Overview:

Though it has been shown previously that high mass accuracy and elemental composition determination is feasible on conventional quadrupole GC/MS and LC/MS systems, it remains to be seen that such capability could be carried over to a more economical compact IMS system so that more units of IMS systems could have access to such capability typically reserved for high resolution MS systems such as TOF, Orbitrap or FT ICR MS which come at significantly more cost while requiring highly trained specialists in their maintenance and operations.

Introduction:

The rapid identification of radiolabeled compounds would clearly be beneficial for applied clinical and preclinical tracers used for imaging with positron emission tomography (PET). The limited uptake of mass spectrometry in the imaging field has been due arguably to several factors including concerning regarding adequate sensitivity, instrument footprint in the highly constrained space requirements for the majority of labs and high initial capital costs plus high ongoing maintenance costs. The introduction of the expression Compact Mass Spectrometer (CMS) at the 2012 Spring ACS/StateWashing attend for the first time the concerns space, capital cost and maintenance costs. Adequate sensitivity is required to measure the small amounts of labeled compound involved, high spectral accuracy is required to allow the CMS MaxiWork special matching software to precisely identify the chemical formula of the analytes. Before testing the system on radio pharmaceuticals, the basic performance was validated using standard compounds.

Methods:

A new compact mass spectrometer is calibrated by direct infusion of a mixture of compounds spanning the m/z range of 100-1000. In this a mixture of Betaine, Hexamethoxyphosphazene, Hexakis(2,2-Difluoroethoxy)Phosphazene, Hexakis(1H, 1H, 1H-Tetrafluoropropoxy)Phosphazene was used. This is available as the Agilent Technologies ESI tuning mix. (Agilent Technologies, P/N G2421A). By acquiring unprocessed profile mode MS data of these standards, it is possible to build a novel comprehensive calibration which could then be applied to a sample containing unknowns in the calibration range of m/z 100-1000 or either direct infusion or LC separation mode. The calibration of MS peak shape with known mathematical functions allows for the accurate determination of m/z values even when the MS peak width is of unit mass resolution.

Results:

The following figure show the MassWorks (Cerno Bioscience, Norwalk, CT) mass calibration and peak shape calibration for these compounds. The average spectral accuracy is 97.8% showing a very close match between the theoretical and actual quadrupole performance.

In order to test the accuracy of the calibration it was applied to an LC-MS run of a standard test mix containing Acetaminophen, Caffeine, Sulfadimethoxine, Reserpine and Terfenadine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Predicted m/z</th>
<th>Observed m/z</th>
<th>Detection Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>156.1</td>
<td>156.1</td>
<td>10 pg</td>
</tr>
<tr>
<td>Caffeine</td>
<td>195.1</td>
<td>195.1</td>
<td>50 pg</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td>327.2</td>
<td>328.2</td>
<td>10 pg</td>
</tr>
<tr>
<td>Reserpine</td>
<td>369.2</td>
<td>369.2</td>
<td>50 pg</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>256.2</td>
<td>256.2</td>
<td>10 pg</td>
</tr>
</tbody>
</table>

The base peak of each of the peaks in the chromatogram were treated as unknown and MassWorks software serached for a chemical formula match based on the calibrated mass and spectral shape for each peak.

Conclusion:

- Eighteen reference compounds were detected at low mass levels (pg to ng) with no MS and confirmed with 95% spectral accuracy.
- Eleven traces (2 CA 18F labeled compounds, 6 NCA 18F labeled compounds, 3 13C-methylated labeled compounds were collected and tested after HPLC purification.
- Eight of these traces 3 19F-labeled compounds (19F-SA4503, 19F-PIB, 19F-FLR), 2 CA 18F labeled compounds (18F-EF5, 18F-TFSB) and 3 NCA 18F labeled compounds (18F-FTC-146, 18F-P3BZA, 18F-FBPA) could be detected by mass identification of respective parent ion of 19F and 13C carrier compounds following HPLC isolation.

- The expression CMS single quadrupole LC/MS with spectrum analysis is fast enough to measure compounds containing short-lived isotopes in a matter of minutes.
- Sensitive enough to measure small amounts of active radiochromophores.
- The rapid spectral accuracy allows accurate determination of chemical formulae.

- Detection and identification of CA 18F labeled and tertiary amino compounds was straightforward.

- Ionization and chromatographic condition optimization is still required for some of the tracers evaluated.