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Experimental and Computational Methods Pertaining to Drug Solubility

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1. Introduction

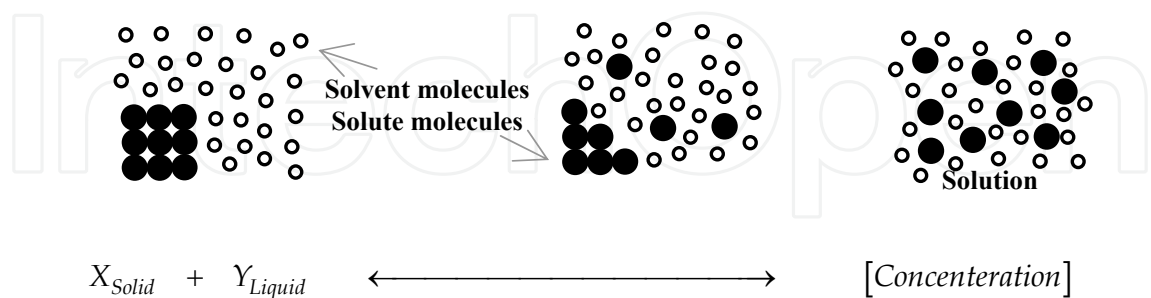
Solubility of a drug is one of its important physico-chemical properties. More attention has been paid to the aqueous solubility since water is the unique solvent of biological systems. It is obvious that a drug should be reached to its receptors in the body through the aqueous and non-aqueous media. The chance of a low water soluble drug to be appeared in the market place is very low and nearly 40 % of the drug candidates fail to reach higher phases of the drug trials simply because of their low water solubility. The solubility in non-aqueous solvents is not too important from clinical viewpoint however these solubilities play curious roles in drug discovery and development investigations. Most of drugs are synthesized in non-aqueous media and/or extracted from natural sources using non-aqueous extracting solvents. Different polymorphs of some drugs could be produced from their crystallization using organic solvents.

There are various methods for solubility determination of drugs which is discussed in this chapter. The experimental determination is tedious and time-consuming process and sometimes there is restrictions in the availability of enough amount of a drug candidate to be used in the solubility measurements, especially in the early stages of drug discovery investigations in which only small amount of a drug is synthesized/extracted and large number of preliminary biological tests should be carried out. To cover this limitation, and in order to provide a faster and easier tool, mathematical models have been developed to correlate/predict the solubility of drugs. These models are discussed in this chapter to provide an overall view for a pharmaceutical scientist who is working in the research and development department of a company and/or a research laboratory within academia. In addition to the accurate calculations which are expected from these models, the simplicity of the required computations is another parameter which should be taken into account, since more complex computations did not attract more attention in the pharmaceutical industry.

1.1 Solubility and dissolution

When talking about solubility, there are two concepts which might be confused with each other: solubility and dissolution. The term solution (i.e. thermodynamic solution) is used to define the state which is thermodynamically stable and shows the neat result of an

equilibrium between a solute (the compound which is going to be dispersed molecularly in another medium which is called solvent) and its dissolved form in the medium. The dissolving process is the migration of the molecules of the solute to the solvent medium and makes the solution which after reaching a steady state is called homogenous solution and can be represented by the following equilibrium:



How much a solute is molecularly dispersed in the solvent is called solubility and the rate of dissolving is called dissolution. Hence, the solubility value is a thermodynamic property while the dissolution rate is a kinetic one. In other words, time has no effect on solubility value and is not important in its related subjects, but it is important in dissolution related subjects. The solubility is important in stable forms including liquid formulations and dissolution is important in transient states including the release of the drug from its formulation to biological fluids and permeability (Sinko and Martin, 2006). In pharmaceutical sciences, especially in formulation, designing a stable liquid formulation requires the knowledge on the solubility value and an effective drug delivery to the body mostly depends on the dissolution rate which is affected by the solubility (Allen et al., 2006). However, they both affect each other based on Noyes-Whitney equation (Sinko and Martin, 2006):

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

(1)

where dW/dt is the rate of dissolution, A is the surface area of the solid which is in direct contact with the molecules of the solvents, C is the concentration of the solute in the medium (dissolved amount), C_s is the concentration of the solute in the diffusion layer, D is the diffusion coefficient, and L is the thickness of the diffusion layer. Based on the discussed topics, solubility and dissolution are in relation with each other, but not the same. So, they must not be used in place of each other as the consequences can be awful! For example, a drug substance might be highly soluble, but dissolves slowly (or vice versa). So, in the formulation of such compounds, the difference between solubility and dissolution must be considered.

1.2 Solubility of base form of drugs

The apparent solubility (S_{App}) of a weak electrolyte is expressed by:

$$S_{App} = S_M + S_I$$

(2)

in which S_M is the molecular form of the drug and S_I is the ionized form of the drug in the solution. For strong electrolytes, S_I is predominant whereas for nonelectrolytes S_M is the

only form of the solubilized drug in the solution. S_M is also called intrinsic solubility or S_0 . In early stages of drug discovery, only small amount of the new drug is available and its purity is not assured. In this stage, the solubility determination in acidic and/or basic solutions could be used in practice. Increased apparent solubility in acidic or basic medium reveals that the new drug is a basic or an acidic solute. No increase in the solubility means that the drug is a nonelectrolyte. Increased solubility in both acidic and basic media indicates either zwitterionic or amphoteric behaviour. The intrinsic solubility of a drug could be determined from apparent solubility data at various pH values. When the purity of a drug candidate is not assured, a phase-solubility diagram, i.e. the solubility at different solute:solvent ratios, is recommended. In this diagram, the co-solute effect (self association, complexation, solubilization) increases the solubility and the common ion effect decreases the solubility and no change in the solubility might mean that drug is pure and no interaction exists.

1.3 Solubility of salt form of drugs

Salt formation of weak acidic or basic drugs is one of their solubility increasing methods since the ionized species have greater solubility in water and other polar solvents and a number of drugs are marketed as their salt forms. The most common salts used for salt formation of acidic drugs are sodium, potassium, calcium and zinc and those for basic drugs are hydrochloride, sulphate, mesylate, maleate, phosphate, tartrate, citrate and besylate (Wells, 1988). Different salts of a given drug possess various solubilities. As an example, the solubility of lamotrigine with the counterions of tartrate, saccharinate, succinate and fumarate are 2.63, 1.37, 0.61 and 0.43 millimole per liter (Galcerà and Molins, 2009). The selection of the salt of a drug is mainly carried out by trial and error basis considering practical issues such as cost of raw materials, ease of crystallization, percent yield, thermal stability and hygroscopicity of the resulting salt. Black et al. (2007) investigated the salt formation of 17 salt forms of ephedrine and reported their physicochemical properties and tried to develop a relationship between these properties which was not successful. Any model representing the properties of salt forms of drugs is a highly in demand subject in the pharmaceutical industry. As an example, the relation between the dielectric constant of the solvent and the solubility of drugs in their salt form, can be mentioned (Fakhree et al., 2010).

