O 27

Ability of physicochemical systems to predict skin permeation of neutral compounds. A comparison study

Martí Rosés[a], Sara Soriano-Meseguer[a], Adriana Port[b], Elisabet Fuguet[a]

[a]*Departament de Química Analítica i Institut de Biomedicina de la Universitat de Barcelona (IBUB,) Barcelona, Spain*
[b]*Welab Barcelona, Parc Científic de Barcelona, Barcelona, Spain*

Direct measurement of biological properties such as blood-brain distribution, skin permeation or protein interaction is difficult and expensive. Surrogation of these properties by physico-chemical methods offers a simpler and lower-cost alternative to estimate the biological parameter by measuring an adequate parameter in a biomimetic physico-chemical system. However, selection of the appropriate physico-chemical system is not straightforward. It requires gathering and analysis of information about the biological process and the physico-chemical candidate systems. This information should be analysed by the same well-founded QSAR model to evaluate the similarity between the biological and the physico-chemical systems.

In this presentation, the comparison procedure is illustrated for the estimation of skin permeation of neutral compounds by several physico-chemical systems. Two parallel artificial membrane permeation assays (PAMPA) with different membranes, two biomimetic chromatography systems (a common reversed-phase and a liposome electrokinetic liquid chromatography systems) and the classical octanol-water partition systems have been characterized and compared to skin permeation.

The Linear-Free Energy Relationships (LFER) of Abraham has been used for characterization and comparison of the systems. This model characterizes the systems in terms of the solute-solvent interactions of creation of a cavity for the solute in the solvent, hydrogen bond donation from the solvent to the solute and from the solute to the solvent, dipolarity-polarizability, and "excess" polarizability, by multiple linear regression of the measured systems property (skin log K_p, PAMPA log P_0, HPLC retention log k, and octanol-water partition log $P_{o/w}$) against the well-known solute descriptors of volume V, hydrogen bond donor ability A, hydrogen bond acceptor ability B, dipolarity-polarizability S, and excess refractivity E.

The coefficients of the regression offer information about the complementary solvent properties and allow comparison between the ones of the different systems. Several tools, mostly based in Euclidean distance or angle between the correlation vectors, are used to evaluate the similarity of physico-chemical systems to skin permeation. They can also evaluate the degree of improvement of the biological/physico-chemical correlation by inclusion of additional descriptors, such as the common solute volume.

It is demonstrated that PAMPA systems should be able to estimate well skin permeation without need of additional descriptors, whereas biomimetic chromatography and octanol water systems require the volume correction factor. Finally, the assertiveness of the theoretical derivations is illustrated by the experimental correlations of skin permeation against the physico-chemical measurements with and without volume correction.