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Ultra-Fast quantitative analysis of Immunosuppressants in Dried Blood Spots using Laser Diode Thermal Desorption coupled to tandem mass spectrometry

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Abstract:
Background:
Immunosuppressant drugs are used as a proliferation signal inhibitor in organ transplants. Dried blood spots (DBS) on paper become a desirable method of sample collection. This technique reduces the steps for sample collection and shipping. To optimize the dosing regimen, concentration results from a sample are rapidly needed. The ultra-fast Laser Diode Thermal Desorption (LDTD) technology combined to a tandem mass spectrometer system is used for rapid turnaround time of sample results.
The Laser Diode Thermal Desorption (LDTD) ion source uses an infrared laser diode to indirectly thermally desorb neutral species of Immunosuppressant molecules from a dried sample extract. These neutral species are carried into a corona discharge region, where they undergo efficient protonation and are introduced directly into the mass spectrometer. Total analysis time is under 9 seconds with no carry-over.
The objective of this experiment is to validate the DBS extraction conditions, the analysis method and test different real patient samples using the LDTD-MS/MS. A cross validation study against the LC-MS/MS approach for the analysis of Immunosuppressants (Cyclosporin A, Tacrolimus, Sirolimus and Everolimus) was performed in order to evaluate the performance of the proposed alternative LDTD-MS/MS method.
Methods:
Lyophilized calibrators for Cyclosporin A, Tacrolimus, Sirolimus and Everolimus as well as Quality Control material were obtained from Chromsystem and UTAK. 25 µL of calibrators, QC and patient specimens are spotted on a Whatman 903 card and dried at room temperature (protected from light) for at least 2 hours. Six DBS punches of 3 mm were transferred in a glass tube. 100 µL of water was added and the tube was transferred to an ultrasonic bath for 10 minutes. 100 µL of internal standard (Ascomycin (5 ng/mL), Cyclosporin A-d4 (250 ng/mL), Ramycin-d3 (3 ng/mL) and Everolimus-d4 (5 ng/mL) in a mixture of ZnSO4 (1M):Methanol (20:80)) was added. The mixture was vortex-mixed. A liquid-liquid extraction was then performed by adding 200 µL methyl-tert-butyl ether (MTBE). After vortexing and centrifugation, 45 µL of the organic layer was transferred in a tube and 5 µL of desorption solution was added and mixed. 4 µL was deposited in the LazWell Plate and evaporated to dryness. The LDTD laser power was ramped to 80% in 6 seconds, and shut down after 2 seconds. Positive ionization mode was used, and the AB Sciex 5500 QTrap system was operated in MRM mode.
Results:
The calibration curves show excellent linearity with r > 0.995 between the quantification ranges of the Chromsystem standard. Intra-run accuracy and precision between 86.4 % and 107.5 % and 0.7 to 18.3%, respectively, were calculated. All QC values meet acceptance criteria of 15%. No matrix effect or carryover was observed. This method was cross validated with results from a traditional LC-MS/MS method with real patient specimens. All negative samples correlated accordingly.

Conclusion:
DBS provides an easier way for sample transport management and is an ideal match to the unique advantages provided by the LDTD technology ultra-fast analysis of Immunosuppressant drugs. This method has demonstrated accurate, precise and stable results with a run time of 9 seconds per sample.
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