1.4 Solubility of pharmaceutical macromolecules

Polymers and macromolecules are important parts of drug design and development. The emerging technology of proteins, peptides, DNA and RNA sequences as pharmaceutical active ingredients makes it necessary for consideration of their physicochemical properties in pharmaceutical sciences, including solubility. For the beginning, in terms of macromolecules, it is better to use dispersion versus solubility in a medium and this makes a difference between their solubility in comparison with small organic molecules. The dispersion of the macromolecules in the solution results in formation of new properties for the solution such as increase in viscosity, light scattering, molecular network formation (e.g. gel) etc (Sinko and Martin, 2006). Another important note about macromolecules, is the fact that they have been produced in an aqueous medium and have philia to watery media (not always, but in most of the cases). Hence, they are sensitive to presence of organic solvents and might be precipitated by addition of the organic solvents (unlike small organic nonelectrolyte molecules which dissolve in organic media more than aqueous solutions).

The solubility of proteins is influenced by the ratio of the hydrophobic and hydrophilic residues of amino acids and their arrangement in the final structure of the protein (Bolen, 2004). For example, globular proteins have hydrophobic residues in their core and hydrophilic residues in their surface. It is also affected by the pH and ionic strength of the water, presence of organic solvents and other polymers (Burgess, 2009). When talking about the solubility of proteins, there are different kinds of low solubility for the proteins:

1. in-vitro low solubility due to structural properties of the protein (hydrophobic residues),
2. in-vivo low solubility due to over expression of the protein in an organism (*E. coli*),
3. amyloid formation which results in aggregation of the proteins because of their hydrophobic, residue charge, and β -sheets in the structure, and
4. low solubility due to conformational changes (Trevino et al., 2008).

For increasing a protein's aqueous solubility, one of the strategies is addition of additives such as L-arginine and L-glutamic acids. Fusion of peptides and proteins is another method which is addition of a solubilizing sequence of amino acids or protein to the structure of the low soluble protein. Mutation in the hydrophobic amino acids sequences to hydrophilic ones is another strategy. However, this might not work in all of the cases (Trevino et al., 2008). Another approach is screening to find a more soluble homologue of that protein in other organisms (Waldo, 2003).

1.5 Solubility of drugs in biological fluids

For understanding the dissolution of a drug in the human body fluids, it is crucial to focus on the solubility of drugs in more realistic environment and to acquire larger amount of experimental data for simulating the solubility at different pHs, in the presence of bile salts etc which exists in the real solubilization media within human body. Solubility data of drugs in biorelevant media are increasingly required in early phases of drug discovery to predict the bioavailability of a drug after oral administration.

1.6 Solubility modifications

Solubility modification of drugs is required in separation, purification, analysis and formulation investigations and different methods are used to achieve the increased/decreased solubility values.

1.6.1 Solubility increasing

Several methods have been used to enhance the aqueous solubility of drugs including cosolvency, hydrotropism, complexation, ionisation, use of the surface active agents, crystal structure modifications and addition of ionic liquids. These methods have been discussed in details in the literature (Myrdal and Yalkowsky, 1998). Mixing a permissible non-toxic organic solvent with water, i.e. cosolvency, is the most common and feasible technique to enhance the aqueous solubility of drugs. The common cosolvents which, are used in the pharmaceutical industry are ethanol, propylene glycol, glycerine, glycofural, polyethylene glycols (mainly 200, 300 and 400), N,N-dimethyl acetamide, dimethyl sulfoxide, 2-propanol, dimethyl isosorbide, N-methyl 2-pyrrolidone (NMP) and room temperature ionic liquids (Rubino, 1990; Mizucci et al., 2008; Jouyban et al., 2010a). Their applications and possible side effects have been discussed in the literature (Spiegel and Noseworthy, 1963; Tsai et al., 1986; Patel et al., 1986; Golightly et al., 1988; Rubino, 1990). Hydrotropes are a class of

amphiphilic molecules that cannot form organized structures, such as micelles, in water but they increase the aqueous solubility of drugs. Often strong synergistic effects are observed when hydrotropes are added to aqueous surfactant or polymer solutions. Caffeine and nicotinamide are well known hydrotropic agents and their ability to solubilize a wide variety of therapeutic drugs including riboflavin (Lim and Go, 2000) has been demonstrated. Complexation of drugs is another solubilization technique and there are a number of reports on complexation of drugs by cyclodextrins. Ionization is applicable for weak electrolytes and the solubility of some drugs could be increased by changing pH of the solution.

1.6.2 Solubility decreasing

In precipitation and crystallization processes as a part of extraction and purification of the pharmaceutically related compounds, lowering the solubility is desirable. Lowering the solubility for pharmaceutical compounds might include using of temperature alteration, addition of antisolvent, using of a low soluble salt or ester of the drug, and producing low soluble polymorphs (Blagden et al., 2007; Widenski et al., 2009).

Precipitation or crystallization both can be used in this regard depending on the rate of solubility decreasing. If it is happened quickly, then the solid state might be in amorphous form and the process called precipitation. If the lowering of solubility takes place in a controlled way that crystal growth can happen, then the process called crystallization. Precipitation of proteins and macromolecules such as DNA and RNA are other examples for this kind of solubility modification. In protein biosynthesis and extraction, different methods of desolubilization are used which include: salting out, isoelectric point precipitation, precipitation with organic solvents, addition of non-ionic hydrophilic polymers, flocculation by polyelectrolytes, and addition of polyvalent metallic ions (Burgess, 2009). Another reason making it desirable to precipitate macromolecules such as proteins, DNA, and RNA is pre-treatment of biological analytes before starting analyses.

Recrystallization is another process which is used in pharmaceutical sciences and means to dissolve a compound in a medium, and by modifying the physicochemical conditions made the dissolved compound to crystallize again. This technique is widely used in crystal engineering technology which can produce amorphous, different polymorphs, and pseudopolymorphs of a drug (Blagden et al., 2007). This is important in modification of pharmaceutically interested physicochemical properties such as compressibility in formulation process, size of particles, dissolution rate, as well as solubility (Allen et al., 2006; Gibaldi et al., 2007).

The above mentioned processes are related to preformulation processes. In formulation of pharmaceutical active ingredients the desire for lowering solubility can be seen in designing of sustained release and depot dosage forms or drug delivery systems (Allen et al., 2006; Gibaldi et al., 2007). For making a sustained release dosage form of a drug, different formulation techniques such as use of polymeric matrix, osmotic pumps, and crystallization of a poorly water soluble compound are used. For designing a depot drug delivery system, possible solutions include: use of low soluble salts or esters of a drug (e.g. methylprednisolone acetate), addition of additives (e.g. zinc and insulin), very concentrated non-aqueous solutions of drug (e.g. Leuprolide and NMP), and depot dosage forms (e.g. implants of low soluble compounds such as sex hormones) (Strickley, 2004; Allen et al., 2006; Gibaldi et al., 2007).

