Determination of Active Pharmaceutical Ingredients by Heteroatom Selective Detection Using Inductively Coupled Plasma Mass Spectrometry with Ultrasonic Nebuilization and Membrane Desolvation Sample Introduction

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The combination of ultrasonic nebulization with membrane desolvation (USN-MD) is utilized to determine active pharmaceutical ingredients (API) by heteroatom inductively coupled mass spectroscopy (ICP-MS) detection. Ultrasonic nebulization provides efficient sampling while use of the membrane desolvator acts to reduce solvent-based interferences. This approach reduces interferences sufficiently so that a standard argon ICP-quadrupole MS can be utilized. Examined APIs and associated heteroatoms included: phosphomycin (P), amoxicillin (S), chlorpropamide (Cl), and ofloxacin (F). The optimum plasma r.f. powers for P, S, and Cl were in the 1000 to 1200 watts range. The high ionization energy of F required that the plasma be operated at 1500 W. The $^{16}O_2^+$ interference at mass 32 precluded determinations using the sulfur-32. The sulfur-34 (4.2% natural isotopic abundance), however, was relatively free of isobaric interferences. Interferences were relatively small at the mass 35 isotope of Cl, but increased with higher ICP r.f. powers. Overlaps were significant at the masses of monoisotopic species, fluorine-19 and phosphorus-31. Detection limits for P, S, Cl, and F of 2, 3, 90, and 3000 ng/mL, respectively, were generally lower than those produced with other quadrupole systems and comparable to or better than values published utilizing high-resolution instruments.

Index Headings: **Ultrasonic nebulization; Membrane desolvation; USN-MD; Inductively coupled plasma mass spectrometry; ICP-MS; Elemental analysis; Heteroatom determination; Pharmaceutical; Direct solution introduction.**

INTRODUCTION

In many applications where trace determinations of metals and metalloids are required, inductively coupled plasma mass spectrometry (ICP-MS) has become the instrument of choice. Calculations based upon the assumption that the plasma has a temperature of 7500 K and an electron density of $10^{15}/cm^3$ show that the argon ICP efficiently ionizes most metals to values exceeding 90% to provide a large pool of ions that can be analyzed by mass spectrometry.[1]

The sensitivity of ICP-MS decreases markedly when non-metals are determined. A dominant reason for this loss of sensitivity can be attributed to the higher ionization potentials of these elements. For example, with the specified ICP conditions, it can be calculated that 9×10^{-4}% of fluorine should be ionized; chlorine ionization is only 0.9%.[1] Additionally, water, nitrogen, and organic solvent decomposition products yield low molecular weight polyatomic ions. These ions produce mass spectral overlaps with lower resolution quadrupole mass analyzers typically utilized in ICP-MS. For example, O_2^+ directly overlaps the major isotope of sulfur, ^{32}S (95.0% isotopic abundance). A number of these interferences for F, P, S, and Cl are listed in Table I, along with the isotopic abundances of those species.

In spite of these issues, successes have been seen. Using ultrasonic nebulization and quadrupole MS, Jiang and Houk[2] obtained detection limits in the range of 150 ppb monitoring $^{34}S^+$ (4.22% isotopic abundance). In the same paper, a phosphorus detection limit of 8 ppb was obtained. While these numbers do not fall into the ppt range of a number of metals, these detection limits are certainly respectable.

A number of strategies have been employed to overcome the limitations of direct solution nebulization with commercially available instruments. The general focus has been to reduce or avoid the spectral interferences and enhance analyte transport to the discharge. These approaches include employing higher resolution mass spectrometers,[3–6] utilizing pre-quadrupole MS collision cells,[7] using mixed gas[8] and low pressure helium plasmas,[9,10] and applying various nebulization and analyte stream desolvation approaches.

