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Accelerator mass spectrometry-enabled microtracer study to evaluate the human mass balance of KD101: Method challenges for analysis of a volatile oil

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The large majority of drugs and not volatile and amenable to standard analytical techniques. Volatile compounds pose a different set of challenges, requiring changes to the total sample preparation procedure and often analytical method. We encountered such situation during a human microtracer study (180 nCi human oral dose) of compound KD101, a single isomeric oil, (-)α-Cedrene (206.23 g/mol). A total of 6 subjects were administered 400 mg of unlabeled KD101 admixed with 180 nCi of radiolabeled drug as a tracer. Detection of the radiolabel was performed using graphite based Accelerator Mass Spectrometry (AMS), with support from Liquid Scintillation Counting (LSC) for early urinary time-points. Post-administration, cumulative urine and fecal voids were collected for 288 hr post-dose. Serial blood collections were taken frequently post-administration and then daily for the duration of the study. Preliminary work showed the KD101 could be completely removed under vacuum concentration in the absence of any trapping agent or biological matrix. This problem was exacerbated by the AMS processing method where samples are also evacuated under vacuum for torch-sealing inside quartz combustion (oxidation to gaseous carbon dioxide, prior to reduction to graphite). We found an acceptable technique to limit volatility losses through the pretreatment of all samples with an excess of tributyrin prior to concentration. The tributyrin served thus as both a carbon source and a chemical trapping agent. Sucrose was also tested but showed little ability to "capture" the compound during dry-down. We showed that parent compound recovery could be improved from <10 to 89% recovery using 2.0 mg of tributyrin per sample or LC fraction, and a minimum dry-down time (20 min). The overall results of the study validated the dilution method. Mean mass balance recovery was 85.21% (77.96% in urine, 7.26% feces). This is considered a good mass balance recovery given the fact that it was difficult to control for losses due to compound volatility. The concentration decay in the plasma was largely bi-exponential after the absorption period, with a wandering baseline out to 288 hr post-dose, with occasional "jumps" in concentration, which was attributed to the displacement of compound in fat depots. Metabolite radiochromatograms from urine and plasma showed intact parent in plasma with metabolites exclusively explaining the urinary components. In summary, we achieved satisfactory results for the mass balance and metabolism of a volatile oil using a chemical trapping agent. The detriment was a lowering of overall detection sensitivity (e.g. 0.88 dpm/mL of plasma vs. 0.05 dpm/mL of unmodified plasma), but sensitivity was still sufficient to achieve mass balance and perform metabolite profiling using highly sensitive AMS detection.

Recent Publications

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Biography

Howard Lee is the Founder and Director of the Center for Convergence Approaches in Drug Development (CCADD). Dr. Lee serves as a Professor at the Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University. Dr. Lee is also appointed at Seoul National University College of Medicine and Hospital, affiliated with the Department of Clinical Pharmacology and Therapeutics. Dr. Lee previously served as Head of Global Strategy and Planning, Clinical Trials Center, SNUH. As of August 2017, Dr. Lee was appointed Chair of the Graduate Program in Clinical Pharmacology, Seoul National University. Dr. Lee has spearhead the introduction of Accelerator Mass Spectrometry (AMS)-enabled exploratory early clinical drug development studies to the Korean biopharmaceutical R&D sector, which has awarded Dr. Lee 2 government grants.

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