



Metabolic Stability

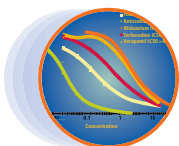
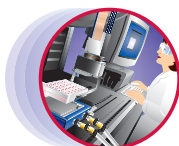
INTRODUCTION

Metabolic stability influences both oral bioavailability and half life.¹ With cytochrome P450 substrates of low and moderate *in vivo* clearance, there is a good correlation between *in vitro* metabolic stability and *in vivo* clearance.² In addition to cytochrome P450, glucuronosyl transferases are also recognized as a major clearance pathway for some drugs.³ BD Biosciences provides rapid *in vitro* metabolic stability testing using several different enzyme sources. Most often, this test utilizes hepatocytes (fresh or cryopreserved⁴) or liver microsomes. However, intestinal microsomes, S9 fraction, or cDNA-expressed enzymes are also available depending on sponsor requirements. Appropriate positive and negative controls are included. The following services are available upon request:

- Assessment of both phase I and phase II enzyme metabolism together or independently. A standard set of substrate concentrations and incubation times may be used.
- Metabolite profiling and species differences in metabolism.
- Analysis by HPLC coupled with absorbance, fluorescence, radiometric, or mass spectrometric detection.
- Alternatively, incubations can be returned to the sponsor for analysis.

EXPERIMENTAL OUTLINE

- 1 Incubate test compound at one or more concentrations with the enzyme source (hepatocytes, microsomes, or S9) with appropriate positive and negative controls.
- 2 At varying time intervals, reactions are terminated. The time spacing and replicate number is flexible.
- 3 The parent drug is analyzed by LC/MS or HPLC/UV/radiometric detection.
- 4 Data is provided in tabular form along with half-life and intrinsic clearance calculations.



METABOLIC STABILITY OF STRUCTURAL ANALOGS IN POOLED HUMAN LIVER MICROSOMES

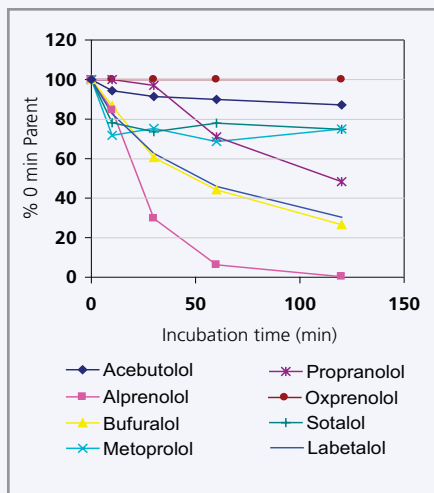


Figure 1: Typical Data from a Metabolic Stability Study.

METABOLIC STABILITY OF MODEL DRUGS IN POOLED CRYOPRESERVED HUMAN HEPATOCYTES

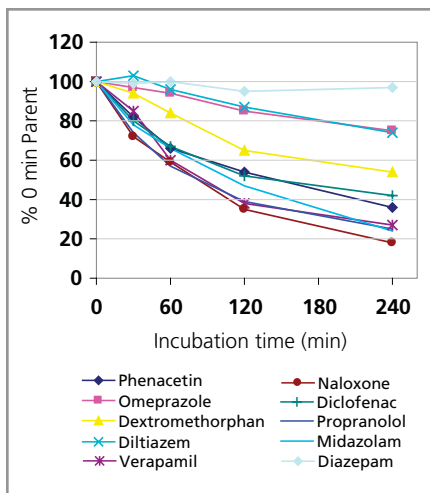


Figure 2: Disappearance of test compounds in an incubation with pooled human cryopreserved hepatocytes over time. The results are the mean of two experiments, conducted in duplicate on independent days.

References

1. Clarke, S.E. and Jeffrey, P. Utility of metabolic stability screening: comparison of *in vitro* and *in vivo* clearance. *Xenobiotica* **31**:591 (2001).
2. Houston, J.B. Utility of *in vitro* drug metabolism data in predicting *in vivo* metabolic clearance. *Biochem. Pharmacol.* **47**:1469 (1994).
3. Soars, M.G., et al. *In vitro* analysis of human drug glucuronidation and prediction of *in vivo* metabolic clearance. *J. Pharmacol. Exp. Ther.* **301**:382 (2002).
4. Zhang, G, et al. Validation of a pool of cryopreserved human hepatocytes as a model for drug metabolism studies. *The Toxicologist. Abstr. No. 1686* (2004).

CONTACT INFORMATION

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