The use of the higher resolution provided by sector instruments allows separation of ions of the same nominal mass, based upon mass defects. For instance, Bu, Wang, and Hall[3] illustrate that $^{19}F^+$ (18.9984 amu) can be mass spectrally differentiated from $^1H_3{}^{16}O^+$ (19.00699 amu). This advantage provided improved detection limits for chlorine and fluorine. Other workers have also used sector instruments to determine sulfur[4,5] and phosphorus.[6] Despite the greater mass resolution, these higher resolution instruments possess some disadvantages compared to quadrupole instruments. Sector instruments are generally larger and require lower operational pressures. Maximization of resolution may cause further ion loss that may limit the sensitivity of the instrument.[3]

Collision and reaction cells have been successfully used to reduce spectral interferences commonly found in ICP-MS spectra.[11] These techniques involve the interaction of post-plasma analyte ions with gases in an appropriate multipole reaction cell. These collisions, through judicious choice of reagent gas, can induce ion neutralization, charge transfer, and/or the formation of analyte containing molecular ions. The objective is to reduce the intensity of the interferent peak or separate the analyte ion peak from the interferent by formation of molecular adducts of either the interferent or analyte peak.[11] The detection of sulfur[12,13] and phosphorus[12] as their oxides has been demonstrated using these approaches. These techniques suffer from enhanced complexity and ion loss that may limit sensitivity.

Helium and mixed-gas ICP have been used to overcome polyatomic interferences and enhance ionization for the

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TABLE I. Possible interferents for isotopes of interest.

Element	Isotope	Natural abundance	Interfering species	Isotope fraction of interferent
fluorine	^{19}F	1.00	$^{38}Ar^{2+}$	0.000630
			$^{18}O^{1}H^{+}$	0.00200
			$^{16}O^{1}H_3^{+}$	0.997
phosphorus	^{31}P	1.00	$^{15}N_2{}^{1}H^{+}$	0.0000137
			$^{15}N^{16}O^{+}$	0.00369
			$^{14}N^{16}O^{1}H^{+}$	0.99376
			$^{13}C^{18}O^{+}$	0.0000220
			$^{12}C^{18}O^{1}H^{+}$	0.00198
			$^{12}C^{16}O^{1}H_3^{+}$	0.986
sulfur	^{32}S	0.950	$^{16}O^{16}O^{+}$	0.995
	^{34}S	0.0422	$^{15}N^{16}O^{1}H^{+}$	0.00369
			$^{14}N^{18}O^{+}$	0.00199
			$^{33}S^{1}H^{+}$	0.00750
			$^{15}N^{18}O^{1}H^{+}$	0.00000740
chlorine	^{35}Cl	0.7553	$^{16}O^{18}O^{1}H^{+}$	0.00199
	^{37}Cl	0.2447	$^{34}S^{1}H^{+}$	0.0421
			$^{36}Ar\ ^{1}H^{+}$	0.00340
			$^{36}S^{1}H^{+}$	0.000200

detection of metals and nonmetals.[8–10,14] The use of He as the carrier gas for ICP-MS has advantages such as better detection limits for nonmetals because of the higher energies of He plasma species. Sheppard, Shen, Davidson, and Caruso[8] obtained significant detection limit enhancements for halogens using a 70:30 Ar:He plasma gas. However, there are some drawbacks to using mixed gas and pure He plasma gases. For instance, it is more difficult to form and contain the He plasma, in part because the thermal conductivity of He is higher than that of Ar. Also, the He plasma has a lower gas temperature and electron density compared to Ar-plasma. Secondary discharges in the expansion region, which reduce analyte ion transport efficiency to the detector, are also more pronounced for He than Ar plasmas. That problem is, by far, the limiting factor for the detection of hard-to-ionize nonmetals.[15] Since the major background ions present in a He plasma are the low-mass ions,[14] this problem may be more significant for certain low-mass nonmetals, especially fluorine. If a commercial Ar-ICP-MS is to be used as a He-ICP-MS, significant instrumentation modifications (e.g., impedance matching network, load coil modifications, sample and skimmer cone spacing, etc.) may be necessary to obtain optimum performance.

An alternate route to improving nonmetal ICP-MS detection limits is to enhance analyte transport to the plasma. ICP-MS instruments typically use pneumatic nebulizers for aerosol production. In comparison, ultrasonic nebulizers (USN) are more efficient in that they produce a larger volume of sample mist to increase analyte flux to the plasma. However, enhanced analyte delivery to the plasma is often accompanied by additional solvent liquid volume and vapor. This is true even in cases where the USN flow stream is directed through a heater–condenser combination to reduce solvent flux. Higher ionization energy elements, such as nonmetals, are more susceptible to interferences and ionization quenching caused by solvent effects upon the plasma. This is especially true in the case of organic solvents.