Also low solubility is useful when stability of a pharmaceutical compound is low in its solubilized form (Sinko and Martin, 2006). Hence, suspension formulations (i.e. ready to use and lyophilized powder for suspension preparation) might be a useful strategy.

In the recent decade, emerging technologies such as micro-formulation, micro-encapsulation, nano-formulation, and nano-encapsulation are using solubility decreasing principals as a part of their processes. This is usually done by addition of antisolvent and fine particle stabilizers to gain a suspension with micro/nano-sized particles.

2. Experimental methods for determination of solubility

The solubility of a drug could be measured experimentally using two procedures, namely the thermodynamic and kinetic solubility methods. The thermodynamic solubility determination methods are not feasible at the early discovery stage because of the large sample requirement, low throughput and laborious sample preparation. The kinetic solubility determinations could be used as an alternative method at this stage.

2.1 Determination of thermodynamic solubility

Solubility determination of drugs in a liquid could be classified as analytical and synthetic methods. The main advantage of the analytical (shake flask) method is the possibility of measuring a large number of samples simultaneously however this method is tedious and time-consuming.

2.1.1 Shake flask method

The shake-flask method of Higuchi and Connors (1965) is the most reliable method for low soluble compounds and widely used solubility measurement method. In this method, an excess amount of drug is added to the solubility medium. The added amount should be enough to make a saturated solution in equilibrium with the solid phase. In case of acidic or basic drugs dissolved in an un-buffered solubility medium, further addition of the solid could change pH of the solution and consequently the solubility of the drug (Wang et al., 2002; Kawakami et al., 2005; Jouyban and Soltanpour, 2010). Depending on the dissolution rate and type of agitation used, the equilibration time between the dissolved drug and the excess solid could be varied. Equilibration is often achieved within 24 hours. To ensure the equilibration condition, the dissolution profile of drug should be investigated. The shortest time needed for reaching the plateau of drug concentration against time could be considered as a suitable equilibration time. Any significant variation on dissolution profile after reaching the equilibration should be inspected, since there are a number of possibilities including degradation of the drug and also its polymorphic transformation. Both these affect the solubility values of a drug dissolved in the dissolution media. Heating, vortexing or sonicating the sample prior to equilibration could shorten the equilibration time. To overcome the poor wettability of low soluble drugs, one may use small glass microspheres or sonication. Then the two phases, solid and solution phases, are separated using two common methods of filtration and/or centrifugation. Filtration is the easiest method, however, the possible sorption of the solute on the filter should be considered as a source of error in solubility determination, especially for very low soluble drugs. Pre-rinsing the filter with the saturated solution could reduce the sorption of the solute on the filter by saturating the adsorption sites. Centrifugation or ultra-centrifugation is preferred in some cases, and

the higher viscosity of the saturated solutions, e.g. in mixed solvents, should be kept in mind as a limitation. A combination of filtration and centrifugation is also could be used. The UV spectrophotometric analysis is the most common and the easiest analytical method. The next is the HPLC methods both in isocratic and gradient elution modes. The HPLC analysis could also detect the possible impurities or degradation products if a highly selective method was used. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) of the residual solid separated from the saturated solution confirm the possible solid phase transformations during equilibration.

2.1.2 Synthetic method

The synthetic method (Hankinson and Thompson, 1965; Ren et al., 2005; Yang et al., 2008; Yu et al., 2009) which is so called laser monitoring technique (Li et al., 2006), last crystal disappearance method (Hao et al., 2005) and dynamic method (Peisheng and Qing, 2001; Weiwei et al., 2007; Wang et al., 2008) is based on disappearance of the solid drug (from the mixture of solvent and drug) monitored by a laser beam. The history of this method backs to 1886 and first introduced by Alexejew and then modified by other research groups (Ward, 1926). The disappearance of drugs could be achieved either by changing the temperature or by addition of a known amount of the solvent. It is claimed that the synthetic method is much faster and more reliable than analytical method (Yang et al., 2008). Figure 1 illustrates a schematic representation of the most completed set up used in the synthetic method.

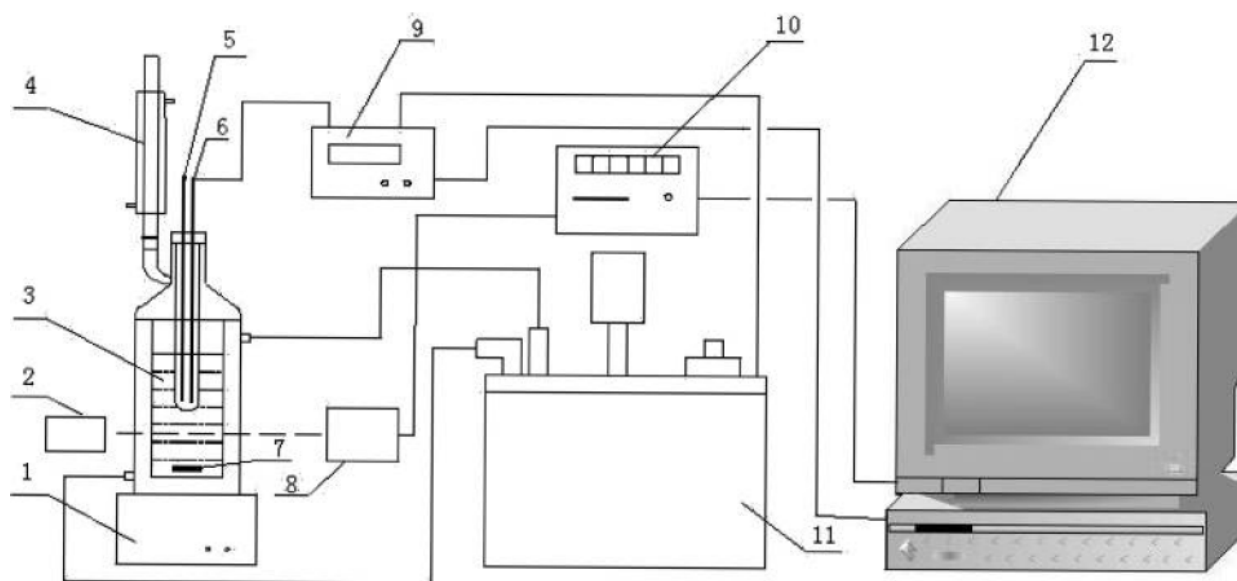


Fig. 1. Schematic representation of the synthetic method for determination of solubility of drugs; 1, magnetic stirrer; 2, laser generator; 3, jacketed glass vessel; 4, condenser pipe; 5, thermometer; 6, thermocouple; 7, rotor; 8, photoelectric transducer; 9, controller; 10, laser strength display; 11, constant temperature bath; 12, workstation. (Figure is reproduced from Ren et al., 2005).

