437d Prediction of Equilibrium Partitioning of Pharmaceuticals in Octanol-Water and Water-Surfactant Systems

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Introduction

The study of partitioning of pharmaceuticals is of importance on the early stage of the drug design process. The drug partition coefficient correlates with the lipophilicity of the drug and is used for the estimation of bioaccumulation, in predicting the toxic effects of substances, and in modelling the distribution among environmental compartments [1]. In order to characterise the partitioning of potential drug candidates in the different media of the human body, the n-octanol/water- (K_{ow}) or the micelle/water- partition coefficient (K_{mw}) has to be known (measured or calculated). Today, two methods are mainly used for calculation: Quantitative Structure – Activity Relationships (QSAR) and Property-Property-Relationships (PPR) [2]. The parameters used in both methods are determined by regression of experimental data and thus strongly depend on the accuracy and type of the data used. Moreover, the parameters valid for one of the properties (e.g. K_{ow}) are to be reestimated in order to predict other ones (e.g. K_{mw}). Since the partition of drug is determined by the thermodynamic equilibrium (equality of the drug chemical potential in both phases), models based on estimation of the chemical potentials (or equivalently activity coefficients) can be principally applied to predict the partition of drug between polar (water) and apolar (n-octanol/micelle) phases. As most pharmaceuticals are poorly investigated in regard to their thermodynamic properties, predictive models for the calculation of partition coefficients are of special value. Present study deals with two models which are used to predict phase equilibria mainly in organic systems: the structure-interpolating UNIFAC model [3] and the a-priori predictive COSMO-RS model [4]. The goal is to demonstrate the applicability of both methods for predicting the partition coefficients of pharmaceuticals.

Methods

- UNIFAC

In the group-contribution method UNIFAC (Universal Quasi-Chemical Functional-Group Activity Coefficient), the molecules of a compound are represented by structural groups which contribute additively to the properties of the system. Thus, a great variety of molecules is represented by a limited number of structural groups. The parameters of more than 50 groups (the number depends on the model modification) are tabulated (group-interaction parameters are estimated from experimental data but not obligatory from those for the drug-containing systems under study). The applicability of the modified UNIFAC (Dortmund) has been already demonstrated [5] for calculation of K_{ow} values. To consider micellar systems, we propose to use the original version of the UNIFAC model [3,6] and to introduce additionally the interfacial contribution to the activity coefficient in terms of the Gibbs-Thompson theory.

- COSMO-RS

The COSMO-RS model (Conductor like Screening Model for Real Solvents) allows an *a priori* prediction of thermodynamic properties such as activity coefficients based only on the molecular structure.

In the COSMO model [7], the solute molecule is considered to be embedded in a cavity surrounded by a virtual conductor. The energy, the geometry, and the screening charge density *s* on the surface of a solute are calculated. The transfer from the state of the molecule embedded in a virtual conductor to the real solvent is done by applying the COSMO-RS concept [4]. From the information on the screening charge density, the chemical potential of a solute is calculated using statistical thermodynamics. The activity coefficients and the partition coefficient K are directly obtained from the chemical potential of a solute in each phase.

Results

· Partition Coefficients of drugs

Figure 1 shows the potential of the COSMO-RS model in predicting the n-octanol/water partition coefficients of 3 ampicillin derivatives as an example. As seen, the results of calculations agree well with the experimental data [8].

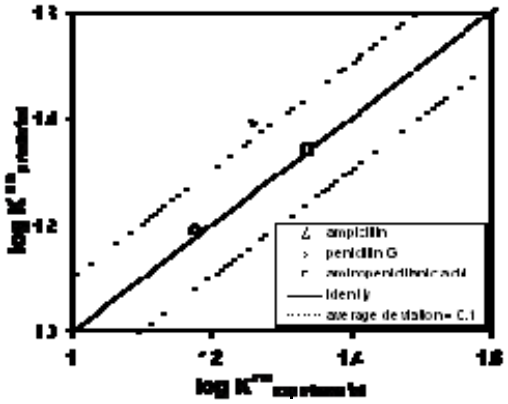


Figure 1 Comparison between experimental and with COSMO-RS predicted log K^{OW} of ampicillin, penicillin G and aminopenicillanic acid at 298.15 K.

· Partition of model solutes in micellar systems

Figure 2 demonstrates the capability of the chosen models to predict the partitioning of one of the model solutes (p-xylene, nonpolar and structurally simple substance) between micelles composed of the nonionic surfactant (Lutensol FSA10; CH_3-$(CH_2)_7$-CH=CH-$(CH_2)_7$-CO-NH-$(CH_2CH_2O)_{10}$H; alkyl amide used as a cleaning agent) and aqueous surroundings.

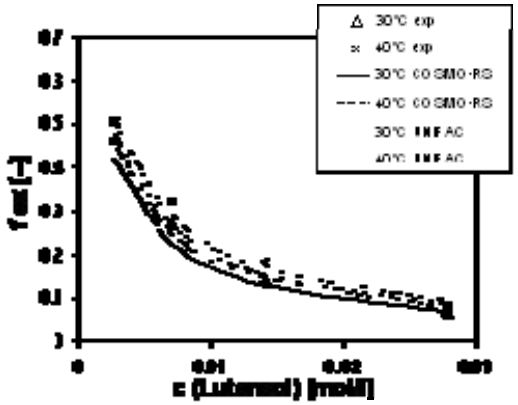
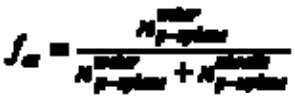


Figure 2. Fraction of p-xylene presented in the aqueous media, f_{ex}, vs total surfactant concentration in the system (experimental data from [9])



Conclusion

The applicability of COSMO-RS and UNIFAC models for prediction of octanol/water and micelle/water- partition coefficients has been investigated. The COSMO-RS model has been shown to predict quantititavely octanol/water partition coefficients for a number of pharmaceuticals. It is worth to note that the calculations are made on the basis of the molecular structure only. The capability of both the UNIFAC and COSMO-RS models to calculate partitioning in micellar systems has been demonstrated for model systems such as organic solute/nonionic surfactant/water. The results of calculations are in agreement with the experimental data. Introduction of the interfacial contribution to the solute chemical potential in micelle phase in the frame of the UNIFAC model leads to a better consistency. Both models promise a high potential when predicting the partitioning of pharmaceuticals in aggregated systems (micelles and liposomes).

References

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