Additional continuous desolvation approaches are in order. An approach that has proven advantageous in atomic spectroscopy is the use of membrane desolvation (MD).[16–18] With this technique, the analyte-containing solvent flow stream is heated to evaporate the solvent and produce analyte-containing particulates. Solvent vapor is removed by osmotic pressure induced diffusion through a microporous membrane, often composed of polytetrafluoroethylene (PTFE), to a region continuously swept by a dry external countercurrent gas stream. Our research group has applied USN-MD to the analysis of chlorine containing organic compounds using LC coupled with microwave induced plasma atomic emission spectrometry.[19–21] MD in combination with USN has been utilized for the liquid chromatographic ICP-MS determination of phospholipids dissolved in organic solvents.[22] Detection limits with the USN-MD system were determined.

The focus of this work is to characterize and compare the analytical performance of USN-MD sample introduction for the determination of sulfur, phosphorus, chlorine, and fluorine containing organic pharmaceutical model compounds using conventional Ar-ICP-MS with a quadrupole mass analyzer. Target analytes are the active pharmaceutical ingredients: phosphomycin (P), amoxicillin (S), chlorpropamide (Cl), and ofloxacin (F).

EXPERIMENTAL

A schematic diagram of the experimental system is shown in Ref. 23. Highlights of the system are detailed below.

Sample Introduction. Flow injection sample volumes of 100 to 300 μL were introduced to a CETAC U5000 USN (CETAC Technologies, Omaha, NE) using a Gilson Minipuls3 peristaltic pump (Gilson, Inc., Middleton, WI). The liquid flow rate was 0.9 mL/min. While maximum steady-state signals were not obtained with this approach, the limited sample volumes avoided analyte residue buildup within the system and allowed multiple parameters to be varied in reasonable time frames. Following the heating–condensation USN apparatus, the nebulized mist was further desolvated utilizing a CETAC MDX-100 PTFE membrane desolvator. Operational parameters are listed in Table II. The desolvated samples were transported to the plasma by the argon gas.

Inductively Coupled Plasma Mass Spectrometry and Data Acquisition. A Fisons (Thermo Electron, Madison, WI) Instruments PlasmaQuad II ICP-MS was used to perform mass analyses. The detector was a Burle Electrooptic, Inc. (Sturbridge, MA) channeltron model number 4870V. Data was acquired utilizing Thermo Electron PlasmaLab software (Version 1.06.007, Ionflight, Boston, MA). Both the single ion monitoring and scanning modes were used. Mass spectra (scanning mode) were obtained to confirm the peak positions for each element. Background and analyte signals were determined using 30 second single ion monitoring observations at a rate of 250 ms/point. Detection limits were calculated as the concentrations giving a signal three times the standard deviation of the background signal. Additional data acquisition parameters are summarized in Table II.

Reagents and Sample Preparation. An 80 ppm phosphorus-containing stock solution was prepared by dissolving an appropriate mass of phosphomycin calcium salt (Sigma-Aldrich, Milwaukee, WI) in deionized water. A 50 ppm sulfur-containing stock solution was prepared by dissolving the appropriate mass of amoxicillin (Sigma-Aldrich, Milwaukee, WI) in aqueous 0.2% HNO_3. A 60 ppm chlorine-containing stock solution was prepared by dissolving chlorpropamide (Sigma-Aldrich, Milwaukee, WI) in aqueous 0.02 M KOH. A 500 ppm fluorine-containing stock solution was prepared by dissolving ofloxacin (Sigma-Aldrich, Milwaukee, WI) in a 4%

TABLE II. ICP-MS and sample introduction operational parameters.

Sample introduction	
Peristaltic pump liquid sample introduction flow rate	0.9 mL/min
Sample volume	100–300 μL
Ultrasonic nebulizer argon flow rate	0.62 L/min
Post ultrasonic nebulizer flow stream heater temperature	140 °C
Post ultrasonic nebulizer flow stream condenser temperature	3 °C
Membrane desolvator countercurrent argon flow rate	1.9 L/min
Membrane desolvator flow stream heater temperature	160 °C
Inductively coupled plasma mass spectrometer	
Argon plasma gas flow rate	0.8 L/min
Argon plasma coolant flow rate	14.0 L/min
Forward power[a]	Fluorine: 1500 W Phosphorus: 1000 W Sulfur: 1200 W Chlorine: 1000 W
Isotopes monitored[a]	Fluorine: 19 Phosphorus: 31 Sulfur: 34 Chlorine: 35
Data acquisition mode	Single ion–pulse counting
Data acquisition dwell time	250 ms

[a] Discussions regarding forward power and isotope selection are contained in the text.