The solubility apparatus consisted of a jacketed glass vessel (varying from 60 to 250 mL) maintained at the desired temperature by circulating water that was provided by a constant-temperature bath. The water temperature was controlled by a workstation with a temperature accuracy of (0.1 K) achieved continuous stirring, and a condenser (or a

perforated rubber cover) was fitted to reduce the solvent's evaporation. A thermometer with an uncertainty of 0.01 K was used to determine the temperature of the system. A laser beam was used as a tool to observe dissolving the solid in liquid. The signal transmitted through the vessel was collected by a detector that decided the rate of temperature rise and estimated the equilibrium point of the given system on the basis of the signal change. The solute and the solvent were prepared using an electronic balance with the estimated uncertainty in the mole fraction of less than 0.001. A predetermined quantity of drug and solvent was placed into the jacketed vessel. The system was slowly heated (heating rate increase is 0.5 to 2 K·hr⁻¹) with continuous stirring. When the solute particles disappeared thoroughly, the signal approached a maximum value. The workstation judged the signal difference at 10-min intervals; if the interval was less than 10, then the workstation gave an order to stop heating and record the temperature. The temperature recorded was the liquid temperature of a given composition upon the complete dissolution of the drug (Ren et al., 2005). In another version of this set up, predetermined masses of drug and solvent were placed in the vessel and the contents were stirred continuously at a constant temperature. As the particles of the drug are dissolved, the intensity of the laser beam increased gradually and reaches to the maximum value when the drug is dissolved completely. Then an additional known mass of the drug is introduced to the vessel and the procedure is repeated until the laser beam could not return to the maximum value which means the last addition could not be dissolved. The total amount of the added drug is recorded and used to calculate the solubility value (Yang et al., 2008). The synthetic method is preferred over shake flask method for solubility determination of drugs in viscous solvents where separation of the excess solids from saturated solutions is not achievable (Grant and Abougela, 1983).

2.2 Determination of kinetic solubility

In drug discovery and development, one of the rationalized methods is high-throughput screening (HTS) which includes the design and synthesis of a large set(s) of chemicals to find hit compounds based on specific physicochemical properties (PCPs) and to develop lead compound. One of the important PCPs in determination of hit and lead compounds is aqueous solubility (Pan et al., 2001; Alsenz and Kansy, 2007; Hoelke et al. 2009). However, in practice it is not possible to experimentally determine thermodynamic solubility value in HTS approaches. This is because of large number of compounds which might be more than 1000 compounds in each HTS experiment or little amount of synthesized compounds which is around a few milligrams and is another limiting factor (Pan et al., 2001; Alsenz and Kansy, 2007; Hoelke et al. 2009).

Kinetic solubility determination methods were used for covering this problem. The advantages of the kinetics solubility determination in comparison with thermodynamic solubility determination methods are capability to being easily automated, accuracy, rapidity and requiring less amount of the solute (Pan et al., 2001; Alsenz and Kansy, 2007; Hoelke et al. 2009). Its disadvantages might include not assessing the crystal effect on the solubility, the cosolvent action of the dimethyl sulfoxide (DMSO), and its applicability is good for compounds which have solubility more than 10⁻⁶ molar. Some of the well established approaches include: nephelometric, UV-Spectroscopic, and HPLC methods which are discussed in the following.

2.2.1 Nephelometric method

The nephelometry is based on turbidimetry. Figure 2 shows a schematic view of the mechanism of turbidimetry. For sample preparation in this method, a 10 millimolar concentration of a solute was prepared by dissolving suitable amounts of the solute in DMSO. Then, this stock solution is used to prepare sample solutions in the range of 5×10^{-7} to 5×10^{-4} molar. For concentrations above the 10^{-4} molar, the solutions prepared by direct dilution of the stock solution and for the lower concentrations, serial dilutions were used where the dilutant is a buffer. These dilutions are directly take place in a 96-well plate with the total 5% concentration of DMSO and the final volume of $\approx 200 \mu\text{L}$ (Pan et al., 2001; Hoelke et al. 2009). This optimum volume is based on the fact that light scattering (for a specific condition) is nearly constant for a range of particle sizes (Pan et al., 2001) which make the process reproducible and accurate.

For sample analyzing after the preparation section, the 96-well plate is placed in a nephelometer apparatus for measurement of the light scattering. It uses a laser beam (with a fixed wavelength in the range of 550-750 nm) as the light source, and a detector which is placed with a specific angle to the light source. Based on plotting turbidity against prepared concentrations, and drawing its asymptotes and finding their meeting point x coordination, gives the kinetic solubility (see Figure 3) (Pan et al., 2001; Hoelke et al. 2009).

With this method, the kinetic solubility for a plate of 96 samples can be measured in a few minutes.

2.2.2 UV/Vis-spectroscopic method

There are two methods using UV/Vis-spectroscopy for kinetic solubility determination: Method 1 is based on turbidimetry and the other is based on light absorbance intensity as a function of concentration (Pan et al., 2001).

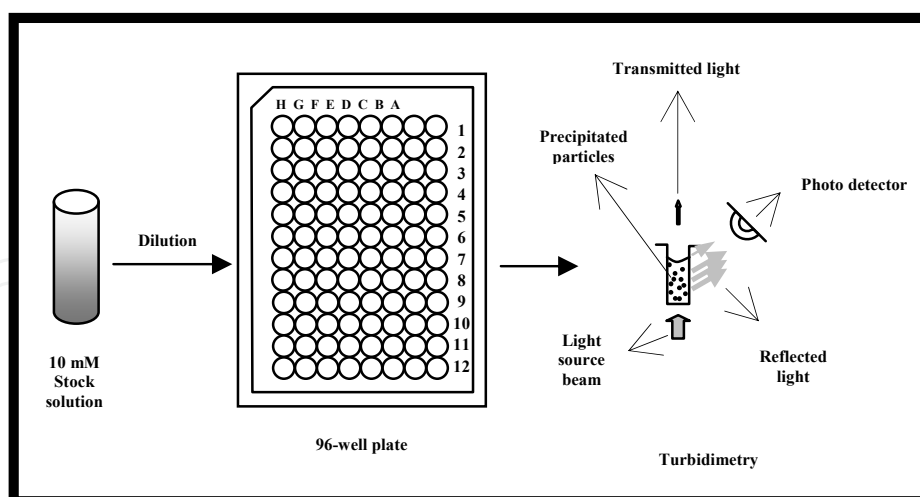
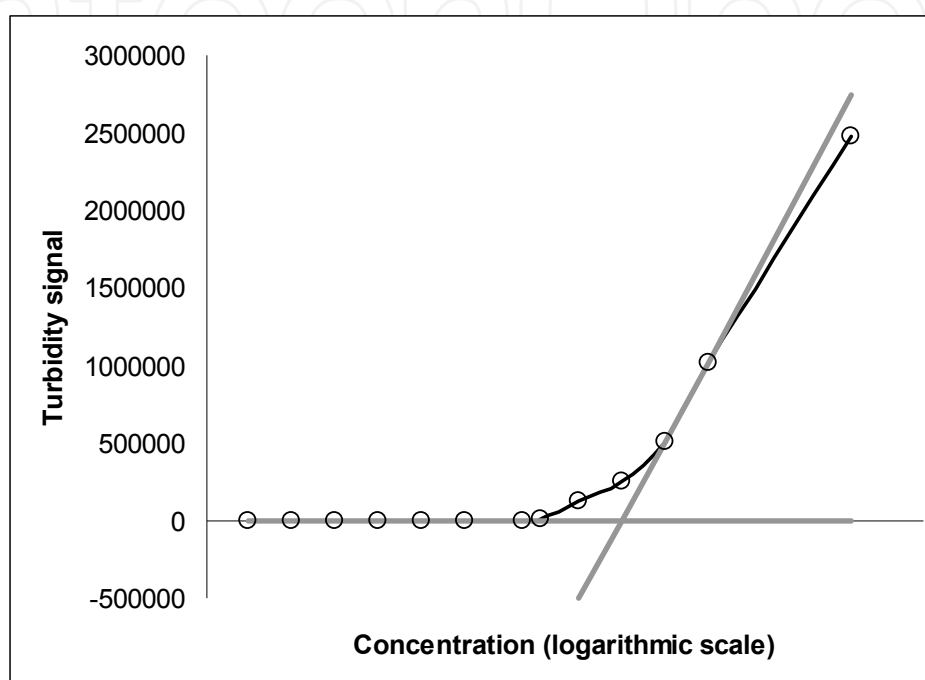


