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Title: Design and utility of open-access liquid chromatography tandem mass spectrometry in quantitative clinical toxicology and therapeutic drug monitoring

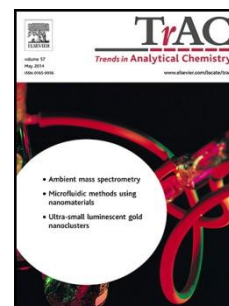
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Design and Utility of Open-Access Liquid Chromatography Tandem Mass Spectrometry in Quantitative Clinical Toxicology and Therapeutic Drug Monitoring

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Highlights

- On-line direct-inject analysis of aqueous diluted blood based matrix samples.
- Measurement of >20 drug panels for therapeutic drug monitoring and clinical toxicology (>100 analytes).
- Panel specific methodologies using generic column and solvents.
- High-throughput multiplexed analysis of >1440 samples per system per day.
- Historical calibration and inter-channel analysis for STAT reporting.

Abstract

The current implementation of LC-MS/MS in drug development presents distinct challenges in the clinical setting for real-time sample analysis in clinical toxicology and therapeutic drug monitoring. Realization of STAT sample analysis using a single instrument within a single shift is the evolutionary goal of the technology. The constraint of performing many different measurements on a diverse array of analytes also confounds this paradigm. In the absence of an approved platform to resolve these issues, we developed a solution using commercially available multiplexing systems to facilitate rapid testing of >100 analytes as sub-panels (3-10 analytes per panel). Each panel is developed with consistent dilution (10 – 20 fold aqueous internal standard solutions) and incorporates assay specific online extraction/LC gradient motifs with generic column and solvent combinations. This paper discusses developmental considerations to ameliorate known MS detection issues such as phospholipids, provides a rational burden of proof for precision based recovery and demonstrates throughput in excess of 1440 samples per day per system. Additional capabilities are shown such as historical calibration and open channel access utility while conforming to the highest standards of analytical validity. Importantly, the concepts described within this manuscript have been reduced to clinical practice in the analysis of >500000 patients over the last 8 years.

Keywords

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