NH_3 solution. The structures of these compounds are shown in Fig. 1. The stock solutions were used to prepare diluted solutions with appropriate solvents for analyses. HPLC grade methanol (Sigma-Aldrich, Milwaukee, WI) and 18 MΩ·cm deionized water obtained with a Millipore Systems (Billerica, MA) Milli-Q Plus deionization system were used for sample preparation. Details are provided in the individual sections regarding the elements.

RESULTS AND DISCUSSION

Solvent Composition. The analytes in this study are pharmaceutical compounds that would often be determined in aqueous based chromatographic mobile phases using organic modifiers and/or ion or pH buffers. As such, various solvent compositions were examined. These results are presented as part of a systematic study in which the behaviors of each solvent system with USN-MD sample introduction are detailed.[23] The solvent compositions listed for each analyte in Table III represent those that produced the best signal-to-noise ratios.

Background Interferences and Isotope Selection. The detection limit for many elements in ICP-MS is greatly influenced by interferences present at the particular *m*/*z* value. The background ion count depends on the plasma chemistry, which varies with operational conditions, the composition of the analyte solution matrix, and the argon purity. This solution may contain high concentrations of an interfering ion or a combination of elements that combine under the correct conditions to produce high molecular ion backgrounds.

Elimination of solvent interferents requires complete desolvation of the analyte stream so that only dry, particulate analyte molecules are transported to the plasma. As shown in a number of other publications, solvent transport measurements[19] and molecular emission spectra[20,21] illustrate the high solvent removal characteristics of membrane desolvation systems coupled with an ultrasonic nebulizer.

However, solvent removal is not 100%. Figure 2 illustrates mass spectra taken at the *m*/*z* ratios corresponding to the analytes with nebulized solvent with and without analyte. The signal at mass 32 was unusable for the dominant ion of sulfur (95.0% abundance) due to the background signal caused by $^{16}O_2^+$. However, the background signal was less than 200 counts per second for the less mass abundant ^{34}S (4.2%) species. Chlorine-35, the most abundant isotope, produced the best chlorine signal-to-noise ratio with a background signal of less than 5000 counts per second. However, the background was significant for the monoisotopic species ^{31}P and ^{19}F. At mass 31 (phosphorus), it is likely that the significant background is caused by nitrogen impurities and products of methanol decomposition. Due to the isotope abundances, likely candidates are $^{14}N^{16}O^1H^+$ and $^{12}C^{16}O^1H_3^+$. At mass 19, it has been shown that background contributions from $^{16}O^1H_3^+$ and $^{18}O^1H^+$ are substantial.[4] Examinations of the ratios of the small background signals at $m/z = 19$ and 20 indicate that $^{38}Ar^{+2}$ is not a significant interferent. The discussed species and other possible, but less likely, interferents are noted in Table I.

