3 Prediction of Solubility

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INTRODUCTION

Solubility has been conventionally attributed to the maximum thermodynamic activity of a solute (Higuchi, 1977, 1982). In pharmaceutical science, solubility is commonly related to the bioavailability of the compound of interest, especially for poorly soluble compounds. In general, a higher bioavailability is easier to achieve for a soluble compound than for an insoluble one. This relationship, together with the intestinal permeability of drug substances, has been extended to form the basis of the scientific framework of the Biopharmaceutics Classification System (BCS) to classify drug substances so as to set expectations for the *in vivo* performance of drug products (Amidon et al., 1995; FDA, 2000). According to the Food and Drug Administration (FDA) BCS guidance (FDA, 2000), solubility may be used as an important criterion to justify the waiver of bioequivalence study (BE) for drug product if the drug substance has high intestinal permeability and the product has a rapid *in vitro* dissolution rate. A high solubility and a successful waiver of BE study for any significant post-approval changes will lead to a significant reduction of regulatory burden for the pharmaceutical industry and FDA. A significant saving may also be realized for development of new chemical entities (NCEs), if the NCEs have adequate water solubility and do not require any special solubilization techniques to achieve some desired bioavailability, leading to a reduced cost for product development and a reduced time for drug product to reach patients. It is thus apparent that being able to predict the solubility is important in the design and development of pharmaceuticals.

Solubility can be studied by thermodynamic and structure–solubility relationship approaches. The thermodynamic approach solves solubility problems using exact theoretical equations to relate the activity of a chemical in solution to the Gibb's free-energy change for the dissolution process. Similar to many other material equilibrium processes, the dissolution process and hence the equilibrium solubility are governed by the Gibb's free-energy change for the process. For an isothermal process under constant pressure, the partial molal Gibb's free-energy change for a dissolution process, $\Delta\bar{G}_{d,2}$, can be written by the following equation:

$$\Delta\bar{G}_{d,2} = \Delta\bar{H}_{d,2} - T\Delta\bar{S}_{d,2} \tag{3.1}$$