Fig. 2. Schematic representation of turbidimetry.

2.2.2.1 UV/Vis-spectroscopic method 1

The sample preparation is like nephelometry method, but the analyzing is with a 96-well plate UV/Vis-spectroscopy apparatus. This provides a wider range of wavelength to choose for reading the samples turbidity (190-1000 nm) (Pan et al., 2001). The lower the wavelength, the smaller particle is detected. However, in practice, wavelengths greater than 500 nm is

used. This is because of the fact that most of organic compounds which have UV absorbance (e.g. contain a benzene ring) also have fluorescence property and might interfere with turbidimetry which reads the amount of reflected light (or fluorescence emission light) (Pan et al., 2001). An example of this is phenol red which has light absorption in 430 and 560 nm and is excited by these wavelengths which results in fluorescence emission (Pan et al., 2001). Another limitation is the UV absorbance of the most plates which are made of plastics (Pan et al., 2001).



Method	Calibration	Specificity	Easy	Cut off	LOD	Rapidity
Nephelometric	Not required	Low	Yes	No	Low	High
UV/Vis 1	Not required	Low	Yes	<500 nm	Low	High
UV/Vis 2	Required	Medium	No	<250 nm	Medium	Medium
HPLC	Required	High	No	No	High	Low

Table 1. The comparison between four kinetic solubility determination methods

Kinetic solubility values are valuable source in early stage of drug discovery in place of thermodynamic solubility values where there is good correlation between trends of these two values for a set of compounds (Hoelke et al. 2009). However, because of the amorphic nature of the solutes, in most of the cases the kinetic solubility is higher than thermodynamic solubility values. The effect of 5% DMSO as a cosolvent on the solubility value in kinetic solubility determination methods also should be considered. This is very important where most of the drugs have very low aqueous solubility and very small amounts of solubilizing agents such as cosolvents (e.g. DMSO) enhance their solubility largely. Also the effect of time after dilution is important, especially in turbidimetry methods. Hoelke et al. have shown that by increasing the time after dilution and precipitation, the determined solubility become smaller (Hoelke et al. 2009).

2.3 Data validation

The collected data could be compared with the previously reported data in order to ensure the accuracy of the experimental procedure employed. Any mistake in the dilution steps, and miscalculations, or using un-calibrated instruments, such as un-calibrated balances, temperature variation and some other factors could be resulted in different solubility values for a given drug dissolved in a solvent at a fixed temperature.

3. Computational methods for solubility prediction

Computational methods in recent decades have become an important part of drug design and discovery. They are classified as theoretical, semi empirical and empirical equations. Most of models used in pharmaceutical sciences are semi-empirical (which is theoretical correlation of experimentally determined values) or empirical equations (which is mathematical correlation of experimentally determined values). Examples for semi-empirical models are those correlations which use physicochemical parameters in their relationships. In other word, it is needed for them to be calculated based on experimental determinations at least for one time. For example in Noyes-Whitney equation, the diffusion coefficient must be determined at least for one time for a solute. So the Noyes-Whitney equation is a semi-empirical model. The quantitative structure property relationships (QSPR) and quantitative structure activity relationships (QSAR) are examples for empirical modelling. The pioneer for this type of equations in pharmaceutical sciences is Prof. Crowin H. Hansch. He has developed a QSPR model for solubility prediction of liquids, based on their partition coefficient (Hansch et al., 1968):

$$-\log S = 1.339 \log P - 0.978$$

(3)

where $\log P$ is the logarithm of the partition coefficient between octanol and water for a specific liquid.

In another grouping, the correlation could be developed using linear modelling or non-linear modelling. Linear modelling is the simple linear regression (or multiple linear regression) and non-linear modelling is artificial neural network, as examples. There are advantages and disadvantages for each type of modelling which is listed in the Table 2:

Modelling type	Advantages	Disadvantages
Linear	<ul style="list-style-type: none">- Simple to perform- Fast- Robust- Reproducible- Easy to use- The resulted model can be analyzed theoretically- Performable with small number of cases	<ul style="list-style-type: none">- It cannot analyze non-linear and complex behaviour- Most of the time the results have low accuracy
Non-linear	<ul style="list-style-type: none">- Can analyze non-linear and complex behaviour- The results have high accuracy	<ul style="list-style-type: none">- Easily over fitting occurs- Many iterations are required- Need almost large number of cases- Reproducibility is hard- You must have the trained model to be able to predict new cases- It gives a black box instead of a model

Table 2. Advantages and disadvantages of linear and non-linear modelling in QSPR studies

In QSPR modelling, the variables used for correlation of physicochemical properties are called descriptors. These descriptors include simple structure derived parameters (e.g. number of carbon atoms, number of single bonds), overall structural parameters (e.g. molecular weight, and molecular volume), structure residues parameters (e.g. distance between two atoms, total charge on oxygen atoms), or physicochemical properties (e.g. melting point, partition coefficient). In solubility correlation almost all kinds of descriptors have been used. Around half of the models use $\log P$ as one of descriptors in modelling (Dearden, 2006). The following categories of descriptors have been used in solubility correlation:

1. PCPs (such as melting point, molecular weight, molar refraction, ...),
2. structure related descriptors (such as molecular volume, solvent accessible surface area, number of rotatable/rigid bonds, number of hydrogen bond donor/acceptor atoms, ...),
3. quantum chemical descriptors (such as optimized total energy, HOMO and LUMO energies, ...),
4. topological parameters,
5. molecular connectivity indices,
6. electrostatic state (E-state) descriptors,

7. group contribution method or fragment based approach (different fragments derived from structure, SMILES/InChI codes),
 8. solvatochromic parameters (Dearden, 2006; Katritzky et al., 2010; Jouyban et al., 2010b).
- Other descriptors have been used as well, and a number of mixtures of the mentioned parameters are used, too. In the next section, the easiest and the most accurate models for solubility prediction are discussed. Also approaches like mobile order theory and differential equations of activity coefficient for the calculation of solubility have been used as semi-empirical methods (Dearden, 2006; Katritzky et al., 2010).