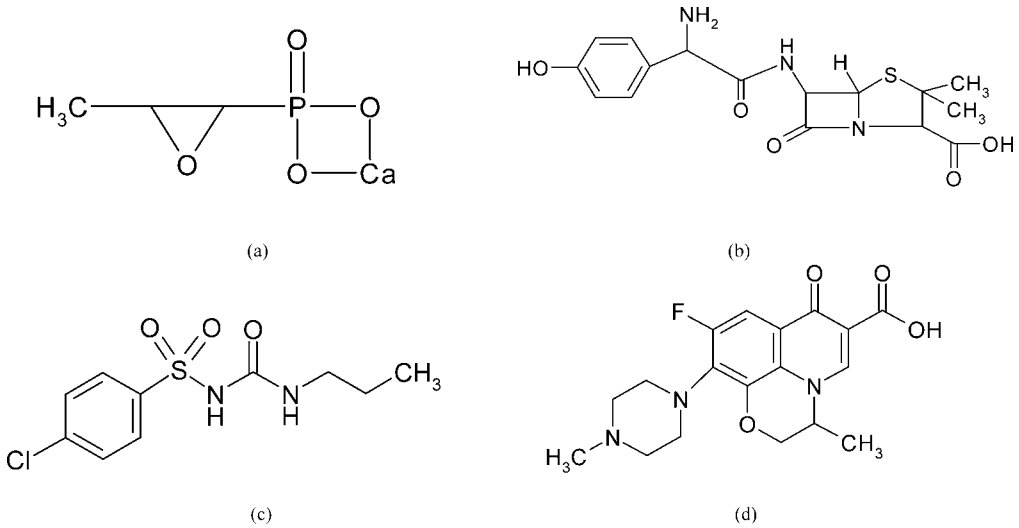

FIG. 1. Structures of (**a**) phosphomycin, (**b**) amoxicillin, (**c**) chlorpropamide, and (**d**) olfoxacin.

TABLE III. Summary of analytical performance of detection of nonmetals using ICP-MS with ultrasonic nebulization and membrane desolvation.

Compound	Monitored isotope	Solvent[a]	Sensitivity (icps/ng)[b]	Detection limit (ng)	Detection limit (ng/mL)
Phosphomycin	^{31}P	20% CH_3OH	20 700	0.3	2
Amoxicillin	^{34}S	20% CH_3OH	1800	0.3	3
Chlorpropamide	^{35}Cl	0.1% CH_3COONH_4	400	9	90
Ofloxacin	^{19}F	4% NH_4OH	0.55	1000	3000

[a] Aqueous solvent mixture with specified components.
[b] icps = integrated counts per second.

Phosphorus Determinations. Optimization of the phosphorus-31 signal, introduced as phosphomycin in a 20% methanol in water solution, consisted of varying gas flow rates and the forward power to maximize the signal-to-noise ratio. Because phosphorus will be significantly ionized under typical plasma operating temperatures, 33% as estimated by Houk,[1] the plasma provides a relatively large abundance of ions for measurement. As seen in Table III, the detection limit is reasonably low at 1.7 ng/mL. That the detection limit does not rival those of metals with similar ionization energies may be due to analyte decomposition issues; phosphorus atomization requires multiple oxygen–phosphorus bond breakages. This speculation is countered by the absence of significant PO^+, PO_2^+, or PO_3^+ signals. However, in the presence of phosphorus, a significant signal at $m/z = 48$ was seen. It is likely that this signal is due to POH^+. Phosphorus detection limits for this and other continuous liquid sample introduction ICP-MS approaches can be seen by examination of Table IV. In all cases, the present detection limits using the USN-MD are superior. The improvement compared to other published values[1,2,6,9] may be attributed to enhanced desolvation of the analyte stream, which limits plasma cooling and minimizes the formation of polyatomic interferents. Utilizing pulse counting, the calibration plot was linear from 20 to 800 ng/mL with an r^2 value of 0.9992. Using analog detection, the range could be extended from 800 to 4000 ng/mL.

Sulfur Determinations. As noted in the Background Interferences subsection, determinations observing the most abundant isotope for sulfur (^{32}S) were precluded due to the large $^{16}O_2^+$ ion background. Although the mass 34 isotope is much less abundant (4.2%), the concomitant decrease in the background ion count produced signal-to-noise ratios superior to those achieved using the mass 32 isotope. Some interferences are still present at mass 34 (Table I); however, the net effect is a relatively small background signal. It was found that operation of the plasma at 1200 W provided the best signal-to-noise ratios for sulfur. This power served to enhance the ionization of sulfur, which is ionized only 14% based upon Houk's[1] previously calculated values. The detection limit was determined to be 3.3 ng/mL and is listed in Table III. Again, as with phosphorus, the sulfur detection limit was superior to those obtained with other methods with the standard plasma sample-and-skimmer-cone plasma quadrupole mass spectrometer interface. It should be noted that the use of a pre-quadrupole octopole dynamic reaction cell[7] or a sector mass spectrometer[4,5] produced somewhat better detection limits. The trade-off of the relative complexities of high resolution mass spectrometry with ultrasonic nebulization and membrane desolvation must be made. Utilizing pulse counting, the calibration plot was linear from 10 to 1000 ng/mL with an r^2 value of 0.997. Using analog detection, the range could be extended from 1000 to 5000 ng/mL.

