by *Advanced Chemistry Development* (1998), in which ACD/pK_a is a program that calculates pK_a values at 25°C and zero ionic strength in aqueous solution. It uses a structure fragment approach and takes into account electronic, steric, charge, tautomeric, vinylogy, and covalent hydration effects. Each calculation is provided with both its 95% confidence limits and a detailed report of how it has been carried out, including the Hammett-type equation(s), substituent constants, and literature references where available. The parameters on which the pK_a calculation is based are drawn from over 8900 structures in the scientific literature with over 23,000 experimental values at different temperatures and ionic strengths in purely aqueous solutions. The accuracy of calculations is usually better than 0.2 pK_a units except for very complex structures or poorly characterized substituents, where the accuracy is usually better than 0.5 pK_a units. Berger et al. (1997) determined the pK_a values for a total of 25 drugs representing a range of structures and liquid-phase properties using both experimental (potentiometric titration) and computational (ACD) methods, and most pK_a values fell well within the ±0.5 pK_a unit range.

LIPOPHILICTY AND PERMEABILITY

Lipophilicity of one drug is generally measured by checking its distribution between an aqueous and non-polar organic phase like *n*-octanol. The partition coefficient ($P_{o/w}$), a measurement of a drug's lipophilicity, is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$$P_{o/w} = \left(\frac{C_{oil}}{C_{water}} \right) \text{equilibrium} \tag{4.35}$$

It should be noted that the partition coefficient is a constant. The apparent partition coefficient of the protolytic forms of the drug substance, which obviously can vary as a function of pH, is defined as the distribution coefficient ($D_{o/w}$). Both log *P* and log *D* have been used widely as indications of lipophilicity of one drug.

Lipophilicity of one drug will affect its distribution in lipid membranes, protein binding, body fluids, and so on, thus affect many biopharmaceutical properties such as ADME (adsorption, distribution, metabolism, and excretion), plasma protein binding, toxicity, activity, plasma protein binding (Suzuki et al. 1970, Dressman et al. 1984, Wells 1988). Although partition coefficient/distribution coefficient data alone do not provide an understanding of *in vivo* absorption, they do provide a means of characterizing the lipophilic/hydrophilic nature of a drug. In general, log *D* of one drug ranges from 0.5 to 3 suggests that the drug has moderate lipophilicity and may have suitable GI tract adsorption (Chemical Sciences 2001).

Permeability of drugs is one of the most important biopharmaceutical properties (Varma et al. 2012, Hermens et al. 2013). For any drug by oral drug delivery systems, in order to reach systemic circulation from gastrointestinal (GI) tract, the drug must permeate the GI cellular barrier. After drug enters systemic circulation, some drugs still need to permeate through cell membrane to have its therapeutic effects. Permeation can occur through different routes, include active transport, efflux, and paracellular diffusion. However, most drugs mainly permeate through passive transcellular diffusion. To assess the passive diffusion of drugs, different artificial membranes, like phospholipids membrane, have been designed to measure permeation across the membrane from the donor side to the acceptor side. In pharmaceutical industry, the most commonly used methods in permeability measurements are Caco-2 cell membrane measurement and rat jejunal perfusion.

Considering the low solubility of those insoluble drugs, solubilizing excipients are often used to increase the drug concentration in permeability measurement. Sometimes, those solubilizing excipients may affect the drug permeability as well. Saha and Kou (2000) studied the effects of solubilizing excipients on Caco-2 transport for three poorly water-soluble compounds, Sch 56592, Sch-X, and Sch-Y. Caco-2 measurement showed that all three compounds have good permeability.