ADME: Metabolic Stability - Hepatocytes

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). The metabolic stability of compounds is commonly investigated early on in the drug discovery process using various *in vitro* test systems, in order to guide project teams on potential metabolic liabilities.

Hepatocytes represent an independent *in vitro* cellular test system, containing both Phase I and Phase II enzymes, cofactors and drug transporters, used to assess the metabolic stability of compounds and for early identification of species specific differences.

In addition to metabolic stability studies, hepatocytes are used to identify and compare metabolite profiles (MetID) among different species.

Assay description

Cells

cryopreserved hepatocytes

$0.5x10^6$ cells/ml

Species

mouse, rat , dog, minipig, rabbit, monkey, human

Compound concentration

metabolic stability: 1µM (0.03% DMSO)

MetID: 10µM (0.03% DMSO)

Compound requirements

50µl of 10mM stock solution or

1-2 mg of dry matter (preferred for metID)

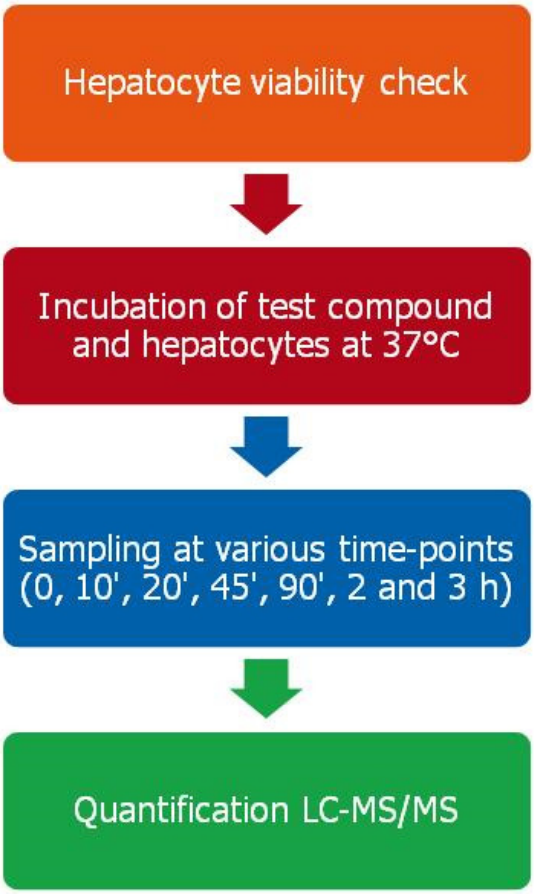
Detection method

LC-MS/MS with internal standard

Results

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

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



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Assay controls

reference compounds:

- testosterone and umbelliferone

stability in KHB buffer and/or inactivated hepatocytes

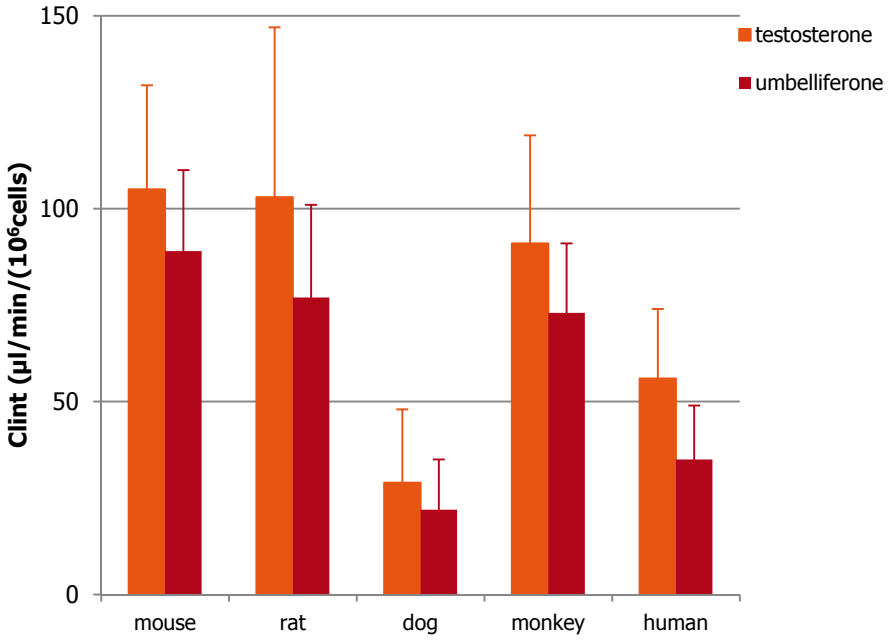

Figure 1.
Clearance values obtained for reference compounds in 5 different species

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

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