# The versatility of membrane-water partitioning in pharmacokinetic modelling

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**Abstract**: In a rational drug design, the modulation of the chemical structure based on drug's pharmacokinetic profile can be the solution to avoid bigger investments in non-promising drugs. Numerous significant correlations between lipophilicity and membrane permeation have been established[1]. Additionally, anisotropic membrane-like systems, such as membranes/water (M/W) partitioning systems, are increasingly described as an alternative to octanol/water for the estimation of pharmacokinetic behaviour[2]. Actually, lipophilicity measured in isotropic octanol/water system only expresses the balance of hydrophobic and polar interactions. However, lipophilicity is the net result of all intermolecular forces, and when measured in the M/W systems, it also considers the ionic bounds, providing a better correlation with the intermolecular forces operating in molecular pharmacology and biochemistry[1]. In the present study, derivative spectroscopy was used to calculate M/W partition coefficient of drugs and to predict several parameters of their pharmacokinetic profile using lipid nanosystems of different constitution as biomembrane mimetic models [3]. Acyclovir, with *LogM/W*=3.05±0.06, showed tendency to be retained in *Stratum Corneum* after topical administration. For camptothecin, the partition in two models (*target* and *off-target* tissues) resulted in a higher value for *off-target* model. *LogM/W* of a newly-synthesized drug was determined in a biomimetic model of blood-brain barrier, in which the drug showed ability to reach its therapeutic target. The gastro-toxicity of Diclofenac was explained based on the interaction of this drug with relevant lipid membrane phases[4]. The results obtained highlighted the relevance of determining the *LogM/W* in biomimetic models to obtain reliable information in the early stages of drug development.

**Selective references:**

[1] X. Liu, B. Testa, A. Fahr, Lipophilicity and its relationship with passive drug permeation, Pharm Res 28(5) (2011) 962-77.
[2] G.P. van Balen, C. Martinet, G. Caron, G. Bouchard, M. Reist, P.A. Carrupt, R. Fruttero, A. Gasco, B. Testa, Liposome/water lipophilicity: methods, information content, and pharmaceutical applications, Med Res Rev 24(3) (2004) 299-324.
[3] E. Fernandes, T.B. Soares, H. Goncalves, M. Lucio, Spectroscopic Studies as a Toolbox for Biophysical and Chemical Characterization of Lipid-Based Nanotherapeutics, Front Chem 6 (2018) 323.
[4] E. Fernandes, T.B. Soares, H. Goncalves, S. Bernstorff, M.C.D. Real Oliveira, C.M. Lopes, M. Lucio, A Molecular Biophysical Approach to Diclofenac Topical Gastrointestinal Damage, Int J Mol Sci 19(11) (2018).

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