For modelling, multiple linear regression (MLR), partial least square (PLS), support vector machine (SVM), artificial neural network (ANN), random forest (RF), Monte Carlo simulation (MCS), and other methods are used. Mostly, correlation coefficients of the non-linear methods are better than linear methods and the related errors are smaller (Dearden, 2006; Katritzky et al., 2010). This might suggest a nature of non-linear behaviour for solubility.

3.1 Aqueous solubility

Available models and software to predict the aqueous solubility of drugs were reviewed in a recent work (Jouyban et al., 2008). Solubility of drugs in water could be predicted using different models presented in the literature. The general single equation of Yalkowsky is the simplest and the most common method in the pharmaceutical area. The model requires experimental melting point (mp) and logarithm of partition coefficient ($\log P$) as input data and is expressed as:

$$\log S_w = 0.5 - 0.01(mp - 25) - \log P \quad (4)$$

where S_w is the molar aqueous solubility of a drug at 25 °C. If the solute has a melting point less than 25 °C, the ($mp-25$) term is set to zero (Ran et al., 2001). The two parameters, $\log P$ and mp are good representatives of effects of hydrophobicity and crystal packing on the solubility of a certain solute. Jain et al. (2008) provided some theoretical background for general single equation from thermodynamic principles. The simplicity of the model is its main advantage and a possible disadvantage is the melting point as an experimental parameter which may not be available for some of the compounds in early stages of drug discovery. An attempt has been made to predict the melting points from chemical structure was not successful (Jain and Yalkowsky, 2010) and it is recommended to use experimental values of melting point in the computations using general single equation (Chu and Yalkowsky, 2009). Also drugs with high melting points which decompose before melting are not suitable to be predicted by this model. The $\log P$ is measured using experimental methods such as HPLC, and/or calculated by some computational methods, then applied to solubility prediction.

The linear solvation energy relationship is another model developed by Abraham and his co-workers (Stovall et al., 2005a) and is presented as:

$$\log S_w = 0.395 - 0.955E + 0.320S + 1.155A + 3.255B - 0.785A \cdot B - 3.330V \quad (5)$$

in which E is excess molar refraction of the compound, S is dipolarity/polarizability, A and B are hydrogen bond acidity and basicity, respectively, which these later three parameter (S ,

A and B) determined from solubility data of a compound in water and different organic solvents, the $A \cdot B$ term is a representative of hydrogen-bond interactions between acidic and basic functional groups of the drug in its pure solid or liquid, V is one percent of the McGowan volume and simply is calculated using group contribution method (Stovall et al., 2005).

In a recent work from our group, a simple equation was proposed to predict the aqueous solubility of drugs trained by the solubility data of pharmaceuticals (220 drugs) and was validated using various validation methods (Shayanfar et al, 2010). The proposed model is:

$$\log S_W = -1.120E - 0.599Clog P \tag{6}$$

Both parameters (E and ClogP or computed logP) employed in equation 6 are computed using Pharma-Algorithms (Pharma Algorithms, 2008), therefore, the model is an *in silico* model and no experimental data is required in the prediction procedure. In the pharmaceutical literature, an external prediction set consisting of aqueous solubility of 21 pharmaceutical and non-pharmaceutical compounds (Ran et al., 2001) usually were used to test the prediction capability of the proposed models. This data could not well represent the aqueous solubility data of pharmaceutical compounds, and another data set has been proposed consisting of the solubility of 75 official drugs collected from the literature. A list of the proposed test set and the experimental and predicted aqueous solubilities using equations 1-3 are listed in Table 3.

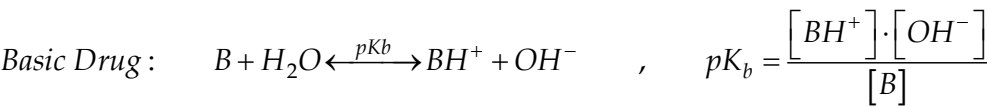
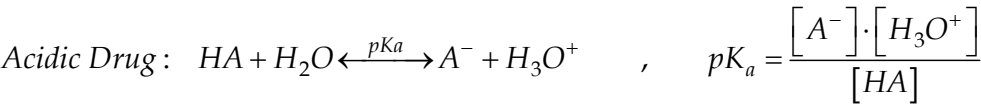
Drug	Experimental	Equation 4	Equation 5	Equation 6
Acetaminophen	-1.06	-1.18	-0.63	-1.39
Acetazolamide	-2.49	-1.18	0.06	-1.43
Acyclovir	-2.24	-0.37	0.91	-1.26
Allopurinol	-2.26	-2.19	0.38	-1.30
Amiloride	-3.36	-1.96	-0.07	-2.74
Amoxicilin	-2.17	-0.11	-1.90	-2.38
Antipyrine	0.39	-0.9	-1.16	-1.91
Atenolol	-1.30	-0.98	-1.85	-1.81
Atropine	-2.12	-1.77	-3.77	-2.43
Azathioprine	-3.21	-1.98	-1.95	-3.16
Baclofen	-1.67	-0.53	-1.84	-0.76
Benzocaine	-2.33	-1.98	-1.82	-2.14
Celecoxib	-3.74	-3.73	-5.38	-4.55
Chloramphenicol	-2.11	-1.57	-2.16	-2.55
Chlorpromazine	-5.27	-4.82	-5.97	-5.72
Ciprofloxacin	-3.73	-1.11	-2.78	-2.04
Colchicine	-0.96	-1.76	-3.93	-3.00
Cortisone	-3.00	-2.72	-4.43	-2.88
Dapsone	-3.19	-2.43	-2.05	-2.94
Diazepam	-3.76	-3.34	-4.58	-4.06

