Evaluation of Toxicokinetic Assumptions Using a 443 Chemical Library

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Abstract

Introduction

Partition Coefficient Prediction with Schmitt’s Method

Partition Coefficients

References

Figure 1 at the left. The PKTK models included in this submission are negligible blood volume in each compartment and have an explicit tissue lumping in the rest of body compartment.

To test the effect of these assumptions on model outcomes, the rest of body compartment was removed from a PKTK model that was lumped into the blood phase by its volume, as shown in the left figure. The volumes of the rest of body compartments were also set to zero. Results of the last organ model.

Partition Coefficients predicted with Schmitt’s method were well correlated with 102 measured partition coefficients. Schmitt’s method reliably predicts hydrophobic partitioning at most one order of magnitude primarily for compounds with high logP, as seen in Figure 1 at the right, on a log-log plot.

Many of these points improved after using a new regression for predicting phospholipid partitioning (membrane affinity), not ensuring higher protein binding than the in vitro measurements or uncorrected for the esterification of phospholipids in vitro.

The function obtained in Equation 1 was modified to predict a more realistic distribution as well as increased in the blood distribution phase, as seen in Figure 2 at the right.

Only highly lipophilic compounds with high logP significantly improved. Figure 2 at the right. A new regression, shown below, was used for predicting partitioning into phospholipids for compounds with high logP, which produced the most improved results.

log(M4) = 1.294 + 0.304 log(M13)

Figure 4 at the right. The in vitro protein binding fup is used as the water to plasma partition coefficient:

The four regions of clinical interest: 1) the whole body on a log-log plot.

Conclusion

• To determine the ratio of the tissue and plasma concentrations at equilibrium, Kp, the partitioning into each individual component of the tissue must be determined.

• In Schmitt’s method, each tissue is composed of cells and interstices in which cells are composed of neutral lipids, neutral phospholipids, acidic phospholipids, proteins, and water.

• The partition coefficients are determined in vitro and stored together as shown in the equation below where Rx represents the log of the total tissue volume for each specific tissue.

• In vitro protein binding fup was used as the water to plasma partition coefficient:

• The volume of distribution is calculated by summing the fup multiplied by their volumes.

• The fraction unbound in plasma, fup, (concentration in unbound plasma divided by the total plasma concentration) is used as the water to plasma partition coefficient:

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