Solubility; still a challenging subject in pharmaceutical sciences

Solubility of a drug/drug candidate is one of the most important required physico-chemical properties in pharmaceutical area and nearly 40% of drug candidates fail to proceed to the higher trial phases of new drug development process because of their poor solubility. The commonly used method is to determine the experimental values of either thermodynamic or kinetic solubility. Numerous efforts were made to develop predictive tools for replacing the time consuming and costly experimental methods. The oldest rule in this area is “like dissolves like” which is translated as the Hildebrand solubility approach in which the maximum solubility of a solute is observed when the solubility parameters of the solvent ($\delta_1$) and solute ($\delta_2$) are the same or ($\delta_1 - \delta_2$)$^2=0$. In 1916, Prof. Joel H. Hildebrand (1881-1983) wrote: “There is scarcely anything more important for a chemist than a knowledge of solubilities, but unfortunately he finds it more difficult to predict how soluble a substance will be in a given solvent than it is to predict almost any other important property.” A simple search from databases like Scopus® shows that the first article including “solubility” in its title was published in 1831 and more than 21500 articles were reported during last 179 years, revealing the position of solubility investigations in the scientific community. The Hildebrand solubility approach is applicable only to the solubility of non-polar solutes in non-polar solvents and is not applicable to the pharmaceutical systems. Its extended versions were reported to provide better predictions for pharmaceutical systems including methods based on partial solubility parameters developed by Prof. Alfred N. Martin (1919-2003) and his co-workers. The linear solvation energy relationship models proposed by Prof. Michael H. Abraham are the most accurate model to predict the solubility of a solute in monosolvent systems. The Abraham solvent coefficients which derived from experimental solubility data are available for a limited number of solvents, however, they are not available for some pharmaceutically relevant cosolvents like propylene glycol or polyethylene glycols. A trained version of Abraham solvation model was reported to predict the aqueous solubility of drug/drug like molecules using Abraham solute parameters computed by Pharma-Algorithm. The model provides solubility values with relatively high prediction error, however, it possesses an advantage of in silico prediction of aqueous solubility of drugs and no experimental data is required as input values. The Abraham model was also applied to other physico-chemical and biological properties of drugs. Another predictive model was developed by Prof. Samuel H. Yalkowsky is the general solubility equation which requires the melting point and logP of the drug as input data. The logP values could be computed using software such as ACD with reasonable accuracy. There is also a number of software which could be used to predict the aqueous solubility of drugs. “Handbook of Aqueous Solubility Data” reports the published data and provides a useful database for developing more accurate quantitative structure property relationships.

When aqueous solubility of a drug/drug candidate is low, numerous methods could be used to enhance the solubility including mixing a permissible organic solvent (or cosolvency), using complexing agents such as cyclodextrins, addition of surface active agents etc. Among these methods, the cosolvency is the more common and effective method to increase the solubility of a low soluble drug. Addition of a pharmaceutical cosolvent possibly is associated with side effects, therefore the cosolvent concentration should be kept as low as possible. It also may affect the chemical stability of a drug in the liquid pharmaceutical formulation. In addition to the collected experimental solubility data of drug or drug related compounds in mixed solvents and also non-aqueous organic solvents in “Handbook of Solubility Data for Pharmaceuticals”, a number of mathematical models were reported to simulate the solubility data in mixed solvent systems. Prof. Anthony N. Paruta and co-workers correlated the solubility of drugs to the dielectric constant of the mixed solvent system in 1964. The log-linear model of Prof. Yalkowsky was the next model providing a simple equation to calculate the solubility of drugs in water + cosolvent mixtures and the constants of this model were reported for most of pharmaceutically relevant cosolvents.
The model requires experimental aqueous solubility data along with its logP as input data. The extended Hildebrand solubility approach of Prof. Martin and co-workers and further extensions of this approach made by Prof. Pilar Bustamante and her co-workers were the other versions of the cosolvency models. The excess free energy models of Prof. Gordon L Amidon and his colleagues was provided more accurate predictions by including experimental solubility data in monosolvents and also molar volumes of water, cosolvent and the drug. Prof. Kenneth A. Connors and his co-workers proposed a phenomenological model derived from the free energy changes of the processes involved in the dissolution of a solute in the solvent system in 1992. The combined nearly ideal binary solvent / Redlich – Kister equation was derived by Prof. William E. Acree Jr. in 1992 and provided the most accurate solubility calculations in comparison with the above mentioned models. The general cosolvency model was reported by Prof. Mohammad Barzegar-Jalali and his co-workers in 1997, which is derived from above mentioned models and converted all the models as a polynomial function of the cosolvent fraction. During last ten years, the combined nearly ideal binary solvent / Redlich – Kister equation was extended to represent solvent composition and temperature effects and applied to other physico-chemical properties of mixed solvent systems and re-named as the Jouyban-Acree model. The model provided reasonably accurate predictions employing experimental solubility data in monosolvents and a number of data in mixed solvents at various temperatures. Its combined versions with the Abraham solvation parameters provided generally trained version model to predict the solubility of drugs in water + cosolvent mixtures. Although this version reduced the prediction error level to ~ 40%, however, more efforts are required to provide more accurate predictive models. It should be noticed that to provide a good model, accurate and precise database of solubilities of drugs in water + cosolvents mixtures are required and in collecting the experimental solubility data, a number of error sources producing inaccurate data should be considered. The mains are; the impurity of drug and cosolvents, equilibration time for reaching the saturated solutions, existence of polymorphic or solvated forms of drugs, enantiomeric forms of drugs, any systematic error by the investigator such as using non-calibrated analytical instruments etc.

Although considerable progress were made in computer sciences and sophisticated software and powerful hardware are available to estimate the physico-chemical properties, it must be frankly stated that we are still not able to predict the solubility of drugs in water, organic solvents and/or mixed solvent systems with an acceptable prediction error and more experimental and computational efforts are demanded. To achieve this valuable task, more comprehensive solubility database in mono- and mixed solvents should be generated by the research groups around the world and also more comprehensive and preferably theoretical predictive tools should be provided.

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