

Microsomal Kit

TRANSIL Microsomal Binding Kit

CATALOG #

AAA60727

PRODUCT SYNONYMS

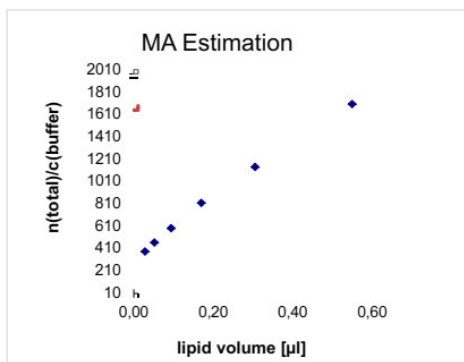
Microsomal; TRANSIL Microsomal Binding Kit; Microsomal kit

PRODUCT SPECIFICATIONS

Preparation and Storage

Store at -20 degree C

IMAGES



Standard Curve (Sample)

Related Product Information for Microsomal kit	Background: The complex, costly, and often uncertain outcome of the drug discovery and development process requires the simultaneous optimization of several properties. It has now long been recognized that favorable potency and selectivity characteristics are not the sole hallmarks of a successful drug discovery program, nor is the safety profile considered to be the only hurdle to be overcome, although it is of paramount importance. The ability to prospectively predict the pharmacokinetics of new chemical entities in humans is a powerful means by which scientists involved in the discovery of new drugs can select for further development only those compounds with the potential to be successful therapeutic agents. The half-life of a drug is a major contributor to the dosing regimen, and it is a function of the clearance and apparent volume of distribution (VD), each of which can be predicted and combined to predict the half-life. Drugs with short half-lives are more likely to be required to be administered more frequently than those with long half-lives. Dosing regimen is also intrinsically linked to other factors such as the pharmacodynamics of the drug and the difference between systemic concentrations associated with side effects vs those minimally required for efficacy. However, these latter attributes are much more difficult to predict from in vitro or animal data and will be different for each therapeutic target. Thus, a great deal of focus has been placed on the prediction of human half-life. While methods using allometric scaling or correlative methods exist for prediction of half-life, greater success is attained if the two major components of half-life, clearance and volume of distribution (note that the TRANSIL Intestinal Absorption Kit is well suited for VD predictions), are predicted separately and combined to generate a half-life prediction (Obach et al 1997). When estimating intrinsic clearance in metabolic stability incubations with microsomes or hepatocytes, the disappearance of the parent compound is measured over a time course. The clearance rate derived from these experiments is only reflecting the intrinsic clearance rate, if the test compound is available to interact freely with the CYP enzymes at the assumed target concentration. However, this is frequently not the case, because compounds tend to bind quantitatively to microsomal membranes, which can significantly reduce the available concentration - even to 1/100 or less of the total concentration in the incubation (Obach, 1999; McLure et al., 2000; Austin et al., 2002; Hallifax and Houston, 2006). Consequently, it is important to estimate microsomal binding in these in vitro incubations. Often, the binding to microsomal membranes is estimated as the free fraction of drug in incubations of microsomes (without cofactor) in dialysis rigs. As equilibration of microsomal binding in dialysis systems tends to require overnight incubations and may suffer more than other experiments from compound instability through hydrolysis and precipitation of poorly soluble drugs. Moreover, the experimentally determined free fraction relates to the experimental concentration of microsomes which will in many cases differ from the incubations of metabolic stability experiments. Microsomal binding not only reduces the concentration of free drug available to be metabolised by CYP enzymes, it also reduces the concentration which is available to inhibit the enzymes. It has been demonstrated that non-specific microsomal binding can account for underestimation of inhibitor potency (i.e., overestimation of IC₅₀ or K_i values) when dealing with lipophilic basic drugs. This in turn can lead to an underestimation of risk of drug-drug interactions. In particular, mechanism based inhibitor studies can be affected to a large extent by microsomal binding, because of the high microsome concentrations that are typically employed in these experiments. Hence, the fraction of drug bound to microsomes is also an important correction of experiments assessing the inhibition potential. Principle of the Assay: The principle of the TRANSIL Microsomal Binding assay is to assess the affinity of test compounds to microsomal membranes (Figure 1). The membrane affinity is determined by incubating a fixed concentration of the drug candidate with varying concentrations of membrane surface area immobilized on the silica beads. A total of 8 wells of a tube unit/plate are used to determine the microsomal membrane affinity for each compound (Figure 2). Six wells contain microsomal membrane silica beads while two serve as references to account for non-specific binding and contain buffer only. Using the spreadsheet and algorithms supplied with the assay, the affinity to the microsomal membranes is calculated from remaining free compound concentration in the supernatant of each well with membrane beads. Any of the available detection systems, such as HPLC-UV, LC-MS/MS, scintillation counting, etc. can be used for quantification, as long as it can quantify μM concentrations in volumes of 50 μl or less.
Product Categories/Family for Microsomal kit	Sovicell ADME Assays

For Research Use Only. Not for use in diagnostic or therapeutic procedures. Small volumes of product may become entrapped in the seal of the vial during shipment and storage; if necessary, briefly centrifuge the vial on a tabletop centrifuge to dislodge any liquid in the cap.