DISCOVERY SERVICES

DRUG DISCOVERY

Metabolic Stability – Microsomes

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 stability, 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 solubleto 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.

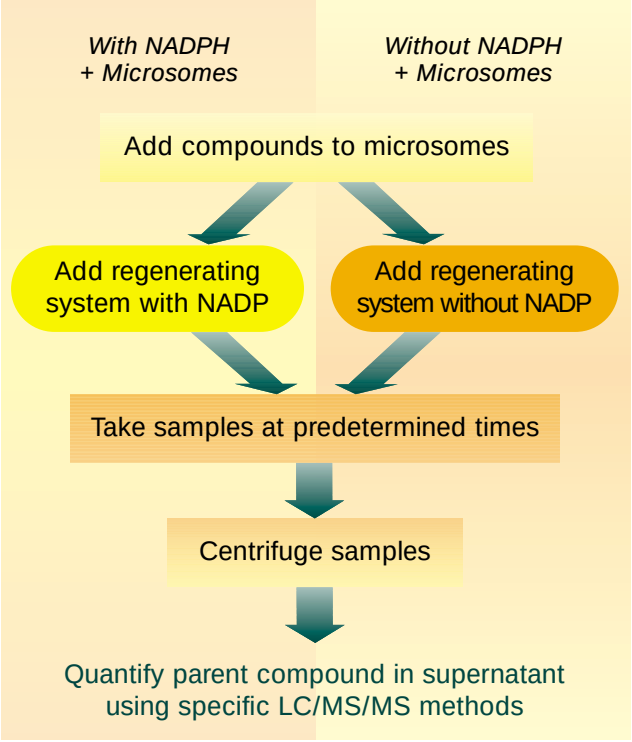
Key Features of the Assay

- subcellular fraction of liver tissue: microsomes are membrane vesicles of the smooth endoplasmic reticulum and contain the CYP enzymes, Flavin-containing Monoxygenases (FMO) and UDP Glucuronyl Transferases (UDPGT)[1]
- no plasma membrane; no complications of cellular uptake or export
- various microsomes available: human, rat, dog, and monkey

Assay Applications

- assessment of the susceptibility of drug candidates to metabolism by CYP and FMO enzymes or UDPGTs
- assessment of drug biotransformation solely as a function of metabolism[1]
- early identification of species specific differences in drug metabolism

Assay Protocol



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Typical Results

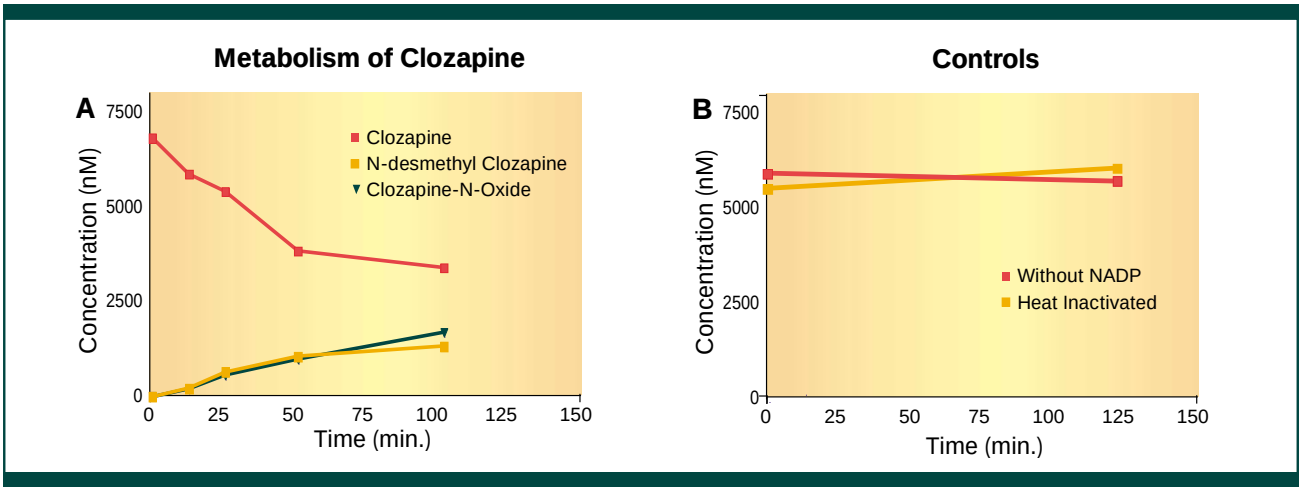

FIG. 1 Metabolism of clozapine and the formation of N-desmethyl clozapine and clozapine N-oxide when incubated with pooled human liver microsomes **(A)** in the presence of NADP, and **(B)** in the absence of NADP and when microsomal enzymes had been inactivated by heating.

Related Services

Metabolic Stability–Hepatocytes

Cytochrome P-450 Subtype Inhibition Studies

References

1. Rodrigues, A.D., *Biochem Pharm*, 48(12): 2147 (1994)

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