Comparative Metabolism of Eight Model Pharmaceutical Compounds in Rat- and Human- Liver Microsomes, Suspension Hepatocytes, and Micropatterned Co-cultures of Primary Hepatocytes

J. Enoru[1], W. DeMaio[1], A. Watanyar[1], K. Draper[1], A. Moore[2], and O. Ukairo[2]
Author affiliations: 1. Ricerca Biosciences, LLC, Concord, OH; 2. Hepregen Corporation, Medford, MA

In vitro metabolism evaluations for compounds in early development are typically conducted using liver microsomes and suspension hepatocytes. While these systems have been serving the drug development community, they have their limitations, with examples of “metabolite surprises” - where metabolites which were not predicted or observed in vitro or in vivo during pre-clinical studies, were observed in the clinic. Such surprises can have a significant impact on the timeline of a drug development program and has prompted investigations aimed at developing in vitro systems that can more accurately predict human in vivo metabolism.

In this study, the metabolite profile of eight model pharmaceutical compounds with various biotransformation reactions was investigated using a functionally stable model of primary hepatocytes [micropatterned co-cultures (MPCCs)] in parallel with the traditional liver microsomal and suspension hepatocyte systems. Incubations were performed for 0 and 60 min in liver microsomes, 0 and 2 hr in suspension hepatocytes and 0, 4 hr, 2 days and 7 days in MPCCs. Metabolites were identified by LC/MS employing a narrow range of chromatographic conditions, representative of drug metabolism screening in an early development setting.

Preliminary results show that MPCCs are more metabolically active than the traditional platforms, based on greater disappearance of test article and formation of metabolites. Formation of metabolites from non-P450 mediated reactions, especially UGTs, and secondary metabolites appear to be more predominant in MPCCs.

Results from this investigation support the usefulness of MPCCs for metabolite profiling studies with the potential of eliminating “metabolite surprises”. MPCCs also provide the advantage that the cells maintain metabolic activity over an extended period in culture, which probably explains why secondary metabolites were more abundantly generated in this system.