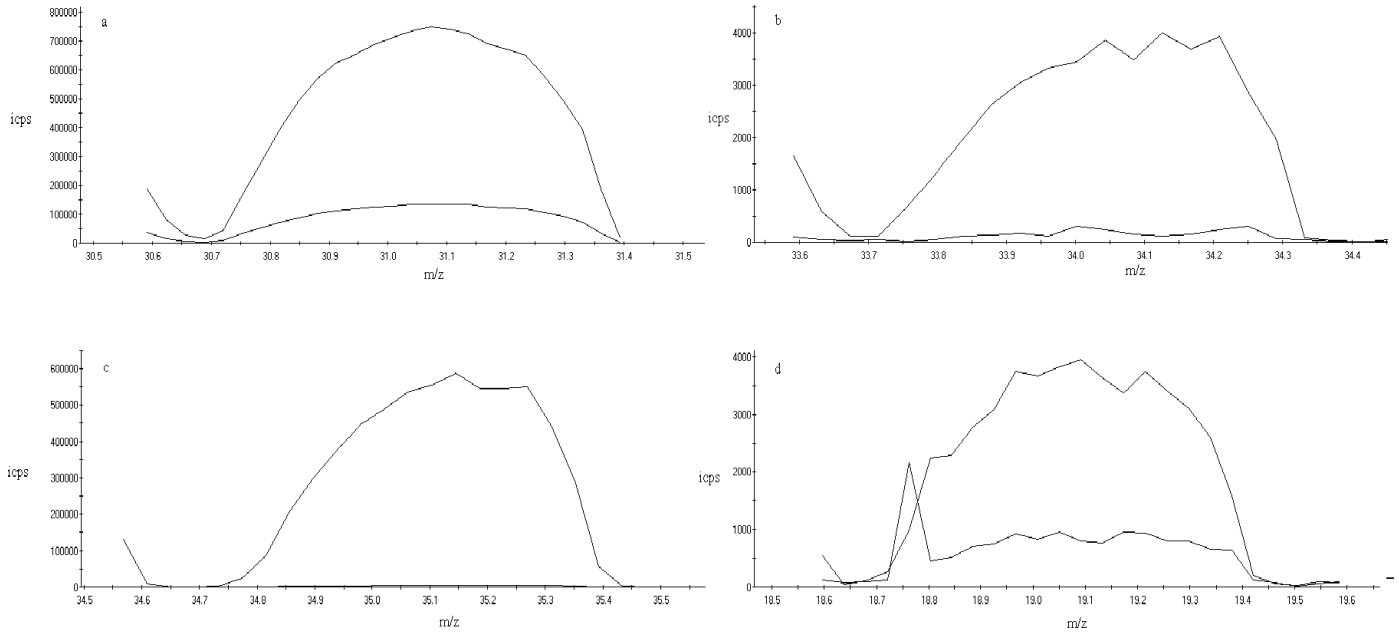

FIG. 2. Mass spectra of (**a**) ^{31}P (4 ppm P as phosphomycin), (**b**) ^{34}S (580 ppb S as amoxicillin), (**c**) ^{35}Cl (6 ppm Cl as chlorpropamide), and (**d**) ^{19}F (100 ppm F as ofloxacin), indicating background (lower lines) and analyte (upper lines) peaks. Experimental conditions as listed in Table II.

TABLE IV. ICP-MS detection limit comparison for continuous sample introduction methods.

Element	Degree of ionization	Plasma gas	Mass spectrometer	Sample introduction[a]	Monitored species	Detection limit (ng/mL)	Reference
Fluorine		Ar	quadrupole	USN-MD	$^{19}F^+$	3000	this work
	0.000009	He (5 torr)	quadrupole	capillary USN	$^{19}F^+$	10 000	9
		Ar	sector	microconcentric PN	$^{19}F^+$	5000	3
		Ar	quadrupole	USN-MD	$^{31}P^+$	2	this work
		Ar	quadrupole	USN	$^{31}P^+$	8	2
		Ar	quadrupole	PN	$^{31}P^+$	200	22
Phosphorus	0.33	He (5 torr)	quadrupole	capillary USN	$^{31}P^+$	13	9
		Ar	sector	PN	$^{31}P^+$	65	6
		Ar	quadrupole	USN-MD	$^{34}S^+$	3	this work
		Ar	quadrupole	USN	$^{34}S^+$	150	2
		He (5 torr)	quadrupole	capillary USN	$^{34}S^+$	4,000	9
		Ar	quadrupole	PN with an octopole reaction cell	$^{34}S^+$	1.3	7
Sulfur	0.14	Ar	sector	microconcentric PN	$^{32}S^+$	1	5
		Ar	sector	PN	$^{32}S^+$	0.6	4
		Ar	quadrupole	USN-MD[a]	$^{35}Cl^+$	90	this work
		Ar-He (7:3)	quadrupole	PN	$^{35}Cl^+$	2.2	8
Chlorine	0.009	He (5 torr)	quadrupole	capillary USN	$^{35}Cl^+$	50	9
		Ar	sector	microconcentric PN	$^{35}Cl^+$	3.2	3

