ADME: Metabolic Stability- Microsomes

Background:

Drugs are eliminated from the body either as unchanged parent or as metabolite. Metabolic stability plays a major role in drug clearance, with the liver being the primary site for drug biotransformation via two major enzymatic reactions: Phase I (modifications to the molecular structure itself) and Phase II reactions (conjugation reactions). A common system for measuring hepatic metabolism in early drug discovery, restricted to Phase I reactions, uses liver microsomes, a subcellular fraction containing major drug-metabolizing enzymes, including the cytochrome P450 (CYP) family and flavin monooxygenase (FMO).

Metabolic stability screening in microsomes alerts to potential liabilities of compounds, provides useful information to develop structure-metabolic stability relationships and helps to identify compounds with favourable pharmacokinetic properties.

This high throughput method is based on measuring the disappearance of parent compound. By using liver microsomes of different animal species and human, potential species related differences in the metabolism can also be detected (preliminary met id study).

Assay description

Species

mouse , rat, dog, monkey, human

Compound concentration

3µM (0.1% DMSO)

Compound requirements

50µl of 10mM solution or

1-2 mg of dry matter

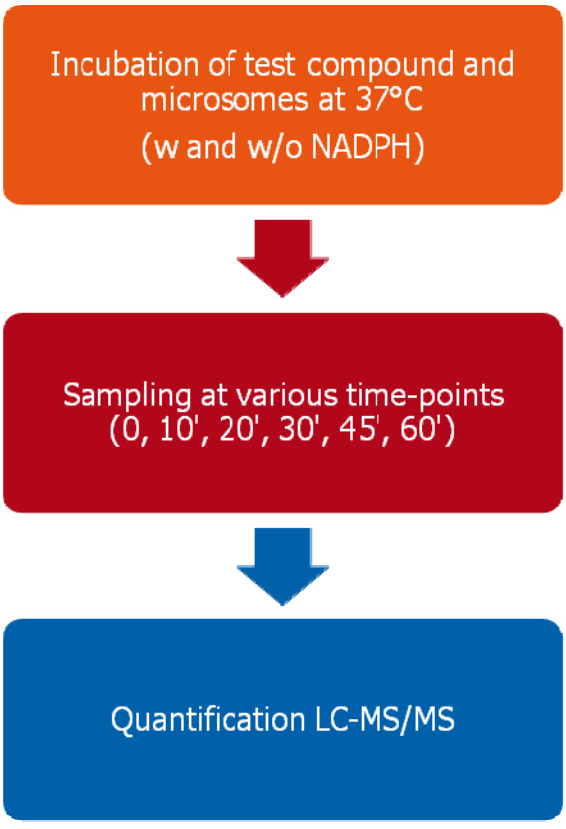
Detection method

LC-MS/MS with internal standard

Results

%remaining, half-life, *in vitro* clearance,

predicted *in vivo* hepatic clearance and %LBF (liver blood flow)



Contact us:
Adrijana Vinter, Business Development
adrijana.vinter@glpg.com
+385 91 265 5527
Mila Vrančić, Business Development
mila.vrancic@glpg.com
+385 91 265 5528

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Assay controls

positive control compounds: testosterone, verapamil and propranolol

negative control: without co-factor

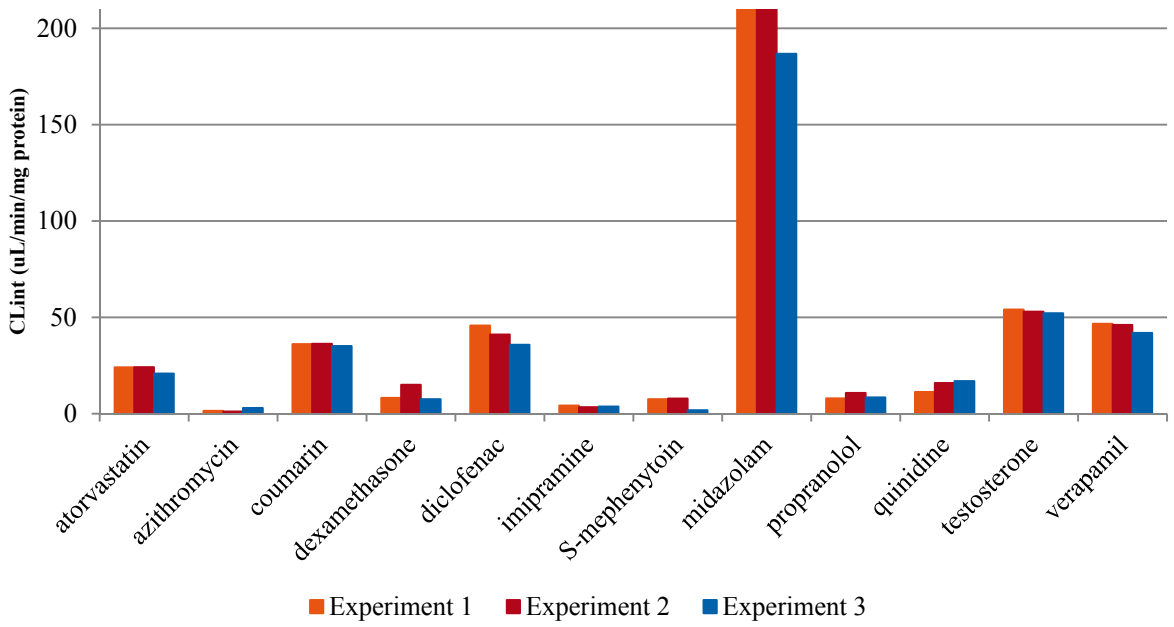

Figure 1. Mean intrinsic clearance (mean value from duplicate incubations within each run) in-house assay data obtained for 12 commercial compounds in three separate experiments

Assay details adjustable to client's and/or project specific requests

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Adrijana Vinter, Business Development
adrijana.vinter@glpg.com
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Mila Vrančić, Business Development
mila.vrancic@glpg.com
+385 91 265 5528