ADME: Plasma protein binding

Background:

The pharmacokinetic and pharmacodynamic properties of drugs are influenced by the extent of binding to plasma proteins, as only unbound "free" drug has the ability to partition across membranes, undergo metabolism and clearance by the kidney, as well as interact with targets to exert an effect.

Drugs generally bind reversibly to plasma proteins (mostly albumin, α1-acid glycoprotein and lipoproteins) with different kinetics and affinity. Highly protein bound drugs are retained in the plasma compartment, with restricted distribution into tissues, decreased metabolism, clearance (low extraction ratio drugs), prolonged half-lives and limited brain penetration.

The degree to which a compound binds to plasma proteins is determined across species during early drug discovery. Equilibrium dialysis is a commonly used technique to measure plasma protein binding (PPB).

Assay description

Technique

equilibrium dialysis

Species

mouse, rat , human, dog, rabbit, monkey

Compound concentration

5µM (0.5% DMSO)

Compound requirements

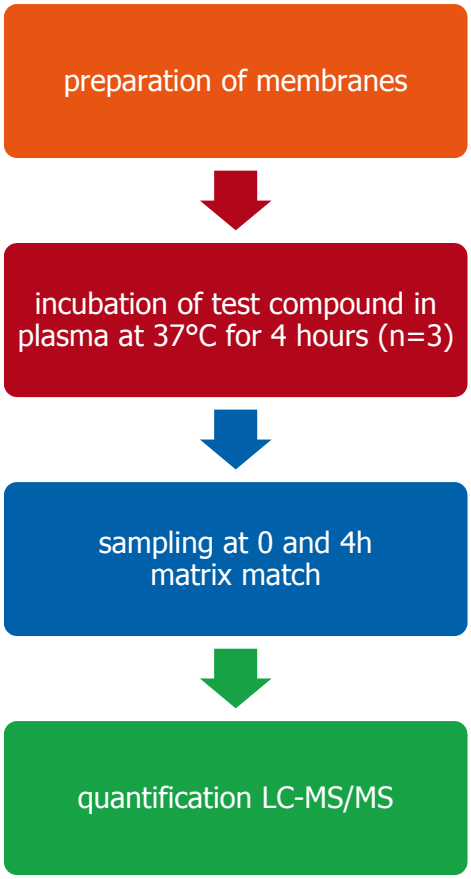
50µl of 10mM stock solution or
1-2 mg of dry matter

Detection method

LC-MS/MS with internal standard

Results

%fraction bound (%Fb)
recovery



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

protein contamination check

reference compounds: acebutolol, propranolol, verapamil and nicardipine (Figure 1)

data obtained for 10 commercial compounds (Figure 2)

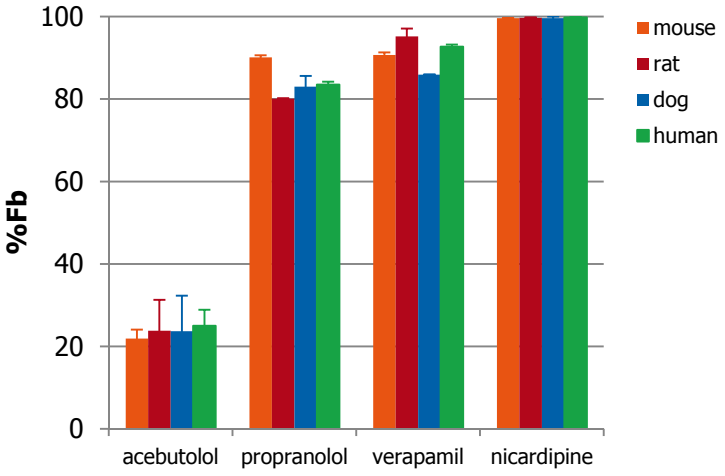

Figure 1. %Fb values obtained for reference compounds in 4 different species

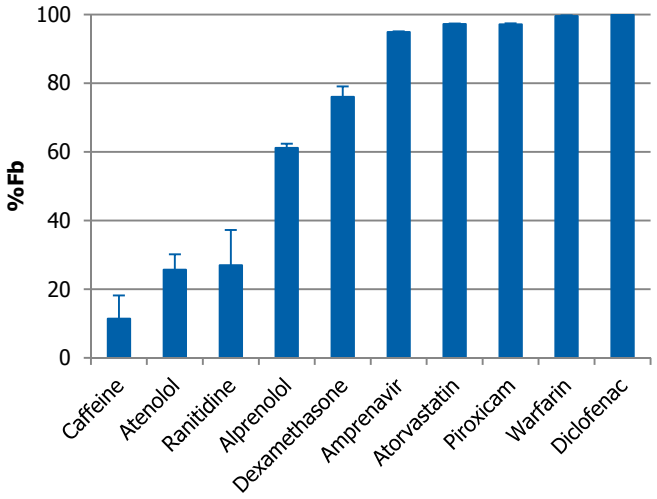

Figure 2. %Fb values of commercial compounds obtained in human plasma in 3 separate experiments

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

Contact us:
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mila.vrancic@glpg.com
+385 91 265 5528