IMMOBILIZED ARTIFICIAL MEMBRANE (IAM) CHROMATOGRAPHIC RETENTION FACTORS OF STRUCTURALLY DIVERSE DRUGS AS A MEASURE OF LIPOPHILICITY.

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Immobilized Artificial Membrane Liquid Chromatography is gaining interest in Drug Design, since it combines the simulation of cell membranes partitioning with rapid measurements. While the solid phase surface in IAM chromatography simulates the phospholipid bilayer, the mobile phase models the aqueous environment surrounding the cells. In order to comply better with this physiological environment, phosphate-buffered saline (PBS) is usually used as the mobile phase. In the present study the IAM retention factors ($\log k_{wIAM}$) of a large number of structurally diverse drugs were determined at pH 7.4 and 5.0. At pH 7.4 both PBS and morpholinepropane soulphonic acid (MOPS) were used as aqueous components in the mobile phase in the aim to investigate the effect of buffer in retention. MOPS is usually used for the assessment of lipophilicity by reversed phase HPLC and due to its zwitterionic character it is consider not to interfere with the solutes and the stationary phase. The use of MOPS significantly increased the retention of the protonated bases as a result of a stronger contribution of electrostatic interactions. IAM retention was compared to octanol-water partitioning. The effect of ionization on retention was found to be less pronounced than expected and $\log k_{wIAM}$ at pH 7.4 were better correlated with logD than with logP. Measurements at pH 5.0 also did not produce significant changes in $\log k_{wIAM}$ in comparison to measurements at pH 7.4. $\log k_{wIAM}$, logP, logD, as well as reversed phase $\log k_w$ values of the investigated drugs were further analysed by multivariate statistics. For this purpose various molecular descriptors expressing bulk, electronic properties, hydrogen bonding capability and flexibility were calculated using Hyperchem/Chemplus and MSI-Cirius software packages. Principal Component Analysis confirmed the better similarity of $\log k_{wIAM}$ to logP than to logD. PLS models revealed a significantly lower contribution of hydrogen bond interaction in IAM retention especially at pH 5.0, in comparison to octanol-water partitioning.