Diethylstilbestrol	-4.57	-5.805	-4.94	-4.82
Digoxin	-4.16	-3.12	-10.31	-4.94
Diltiazem	-2.95	-4.39	-4.64	-4.41
Ephedrine	-0.47	-0.52	-1.28	-1.65
Estradiol	-4.84	-4.95	-4.53	-4.43
Famotidine	-2.48	-0.09	-1.18	-2.53
Fluorouracil	-1.03	-1.24	0.55	-0.38
Gemfibrozil	-3.16	-4.26	-4.44	-3.54
Griseofulvin	-4.61	-3.45	-3.47	-3.28
Guaifenesin	-0.60	-0.36	-1.10	-1.45
Haloperidol	-4.43	-4.08	-5.44	-4.22
Halothane	-1.71	-1.68	-1.99	-1.56
Hydrochlorothiazide	-2.63	-1.61	-1.04	-2.18
Hydroquinone	-0.18	-1.66	-0.23	-1.56
Isoniazid	0.01	-0.154	0.97	-0.85
Ketoprofen	-3.25	-2.73	-3.95	-3.27
Labetalol	-3.45	-3.44	-4.32	-3.75
Lamotrigine	-3.14	-4.05	-3.48	-4.26
Levodopa	-1.72	-0.02	-0.35	-0.29
Lindane	-4.60	-4.08	-4.53	-3.76
Lovastatin	-6.01	-5.40	-6.42	-4.18
Manitol	0.06	1.08	0.89	-0.18
Maprotiline	-4.69	-5.28	-5.91	-5.03
Meprobamate	-1.82	-1.36	-1.62	-1.44
Mercaptopurine	-3.09	-1.84	-0.70	-1.66
Metoclopramide	-3.18	-2.99	-2.85	-3.04
Metronidazole	-1.22	-0.585	-1.14	-1.09
Minoxidil	-1.98	-2.97	-2.19	-2.46
Mitomycin C	-2.56	-2.53	-0.12	-2.46
Mycophenolic acid	-4.39	-3.30	-4.99	-3.19
Nifedipine	-4.78	-2.10	-3.71	-2.42
Nitrofurantoin	-3.24	-2.19	-0.98	-2.03
Nitroglycerin	-2.26	-1.19	-2.22	-1.66
Omeprazole	-3.62	-3.21	-3.00	-4.43
Oxytetracycline	-3.09	0.07	-4.04	-3.30
p-Aminobenzoic acid	-1.37	-1.93	-0.65	-1.65
Papaverine	-3.87	-4.43	-4.66	-4.67
Phenobarbital	-2.29	-2.39	-1.90	-2.59
Phenytoin	-3.99	-4.07	-3.20	-3.35
Progesterone	-4.40	-4.35	-5.64	-4.08
Propofol	-3.05	-3.38	-3.82	-3.28
Propoxyphene	-5.01	-4.38	-6.45	-4.14
Prostaglandin-E ₂	-2.47	-2.73	-5.22	-3.16

Quinine	-2.82	-2.11	-4.01	-4.06
Riboflavin	-3.65	-0.43	-2.77	-2.21
Salicylic acid	-1.93	-2.87	-1.53	-2.24
Sertraline	-4.94	-6.59	-6.17	-4.98
Sulfacetamide	-1.23	-0.99	-0.83	-1.64
Terfenadine	-6.69	-6.63	-9.05	-6.39
Testosterone	-4.06	-4.02	-4.89	-3.66
Theophylline	-1.38	-2.09	-0.18	-1.71
Thiabendazole	-3.48	-4.68	-3.21	-3.94
Tolbutamide	-3.46	-2.93	-3.13	-2.93
Trimethoprim	-2.95	-2.22	-6.11	-2.61
Warfarin	-3.89	-3.19	-7.40	-3.61

Table 3. List of the test data set for evaluating the capability of the models for aqueous solubility prediction, the experimental (log*S_w*) and predicted values by equations 4-6

The solubility value of a drug is affected by pH which is largely depends on whether the compound has acid/base ionizable functional groups. Most of the pharmaceutical compounds are weak acids or bases which could be dissociated according to the following equilibria:



where HA and B are acidic and basic drugs, respectively, *pK_a* is the acid dissociation constant, and *pK_b* is basic dissociation constant. The solubility of a weak acid or base in solutions with different pH is calculated by Henderson–Hasselbalch equation:

Acidic Drug : $\log S_T = \log S_0 + \log (10^{pH-pK_a} + 1)$ (7a)

Basic Drug : $\log S_T = \log S_0 + \log (10^{pK_a-pH} + 1)$ (7b)

where *S_T* and *S₀* are total and intrinsic solubility, respectively. So for solubility prediction of a drug at different pH values we need to have intrinsic solubility and *pK_a* value for the drug (Sinko and Martin, 2006).

However, having a specific *pK_a* value for a compound does not mean it will have complete activity in every pH values which is the case for most of the drugs which do not have complete activity in aqueous solutions.

There are some mathematical models for calculation of the solubility and *pK_a* of the compounds (Dearden, 2006; Jouyban, 2009; Katritzky et al., 2010). However, complete activity will be gained in two conditions: 1- infinite dilution and 2- strong acidic condition for basic compounds (or strong basic condition for acidic compounds).

3.2 Solubility in organic solvents

Few models were presented to calculate the solubility of drugs in organic solvents. Yalkowsky et al. (1983) calculated the mole fraction solubility of weak electrolytes and non-electrolytes in n-octanol at 30 °C as:

$$\log X_{Oct} = -0.011mp + 0.15 \quad (8)$$

$$\log X_{Oct} = -0.013mp + 0.44 \quad (9)$$

Dearden and O'Sullivan (1988) proposed the following equation for calculating the molar solubility of drugs in cyclohexane (S_{Cyc}):

$$\log S_{Cyc} = -0.0423mp + 1.45 \quad (10)$$

which was tested on the solubility of 12 pharmaceuticals and the mean percentage deviation was 85.1 (± 21.6) % (Jouyban, 2009).

Sepassi and Yalkowsky (2006) proposed another version of equation 8 to compute the molar solubility of drugs in octanol as:

$$\log S_{Oct} = -0.01(mp - 25) + 0.5 \quad (11)$$

The mean percentage value of equation 11 was 147 (± 247) % (Jouyban, 2009).

The Abraham solvation model provides a more comprehensive solubility prediction method for organic solvents (Abraham et al., 2010). The Abraham model written in terms of solubility is:

$$\log \left(\frac{S_S}{S_W} \right) = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \quad (12)$$

where S_S and S_W are the solute solubility in the organic solvent and water (in mole/L), respectively. In equation 12, the coefficients c , e , s , a , b and v are the model constants (i.e. solvent's coefficients), which depend upon the solvent system under consideration. These coefficients were computed by regression analysis of measured $\log \left(\frac{S_S}{S_W} \right)$ values, infinite dilution activity coefficients and partition coefficients of various solutes against the corresponding solute parameters (Abraham and Acree, 2005). The Abraham solvent coefficients (c , e , s , a , b and v) and Abraham solute parameters (E , S , A , B and V) represent the extent of all known interactions between solute and solvents in the solution (Stovall et al., 2005b).

