Effect of Sample Introduction on ICP-MS Detection of Nonmetal Analytes in a Simulated HPLC Matrix

Adam E. Dill and Jon W. Carnahan
Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL, 60115

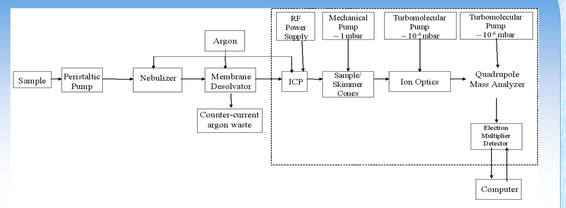
Overview

- With the increase in heteroatom moieties (P, S, Cl, F, for example) in pharmaceutical compounds and impurities, the detection and quantification of nonmetals has become increasingly important to the pharmaceutical industry.
- Demand for heteroatom detection in the pharmaceutical industry is a function of the high sensitivity and genotoxic impurity requirements for the manufacturing of pharmaceutical compounds.
- An argon inductively coupled plasma (ICP) is a versatile, robust, and nearly structurally independent source for trace elemental analysis that can be applied to the detection of heteroatom moieties in pharmaceutical compounds.
- Solutions containing the active pharmaceutical ingredient phosphomycin in one of three buffers common LC buffers; ammonium acetate, ammonium hydroxide, and formic acid; are used to monitor phosphorus.
- Operational parameters of several nebulizers are varied to determine which nebulizers may be useful for coupling ICP-MS to LC separations.

•One general comment – You have a great set of results – it would be nice if the results in terms of trends related to nebulizer characteristics ….. this is important info !!!

1. Experimental Setup

The experimental setup for all experiments is diagramed below:



ICP-MS operating parameters are listed below in Table 1:

Table 1: ICP-MS Optimized Operating Parameters

ICP-MS Parameters:	Setting
Forward Power (W)	475
Cool Gas Flow Rate (L/min)	14
Auxiliary Gas Flow Rate (L/min)	0.8
Desolvator Temperature (°C)	160
Desolvator Counter Current Gas Flow Rate (L/min)	2.4

2. Methods and Materials

Methods:

- Phosphorus containing solutions were continuously nebulized and phosphorus was monitored at m/z=31
- All solutions contained 250 ppb P in the form of phosphomycin
- All solutions were 80:20 (v/v%) methanol:water and contained one of three buffers:
  1. 0.1% (v/v%) Ammonium Hydroxide
  2. 10 mM Ammonium Acetate
  3. 0.1% (v/v%) Formic Acid
- Q_l (liquid sample flow rate) varied by calibrated peristaltic pump
- Q_g (nebulizer gas flow rate) varied by $Ar_{(g)}$ calibrated mass flow controller
- For each nebulizer and solution, maximum phosphorus signal was obtained by optimizing:
  1. Torch position
  2. Q_g
  3. Q_l

  Once maximum phosphorus signal was obtained, various Qg and Ql values were (spacing issues on orig) tested

Materials:

- HPLC grade methanol (Fischer)
- 28(?)% (w/w%) Certified ACS plus ammonium hydroxide (Sigma-Aldrich)
- 96% (wt/wt%) ACS reagent formic acid (Sigma-Aldrich)
- Reagent grade ammonium acetate (Sigma-Aldrich)
- Phosphomycin calcium salt (Sigma-Aldrich)

Instrumentation used in these experiments included:

- Fisons (Thermo Electron) Instruments PlasmaQuad II ICP-MS:
- Nebulizers:
  1. Cetac U5000AT Ultra Sonic Nebulizer
  2. Meinhard HEN170A
  3. Meinhard HEN90A
  4. Meinhard TR30-C1
- Membrane Desolvation:
  1. Cetac MDX-200
- Scott-Type Dual Pass Spray Chamber
- Rainin Rabbit Peristaltic Pump
- Brooks 5890 Mass flow Controller

Acknowledgements

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3. Results for U5000AT

- See section 12 for a graphical representation of the data

Signal To Noise Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.5	317	471	811	368	947	871	122	191	669
0.6	319	543	846	365	965	1332	178	232	1142
0.8	398	613	855	439	715	1239	174	246	1245
1.0	495	702	908	484	675	1439	151	276	1300

Signal To Background Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.5	78	81	74	77	143	129	53	47	82
0.6	86	91	96	94	144	169	59	51	134
0.8	95	112	105	124	141	180	50	56	126
1.0	115	105	130	137	150	180	33	48	141

Detection Limit (ppb)

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.5	2	2	1	2	0.8	0.9	6	4	1
0.6	2	1	1	2	0.8	0.6	4	3	0.7
0.8	2	1	1	2	1	0.6	4	3	0.6
1.0	2	1	1	2	1	0.5	5	3	0.6

4. U5000AT Discussion

- Best detection occurs at higher values of Q_g and Q_l
- Can easily nebulize entire range of Q_l values tested
- Droplets formed such that residence time affects overall detection limit at most by one order of magnitude
- Large range of Qg and Ql (l subscript- also sec 6) work well for optimal detection with this nebulizer
- RSD% of all signals higher than other nebulizers:
  - May be poor for maintaining peak shape post UV detection
  - See table comparing signal RSD% of all nebulizers in section 11
- Performance profile (surface plot) seen in section 12 is similar in shape to other high efficiency nebulizers such as HEN90A and HEN170A:
  - Likely a result of similar droplet size and size distribution
- Performance makes nebulizer attractive for coupling to HPLC:
  - Although high signal RSD% may pose a problem