[a] USN, MD, and PN indicate ultrasonic nebulization, membrane desolvation, and pneumatic nebulization, respectively.

Chlorine Determinations. The most abundant chlorine isotope, ^{35}Cl, was monitored. As seen in Fig. 2, this isotope is relatively free of interferences. Bu, Wang, and Hall[4] noted similar behavior. With the fairly low calculated ionization efficiency for chlorine, ~0.9%,[1] higher forward powers were initially used when examining the chlorpropamide-containing samples. However, the increase in forward power resulted in an increase in the background ion signal and noise, degrading detection limits. Based upon available information, the nature of the interference is not clear. The optimal plasma power for chlorine detection was 1000 W. A detection limit of 90 ng/mL was obtained (Table III). Utilizing pulse counting, the calibration plot was linear from 180 to 60 000 ng/mL with an r^2 value of 0.99991.

These authors found no other chlorine detection limits with direct solution sampling into a standard argon ICP quadrupole mass spectrometer system. Again, that chlorine was detectable at these levels is attributed to the USN-MD system. Using a sector mass spectrometer, Bu and Hall[3] obtained detection limits of 3 ng/mL. Sheppard, Shen, Davidson, and Caruso[8] were able to reduce detection limits to 2.2 ng/mL with a mixed argon–helium plasma.

Fluorine Determinations. Fluorine has the highest ionization energy of all the halogens. The calculated ionization efficiency is only 9×10^{-4}%.[1] Additionally, with significant water and argon derived interferences possibly present at the mass of it's only isotope, fluorine-19 determinations have presented a significant challenge for ICP-MS spectroscopists. Even with MD in the present study, the background signal is significant. Increasing the forward power to 1500 W served to maximize the signal-to-noise ratio by enhancing the fluorine ion signal. Powers exceeding 1500 W increased the background noise without further significant increases in the $^{19}F^+$ signal.

Although this is the first report of solution sample introduction directly into a conventional ICP-MS system, the detection limit of 3300 ng/mL is high compared to the other nonmetals discussed in this study. As illustrated in Table IV, this value is comparable to, or slightly better than, published results using a low pressure helium ICP[9] or an argon plasma with a sector mass analyzer.[4] While the sector instrument produced higher resolution than the quadrupole mass spectrometer used in this study, it can be presumed that the sector MS tradeoff between resolution and reduced ion flux and reduced water-derived interferences with membrane desolvation is the reason that the our detection limits are comparable. Utilizing pulse counting, the calibration plot was linear from 50 to 200 μg/mL with an r^2 value of 0.98. At higher concentrations, a calibration plot rollover occurred. While detailed studies of this phenomenon are required to fully understand the cause of this rollover, it is highly possible that charge-repulsion effects involving the lower mass fluorine ion may play a major role.

CONCLUSION

Determinations of phosphorus, sulfur, chlorine, and fluorine heteroatoms containing active pharmaceutical ingredients have been demonstrated using ICP-MS coupled with ultrasonic nebulization and membrane desolvation. A general trend of decreasing detection limits with increasing ionization efficiency was observed. Detection limits in the sub- to few ng/mL range were obtained for P, S, and Cl. The detection limit for F was 3300 ng/mL. For these elements, these are the best detection limits reported with continuous solution nebulization and a standard argon ICP-MS. These detection limits can be attributed to the high efficiency of ultrasonic nebulization combined with a reduction of matrix-induced interferences by the membrane desolvation system. This sample introduction system provides a simple and effective way to enhance ICP-MS performance for nonmetal determinations.

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