

# Measurement of Solvation Energies, the Key to Understand Partitioning and Passive Transport of Drugs

A. Bauer-Brandl<sup>a</sup>, G. Perlovich<sup>a,b</sup>

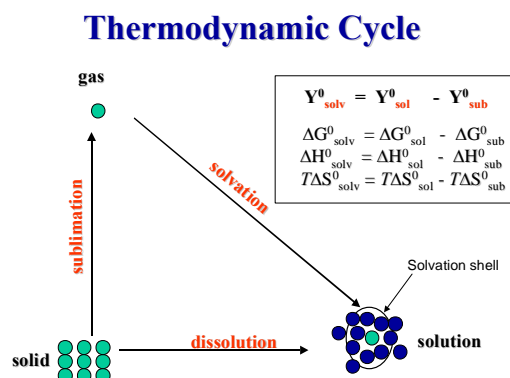
<sup>a</sup> Department of Pharmaceutics and Biopharmaceutics, Institute of Pharmacy, University of Tromsø, N-9037 Tromsø, Norway

<sup>b</sup> Institute of Solution Chemistry, Russian Academy of Sciences, 153045, Ivanovo, Russia

*in-vivo* effectiveness of many drug molecules is determined by their passive transport properties. Diffusion of the molecules in different physiological media, as well as permeation through lipid bilayers are rate-determining steps for uptake and distribution in the body, and consequently for their biopharmaceutical characteristics. The importance of the solvation shell of the drug molecules for the named processes - diffusion, distribution / partitioning - is widely acknowledged. Unfortunately, the interaction of single molecules with molecules of the solvent forming the solvation shell is experimentally not directly accessible, and up to now mostly molecular dynamic calculations have been used for description.

The present approach, however, combines independent classical experimental methods to quantify the standard energies of solvation by an absolute scale. Gibbs energy, and the enthalpic and entropic terms of the Gibbs energy of both dissolution and sublimation are measured. While the experimental approach to dissolution (isothermal saturated solubility; solution calorimetry) is standard, the sublimation experiment for drug substances needs special care. The transpiration method with a carrier gas is used in order to provide the mild conditions necessary to avoid chemical degradation of the compounds.

Using the thermodynamic cycle (Figure 1), the respective thermodynamic characteristics (Gibbs energy, enthalpy, entropy) of solvation of the drug molecules can be derived quantitatively. The goal is to correlate these values describing the solvation behaviour of the drug molecules with the diffusion and permeation properties as well as with biopharmaceutically relevant issues.



Non-steroidal anti-inflammatory drugs, NSAIDs, have been chosen as the object of study because they are of widely different molecular structure, and many of them have already been studied thoroughly regarding properties in the solid state and in solution. A set of aliphatic alcohols is being used as a model for compartments of different lipophilic / hydrophilic properties.

The thermodynamic parameters derived are discussed in connection to properties of dissolution and diffusion. Correlations between *in-vitro*- data (partitioning coefficient, enthalpy of solvation) with biopharmaceutically relevant characteristics (e.g. plasma half-life) are also discussed.

## References

- 1 Perlovich, G.L., Bauer-Brandl, A., Pharm. Res. 20 (2003), 471-478
- 2 Perlovich, G.L., Bauer-Brandl, A., Current Drug Delivery, 2004, 1, 213-226