, 1988, **3**, 659–667.
20 W. Kerl, J. S. Becker and H. Dietze, *J. Anal. At. Spectrom*, 1996, **11**, 723–726.
21 Y. K. Xiao, R. D. Vocke, Jr., G. H. Swihart and Y. Xiao, *Anal. Chem.*, 1997, **69**, 5203–5207.