5. Results for TR30-C1

- See section 13 for a graphical representation of the data

Signal To Noise Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.5	76	155	85	118	125	51	132	168	108
0.6	90	156	81	138	126	44	163	183	105
0.8	95	153	67	143	124	40	170	188	69
1.0	103	150	55	152	123	40	228	205	60

Signal To Background Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.5	38	108	42	50	41	24	56	52	27
0.6	50	102	39	57	43	23	67	50	26
0.8	42	100	30	70	47	22	70	61	17
1.0	58	122	24	77	51	21	99	71	11

Detection Limit (ppb)

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.5	10	5	9	6	6	15	6	4	7
0.6	8	5	9	5	6	17	5	4	7
0.8	8	5	11	5	6	19	5	4	11
1.0	7	5	14	5	6	19	3	4	13

6. TR30-C1 Discussion

- Best detection occurs at moderate and lower values of Qg and Ql
- Efficiently nebulizes with only a small range of Q_l values tested:
  - At lower Q_l there is an increase in the ration of gas kinetic energy to liquid mass ratio
- Droplets formed such that residence time affects overall detection limit by at most by a factor of 3
- RSD% of all signals higher than HEN style nebulizers but lower than USN:
  - Likely less problematic than USN for maintaining peak shape post UV detection
  - See table comparing signal RSD% of all nebulizers in section 11
- Performance profile (surface plot), seen in section 13, maximum generally occurs at different position from HEN and USN style nebulizers:
  - A result of different efficiency, droplet size, and droplet size distribution
- Performance makes nebulizer possible but not as attractive as other nebulizers for coupling to HPLC

7. Results for HEN170A

- See section 14 for a graphical representation of the data

Signal To Noise Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.1	94	193	329	92	205	252	89	157	223
0.2	121	273	375	94	216	282	90	170	228
0.3	166	342	413	142	283	328	147	230	271
0.5	184	332	369	170	316	236	147	258	250

Signal To Background Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.1	61	68	91	56	62	57	88	67	60
0.2	80	78	104	55	73	68	76	65	66
0.3	97	101	115	78	86	75	98	79	75
0.5	108	113	100	79	101	53	98	78	79

Detection Limit (ppb)

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.1	8	4	2	8	4	3	8	5	3
0.2	6	3	2	8	3	3	8	4	3
0.3	5	2	2	5	3	2	5	3	3
0.5	4	2	2	4	2	3	5	3	3

8. HEN170A Discussion

- Best detection occurs at higher values of Q_g and Q_l
- Can easily nebulize entire range of Q_l values tested
- Droplets formed such that residence time affects overall detection limit at most by a factor of 3
- Large range of Qg and Ql work well for optimal detection with this nebulizer
- RSD% of all signals lower than USN or C30:
  - May be good for maintaining peak shape post UV detection
  - See table comparing signal RSD% of all nebulizers in section 11
- Performance profile (surface plot) seen in section 12 is similar in shape to other high efficiency nebulizers such as HEN90A and USN:
  - Likely a result of similar droplet size and size distribution
- Performance makes nebulizer attractive for coupling to HPLC
- Performance equivalent or better than C30 with ~10X less sample

9. Results for HEN90A

- See section 15 for a graphical representation of the data

Signal To Noise Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.1	37	83	100	33	45	67	35	66	101
0.2	44	87	118	47	62	85	38	80	112
0.3	47	96	128	51	76	114	46	87	137
0.5	46	107	132	65	68	104	51	88	126

Signal To Background Ratio

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.1	11	32	29	13	14	13	11	17	20
0.2	12	33	32	16	17	16	14	20	23
0.3	13	32	37	18	20	19	15	21	26
0.5	14	39	39	24	20	19	13	20	24

Detection Limit (ppb)

	Ammonium Hydroxide			Ammonium Acetate			Formic Acid		
	Q_g (L/min)			Q_g (L/min)			Q_g (L/min)		
Q_l (mL/min)	0.8	0.9	1.0	0.8	0.9	1.0	0.8	0.9	1.0
0.1	20	9	8	23	17	11	22	11	7
0.2	17	9	6	16	12	9	20	10	7
0.3	16	8	6	15	10	7	16	9	5
0.5	16	7	6	12	11	7	15	9	6

10. HEN90A Discussion

- Best detection occurs at higher values of Q_g and Q_l
- Can easily nebulize entire range of Q_l values tested
- Droplets formed such that residence time affects overall detection limit at most by a factor of 3
- Large range of Qg and Ql work well for optimal detection with this nebulizer
- RSD% of all signals lower than USN or C30:
  - May be good for maintaining peak shape post UV detection
  - See table comparing signal RSD% of all nebulizers in section 11
- Performance profile (surface plot) seen in section 12 is similar in shape to other high efficiency nebulizers such as HEN170A and USN:
  - Likely a result of similar droplet size and size distribution
- Performance makes nebulizer attractive for coupling to HPLC
- Performance equivalent or better than C30 with ~10X less sample