Chromatographic Hydrophobicity Index (CHI)

In reversed phase liquid chromatography, the lipophilicity of compounds governs their retention. The properly transformed retention data should reveal the lipophilicity of the compounds. Valko et al. (1997) converted a fast gradient reversed-phase retention time to a Chromatographic Hydrophobicity Index (CHI) using a set of test compounds to calibrate the HPLC system. CHI values have been found to correlate well with the log *D* well, suggesting that the CHI can serve as an alternative to log *P* or log *D*. Because no actual concentration needs to be determined, and organic solvents can be used to dissolve the compounds, the method is particularly suitable for compounds with poor aqueous solubility.

Partition Coefficient Prediction

Predictive software for the determination of log *P* is also available from *Advanced Chemistry Development* (ACD) (1998). ACD/log *P* calculates octanol/water partition coefficients for the neutral form of the molecule using a structure fragment approach with parameters derived from a large database. The accuracy of the predictive calculations is usually better than ±0.3 log *P* units except for very complex structures or poorly -characterized substituents, where the accuracy is usually better than ±0.5 log *P* units. In studies on 25 drugs (Berger et al. 1997), log *P* data generated by the shake-flask method, Sirius potentiometric method and computational (ACD) methods matched very well.

Choice of Partitioning Solvent

As mentioned earlier, one of the most important uses of log *P*/log *D* is to correlate to the rate and extent of drug absorption as well as the biological response by offering a prediction of the tendency for a drug to move from an aqueous compartment into a biological membrane. Traditionally, the octanol–water partition coefficient was the most widely used to study the lipophilic character of drug molecules. In the octanol–water system, the partitioning of drug molecules in the neutral form is favored relative to the ionized form. In the membrane-water system, it has been found that partitioning of the ionized species is significantly enhanced over that shown in the octanol–water system (Miyazaki et al. 1992, Austin et al. 1995, Hellwich and Schubert 1995). Clearly, the octanol–water system is inadequate to account for certain critical characteristics of biological membranes, which are comprised of lipid bilayers consisting of amphipathic groups having strong electrostatic interactions (Schwarz 1996).

Rogers and Choi (1993) have shown that partition coefficients in liposome-water systems outperformed the oactanol-water system for the prediction of biological activities of certain classes of drugs. Dialysis (Formelova et al. 1991, Kuhnvelten 1991, Pauletti and Wunderli-Allenspach 1994) and ultrafiltration (Kuhnvelten 1991, Austin et al. 1995) methods have been used to measure liposomal membrane-water partition coefficients. Avdeef et al. (1998) successfully applied the pH-metric technique, an efficient and accurate way to determine liposomal membrane-water partition coefficients for ionizable drugs, and the results are consistent with those obtained from the ultrafiltration and dialysis methods. Despite the limitation of octanol as a solvent for predicting membrane partitioning, because of the enormous body of data that already exists and the ease of generating data, it undoubtedly remains the partitioning solvent of choice.

Caco-2 Measurement

The permeability of a drug can be determined in the Caco-2 Transwell polycarbonate filter cell culture system. The dose solution is prepared by dissolving the drug in DMSO and diluting the HBSS/HEPES to a suitable drug concentration. Sometimes, suitable amount of Tween 80 is added to the dose solution to ensure that the drug does not precipitate upon further dilution in the Caco-2 donor