

Plasma Stability

Background Information



'Plasma stability assay has many applications in drug discovery: to alert teams to liable structural motifs, to prioritize compounds for *in vivo* studies and to screen prodrugs and antedugs.'

¹Di L., Kerns E.H., Hong Y and Chen H. (2005) *International Journal of Pharmaceutics* **297**; 110-119.

- Determination of the stability of new chemical entities in plasma is important as compounds (with the exception of pro-drugs) which rapidly degrade in plasma generally show poor *in vivo* efficacy.
- Instability in plasma can result in misleading *in vitro* data which can be difficult to interpret (e.g., plasma protein binding data). Storing and analysing clinical samples from *in vivo* pharmacokinetic studies may also prove challenging.
- Compounds with the following functional groups tend to be more susceptible to hydrolysis in plasma: esters, amides, lactones, lactams, carbamides, sulphonamides, and peptic mimetics¹.
- Compounds may exhibit interspecies differences in their stability in plasma.
- Plasma stability is very useful for screening of prodrugs and antedugs, where rapid conversion in plasma is desirable.

Protocol

Test Article Concentration

1 μ M (different concentrations available)

DMSO Concentration

2.5%

Incubation Time

0, 15, 60 and 120 min

Test Article Requirements

30 μ L of 10 mM DMSO solution

Analysis Method

LC-MS/MS quantification

Assay Controls

Positive control compound which undergoes degradation in plasma

Data Delivery

Percent parent compound remaining at each time point

Follow on metabolite profiling studies

Cyprotex's Plasma Stability assay can be extended to profile the main breakdown product that is formed. Options include a low resolution analysis to identify whether a metabolite is formed, or a cross species comparison to identify potential differences in metabolism which could in turn help to interpret pharmacology and toxicity data. We can also perform ion-transition analysis in order to understand the derivation of metabolites.

Please refer to Cyprotex's Metabolite Profiling and Identification section for further details.

Plasma stability has several applications: to understand data where compounds are unexpectedly rapidly cleared; to screen for prodrugs and antedugs; and to determine the liability of drugs with susceptible structural motifs.

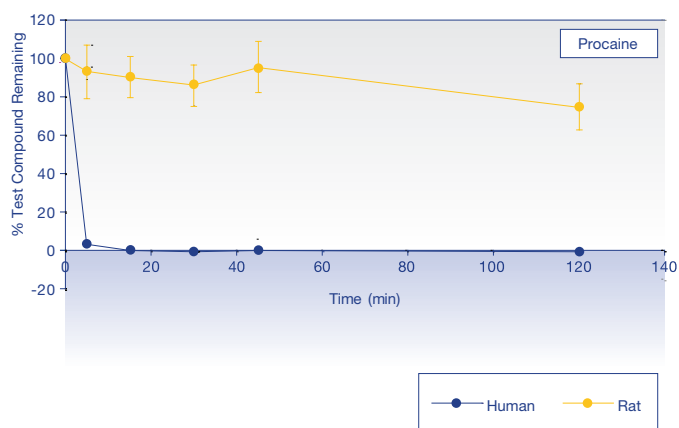
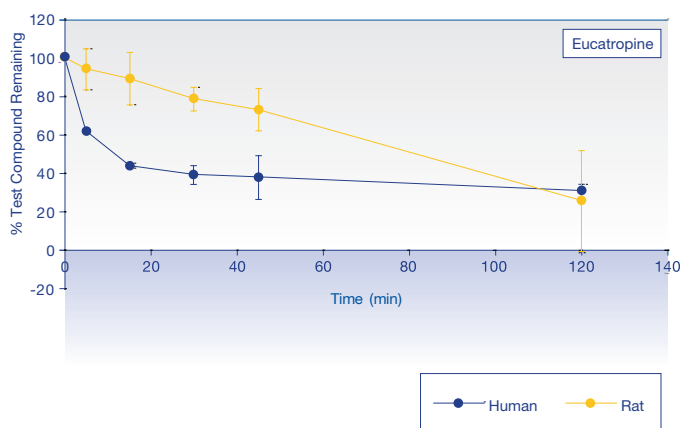
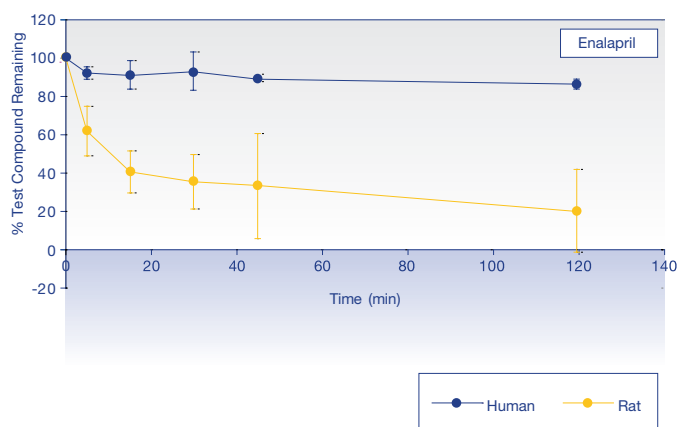
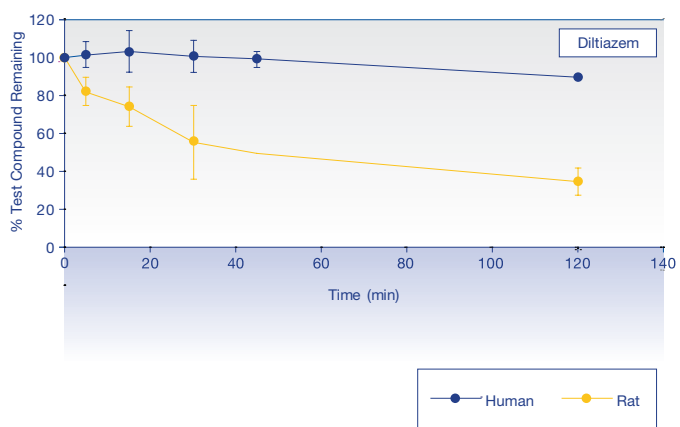


Plasma Stability

4 compounds were incubated with human liver and rat plasma over 120 min. These compounds show clear differences in stability following incubations with human and rat plasma (Figure 1). These data may be useful in interpreting *in vivo* efficacy, toxicity and pharmacokinetic studies.

Figure 1

Cyprotex's Plasma Stability data for diltiazem, enalapril, eucatropine, and procaine in human and rat plasma (mean \pm sd, n=3).



References

¹ Di L. et al. (2005) *International Journal of Pharmaceutics* 297; 110-119.