PUSHING THE DETECTION LIMITS OF ITC – DETERMINING PARTITION COEFFICIENTS OF POORLY SOLUBLE DRUGS

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Modern formulation technologies have been extending the range of well developable active pharmaceutic ingredients (API) to poorly soluble compounds that suffer from low bioavailability and technological problems in traditional formulations. For those poorly soluble compounds a detailed knowledge of the membrane-water partition coefficient K becomes critical as it determines their incorporation into and release from delivery systems as well as their uptake and permeation through cellular membranes. Unfortunately, for poorly soluble drugs, where K is needed most urgently, it is particularly hard to measure. This is due to the facts that i) such an experiment needs to be performed at lipid concentration low enough to find a significant fraction of the drug in solution and ii) the drug concentration needs to be constantly kept below the solubility limit. Here we demonstrate a new ITC strategy to resolve this problem on the example of lapatinib, a poorly soluble kinase inhibitor used for the treatment of breast cancer. Partitioning experiments at various contents of DMSO (5 – 20v%) confirmed that logK of the drug decreased proportionally to the DMSO volume fraction. Extrapolating back to zero DMSO yields the expected K value in DMSO-free buffer. The established experimental approach is presumed to be transferable to other poorly soluble drugs and further detection methods.