DISCOVERY SERVICES

DRUG DISCOVERY

Metabolic Stability – Hepatocytes

Background

Drugs are most often eliminated by biotransformation and/or excretion into urine or bile. The liver is the major organ for xenobiotic biotransformation and is thereby important in characterizing the metabolism, toxicology, and drug-drug interaction properties of drugs. Drug metabolism is achieved via two major enzyme reactions within the liver, Phase I and Phase II reactions. Phase I enzymes include the cytochrome P450 (CYP) family of enzymes which are located in the smooth endoplasmic reticulum. The basic processes in phase I reactions are oxidation, reduction and/or hydrolysis many of which are catalyzed by the CYP system and require NADPH as a cofactor. Phase II enzymes are located in the cytoplasm and endoplasmic reticulum and are characteristic of conjugation reactions including glucuronic acid, glutathione, sulfate, and glutamine conjugations. Phase II reactions generally inactivate the drug if it is not already therapeutically inactive following Phase I metabolism, and make the drug more water soluble to facilitate its elimination. Some drugs are metabolized by Phase I or Phase II enzymes alone whereas others are metabolized by both Phase I and Phase II enzymes.

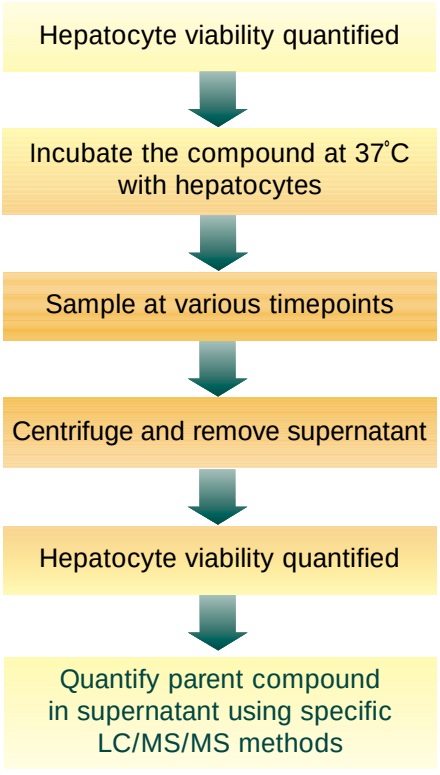
Key Features of the Assay

- intact cell model of the liver: complete metabolic pathways with physiological levels of enzymes and cofactors
- intact plasma membrane: important in drug permeability and transport
- various hepatocytes available: human, rat, dog, and monkey

Assay Applications

- assessment of the susceptibility of drug candidates to metabolism by Phase I and Phase II drug-metabolizing enzymes[1,2]
- early identification of species specific differences in drug metabolism

Assay Protocol



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Typical Results

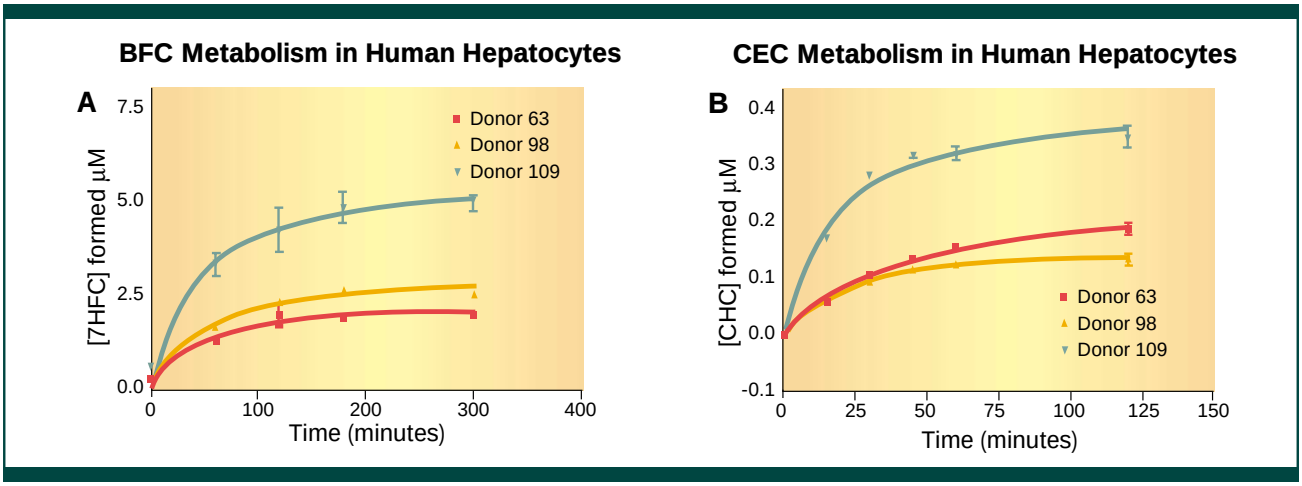

FIG. 1 **A.** BFC is metabolized by CYP450 to form the fluorescent metabolite 7-HFC. **B.** CEC is metabolized to the fluorescent metabolite CHC. Both CHC and 7-HFC formation were quantified using a fluorometer.

Related Services

Metabolic Stability-Microsomes

Cytochrome P-450 Subtype Inhibition Studies

References

1. Berthou et al., *Xenobiotica*, 19: 401 (1989)
2. Seddon et al., *Biochem Pharmacol.*, 38, 1657 (1989)

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