

Introduction to High Resolution Mass Spectrometry for Qualitative and Quantitative Analysis: A Summary

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Fundamental Concepts for HRMS

- Mass Terminology: nominal, average, accurate, exact, monoisotopic
- Mass Separation: resolution, resolving power
- Mass Measurement: centroid, profile, peak top, millimass units vs. parts per million
- Mass Defect: the story in the decimal places
- Isotopes

Instrument Types and Concepts

Major operating principles and challenges in

- Time of Flight MS: delayed extraction, reflectron, orthogonal acceleration
- Fourier Transform Ion Cyclotron Resonance (FTICR) MS: Magnet, cell types, pressure/vacuum requirements, ultrahigh resolution
- Orbitrap MS: ion storage and injection techniques, MS/MS options, scan speed vs. resolution
- Quadrupole and Quadrupole--based ion traps: resolution capability, impact on hybrid MS/MS systems

MS/MS

- Major options
 - Resolution in each mass analyzer
 - Scan speed compatibility (full scan and MS/MS switching, parallel processing options)
- Fragmentation Options: CAD, CID, ETD, EAD, UVPD, etc

Qualitative Analysis

- HRMS-based options for metabolite/ degradant/ unknown structural elucidation
- Interpretation of elemental composition
 - Mass Defect Filter
 - Nitrogen Rule
 - Ring Double Bond
- Interpretation of MS/MS data-Narrowing the site of Metabolic modification
- Utility of Hydrogen--Deuterium Exchange for structural Elucidation
- HRMS options for ADCs and Oligonucleotides
- HRMS options for Drug-to-Antibody (DAR) ratio determination
- HRMS for biomarker discovery

Quantitative Analysis

- Key variables in HRMS quantitation:
 - Operating resolution during acquisition
 - Selection of m/z for quantitation: peak summing; multiply charged analytes; resolved isotopic envelopes
 - Data processing peak widths
 - Processing of centroid vs. profile data
- Data mining for metabolites, biomarkers, and other non-targeted and non-anticipated components
- ADC Payload Quantitation

Qual-Quan Workflows

- Instrument requirements and options
 - Strengths and weaknesses
- Major decisions prior to data acquisition
 - Role, limitations of MS and MS/MS in alternating scans
- Example workflows and data sets.
- Applications to small molecules, peptides, ADC payloads, and biomarkers
- On-the-fly MS/MS vs post-acquisition data mining