For Sch 56592, 1% Povidone could not only improve its solubility, but also improve its flux through Caco-2 membrane by 40%. Even though some other solubilizing excipients could also solubilize Sch 56592, they either did not change or even decrease its flux through the membrane. For Sch-X, 1% povidone, pluronic F68, Gelucire 44/14, and 3:2 propylene glycol/Tween-80 could significantly improve its solubility as well it flux through the membrane. The solubility of Sch-Y could be enhanced by quite a few solubilizing excipients, but only 1% pluronic F68 and PEG300 could increase its flux by 35%–50%. The study shows that for different drugs, solubilizing excipients may not enhance flux across Caco-2 membrane to the same extent as solubility enhancement, and some even decreased drug permeability. The effects of solubilizing excipients on oral drug adsorption will be determined by their contribution on both soluble drug concentration and transport parameters. Therefore, for insoluble drugs, solubilizing excipients should be carefully evaluated on drug permeation as well for developing bioavailable formulations.

MEASUREMENT OF PARTITION COEFFICIENTS

The methods commonly used for the measurement of partition coefficients include the traditional shake-flask method, HPLC, filter-probe, and pH-metric techniques (Dunn III et al. 1986, Avdeef 1993). Dearden and Bresnen (1988) gave *GLP* recommendations on experimental procedures. Hersey et al. (1989) presented a method selection guide. Additionally, several methods are available for partition coefficient calculations (Lipinski et al. 2012).

Shake Flask Method

The shake flask method is the most commonly used method for the measurement of partition coefficients (Leo et al. 1971). However, for many insoluble compounds, the solubility in the aqueous phase may be too low to be accurately determined. In these cases, an alternative method needs to be applied.

Potentiometric Titration

The determination of partition coefficients by the potentiometric method is part of the function of the Sirus PCA 101 (Avdeef 1993). Typically, a preacidified solution of a weak acid is alkalimetrically titrated to some appropriately high pH; the partition solvent such as octanol is then added, and the dual-solvent mixture is acidimetrically titrated back to the starting pH. Analysis of the two titration curves will yield two pK_as: pK_a and poK_a, where poK_a is the apparent constant derived from the octanol-containing segment of data. The partition coefficient is calculated from the following equations:

$$\text{For an acid: } \mathrm{P_{HA}} = \frac{(10^{+(\mathrm{po}K_a - \mathrm{p}K_a)} - 1)}{r} \tag{4.36}$$

$$\text{For a base: } \mathrm{P_{B}} = \frac{(10^{-(\mathrm{po}K_a - \mathrm{p}K_a)} - 1)}{r} \tag{4.37}$$

where

$$r = \frac{\text{Volume of the organic phase}}{\text{Volume of the aqueous phase}} \tag{4.38}$$

The converse of this technique is the partition-derived pK_a determination which may be very useful for the pK_a estimation for insoluble compounds. If log P data can be obtained by some alternative methods, a titration of a weak acid in the presence of octanol will give the apparent pK_a, poK_a. Equations 4.36 and 4.37 can be used to calculate the aqueous pK_a.