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Pharmaceutical Analytical Chemistry: Open Access

Commentary

LC-MS/MS Methods for Quantifying Drugs and Metabolites in Plasma

Olivia Henderson*

Department of Pharmaceutical Chemistry, Harvard Medical School, Boston, USA

DESCRIPTION

Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) is widely regarded as the gold standard for the quantitative analysis of drugs and their metabolites in biological matrices such as plasma. Its application spans preclinical research, pharmacokinetic studies, clinical trials and Therapeutic Drug Monitoring (TDM). The technique combines the separation power of liquid chromatography with the sensitivity and specificity of mass spectrometry, enabling accurate detection even at sub-nanogram levels.

In pharmaceutical development, quantification of drugs in plasma is essential for determining pharmacokinetic parameters such as Absorption, Distribution, Metabolism and Excretion (ADME). LC-MS/MS offers unparalleled sensitivity and selectivity, making it possible to measure trace concentrations of parent compounds and their metabolites in complex biological matrices. This capability is important in early-phase clinical trials, where the pharmacokinetic profile guides dosing and safety assessments. Developing a robust LC-MS/MS method involves several steps: selection of an appropriate sample preparation technique, chromatographic separation conditions, ionization mode and Multiple Reaction Monitoring (MRM) transitions. Sample preparation is a critical step to reduce matrix effects and improve signal quality. Common approaches include protein precipitation, Liquid-Liquid Extraction (LLE) and Solid-Phase Extraction (SPE). SPE, in particular, offers superior purification and is preferred in methods requiring high sensitivity.

The selection of chromatographic conditions such as mobile phase composition, flow rate, column type and gradient profile is optimized to achieve adequate resolution and peak shape. Reversed-phase columns are commonly used due to their versatility, although Hydrophilic Interaction Chromatography (HILIC) has gained popularity for polar analytes. The use of volatile buffers like ammonium acetate or formate ensures compatibility with mass spectrometric detection.

Electrospray Ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI) are the most frequently employed ionization techniques in LC-MS/MS. ESI is suitable for polar, thermally labile compounds and is often used for small molecule drugs. MRM mode enables the monitoring of specific precursor-to-product ion transitions, offering high sensitivity and selectivity for targeted analyses.

Method validation is governed by stringent guidelines issued by the FDA, EMA and ICH. Parameters such as accuracy, precision, linearity, selectivity, carryover and stability must be evaluated under both intra and inter-day conditions. Matrix effects, a common challenge in LC-MS/MS analysis, are assessed through post-extraction addition experiments to ensure ion suppression or enhancement does not compromise quantification.

Beyond early-stage research, LC-MS/MS plays a pivotal role in Therapeutic Drug Monitoring (TDM), especially for drugs with narrow therapeutic windows such as immune suppressants, antiepileptic and chemotherapeutics. The ability to personalize treatment based on plasma concentrations significantly enhances patient outcomes and reduces adverse effects.

The technique is also critical in forensic and toxicological analysis, enabling the detection of drugs of abuse, poisons and environmental contaminants in biological samples. In these applications, the accuracy and defensibility of results are paramount and LC-MS/MS offers the level of confidence required for legal and clinical decision-making.

Recent advances in instrumentation, including High-Resolution Mass Spectrometry (HRMS), have further expanded the capabilities of LC-MS/MS. While HRMS offers broader screening applications, LC-MS/MS remains the preferred method for quantitative bioanalysis due to its reproducibility and regulatory acceptance.

Automation and miniaturization are shaping the future of LC-MS/MS. Techniques such as online SPE, multiplexing and micro flow LC are being adopted to increase throughput and reduce sample and reagent consumption. These innovations make LC-MS/MS more accessible to smaller laboratories while maintaining analytical performance.

LC-MS/MS is an indispensable tool in pharmaceutical analytical chemistry. Its unmatched sensitivity, specificity and versatility make it the method of choice for quantifying drugs and

Correspondence to: Olivia Henderson, Department of Pharmaceutical Chemistry, Harvard Medical School, Boston, USA, E-mail: olivia.henderson@hms.harvard.edu

Received: 10-Feb-2025, Manuscript No. PACO-25-38189; **Editor assigned:** 13-Feb-2025, PreQC No. PACO-25-38189 (PQ); **Reviewed:** 27-Feb-2025, QC No. PACO-25-38189; **Revised:** 04-Mar-2025, Manuscript No. PACO-25-38189 (R); **Published:** 11-Mar-2025, DOI: 10.35248/2471-2698.10.277

Citation: Henderson O (2025) LC-MS/MS Methods for Quantifying Drugs and Metabolites in Plasma. Pharm Anal Chem. 10:277.

metabolites in plasma. As the demand for personalized medicine, high-throughput analysis and regulatory compliance grows, LC-MS/MS will continue to play a central role in both research and clinical practice.