3.3 Solubility at different temperatures

Solubility of a solute in an ideal solution could be mathematically represented by van't Hoff equation:

$$\log S = \frac{a}{T} + b \quad (13)$$

where a is the slope of the linear plot of $\ln S$ against $\frac{1}{T}$ and b is the intercept. The a term is equal to $\frac{-\Delta H_f}{2.303R}$ and b is equal to $\frac{\Delta H_f}{2.303RT_m}$ for ideal solutions in which R is the molar gas constant and T_m is the melting point expressed as K. Equation 13 provides good relationship in the narrow range of temperature. For ideal solutions, the enthalpy of mixing is zero, therefore the enthalpy of solution (ΔH_s) is equal to the enthalpy of fusion (ΔH_f). The ΔH_s is always endothermic for ideal solutions, and the solute solubility will be increased by increasing the temperature. The pattern is different for gases, liquids and solids as shown in Figure 4 where the solubility of gases decreases with increased temperature. The Hildebrand equation is an alternative model and expressed as:

$$\log S = a \ln T + b \quad (14)$$

in which a and b are the adjustable parameters. Equations 13 and 14 fail to represent the solubility-temperature relationship of most of pharmaceutical compounds in water and other pharmaceutically interested solvents especially at a wide temperature range. There are some physico-chemical reasons for this deviation from linear relationships, e.g. formation of polymorphs or solvate forms of the drug, which was discussed in details by Grant et al. (1984). To represent such data, a combined version of the van't Hoff and Hildebrand equations could be used. The equation is:

$$\log S = \frac{a}{T} + b \ln T + c \quad (15)$$

in which a , b and c are the adjustable parameters calculated by a least square analysis (Grant et al., 1984).

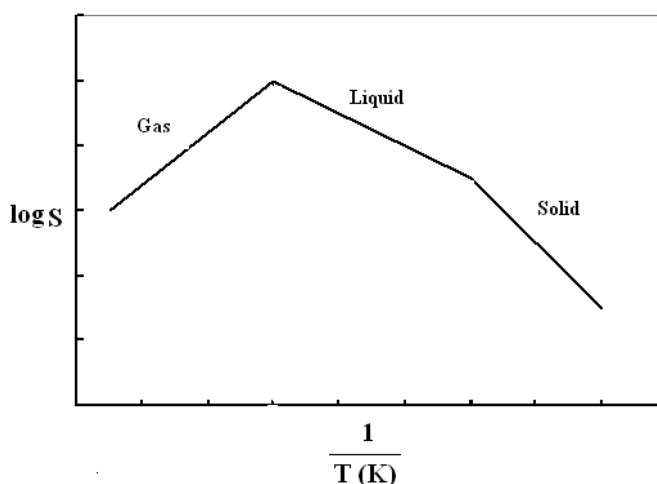


Fig. 4. The van't Hoff plot for gases, liquids and solids

3.4 Solubility in mixed solvents

The log-linear model of Yalkowsky is the simplest and famous model to calculate the solubility of pharmaceuticals in mixed solvent systems and is expressed by:

$$\log S_m = \log S_2 + \sigma \cdot f_1 \quad (16)$$

where S_m is the solubility of the solute in the mixed solvent system, S_2 denote the aqueous solubility of drug, σ is the solubilization power of the cosolvent and theoretically is equal to $(\log(S_1 / S_2))$ in which S_1 is the solubility in the neat cosolvent (Yalkowsky and Roseman, 1981). The general form of the log-linear model for multi-component solvent systems could be written as:

$$\log S_m = \log S_2 + \sum \sigma_i f_i$$

(17)

where σ_i and f_i are the solubilization power and the fractions of cosolvent i (Li, 2001). Valvani *et al.* (1981) reported a linear relationship between σ and logarithm of drug's partition coefficient ($\log P$) which is a key relationship and could improve the prediction capability of the log-linear model. The relationship was expressed as:

$$\sigma = M \cdot \log P + N$$

(18)

where M and N are the cosolvent constants and are not dependent on the solute's nature. The numerical values of M and N were reported for most of the common cosolvents earlier (Li and Yalkowsky, 1998) and listed in Table 4. This version of the log-linear model could be considered as a predictive model and provided the simplest solubility estimation method and requires the aqueous solubility of the drug and its experimental/calculated $\log P$ value as input data. The log-linear model was developed to predict the solubility of drugs at room temperature (22 – 27 °C) however the solubility at other temperatures are also required in the pharmaceutical industry.

Solvent system	M	N
Acetone - water	1.14	-0.10
Acetonitrile - water	1.16	-0.49
Butylamine - water	0.64	1.86
Dimethylacetamide - water	0.96	0.75
Dimethylformamide - water	0.83	0.92
Dimethylsulphoxide - water	0.79	0.95
Dioxane - water	1.08	0.40
Ethanol - water	0.93	0.40
Ethylene glycol - water	0.68	0.37
Glycerol - water	0.35	0.26
Methanol - water	0.89	0.36
Polyethylene glycol 400 - water	0.74	1.26
1-Propanol - water	1.09	0.01
2-Propanol - water	1.11	-0.50
Propylene glycol - water	0.77	0.58

Table 4. Updated Table from (Li and Yalkowsky, 1998; Millard et al., 2002.)

The Jouyban-Acree model was adopted from the combined nearly ideal binary solvent/Redlich-Kister equation proposed by Prof. Acree (1992) which was derived from a thermodynamic mixing model that includes contributions from both two-body and three-body interactions (Hwang et al., 1991). The model was presented for solubility calculations in binary solvents at a fixed temperature and expressed as:

$$\log S_m = f_1 \log S_1 + f_2 \log S_2 + f_1 f_2 \sum_{i=0}^2 A_i (f_1 - f_2)^i \tag{19}$$

where A_i stands for the model constants. The A_i values are calculated by regressing $(\log S_m - f_1 \log S_1 - f_2 \log S_2)$ against $f_1 f_2$, $f_1 f_2 (f_1 - f_2)$ and $f_1 f_2 (f_1 - f_2)^2$ by a no intercept least squares analysis (Jouyban-Gharamaleki and Hanaee, 1997). The applicability of the model was extended to other physico-chemical properties in mixed solvents at various temperatures as:

$$\log S_{m,T} = f_1 \log S_{1,T} + f_2 \log S_{2,T} + \frac{f_1 f_2}{T} \sum_{i=0}^2 J_i (f_1 - f_2)^i \tag{20}$$

where $S_{m,T}$, $S_{1,T}$ and $S_{2,T}$ are the solubility in solvent mixture, mono-solvents 1 and 2 at temperature T (K) and J_i is the model constants. The main limitations of the Jouyban-Acree model for predicting drug solubilities in solvent mixtures are: a) it requires two data points of solubilities in mono-solvent systems, and b) numerical values of the model constants. To overcome the first limitation, the solubility prediction methods in mono-solvent system should be improved. To address the second limitation, the following solutions were examined during last couple of years:

- i. the J_i terms are obtained using solubility of structurally related drugs in a given mixed solvent system, and then predict the un-measured solubility of the related drugs where the expected mean percentage deviation was $\sim 17\%$ (Jouyban-Gharamaleki et al., 1998).
- ii. the model constants could be calculated using a minimum number of experimental data points, i.e. three data points, and then predict the solubilities at the rest of solvent compositions where the expected prediction mean percentage deviation was $< 15\%$ (Jouyban-Gharamaleki et al., 2001).
- iii. the trained versions of the Jouyban-Acree models could be employed for solubility prediction of drugs in the aqueous mixtures of a number of organic solvents were reported. Using this version of the model, only the solubility data in mono-solvents are required. Table 5 listed the numerical values of the Jouyban-Acree model constants for the 5 cosolvents studied.

Solvent system	J_0	J_1	J_2	Prediction % error
Dioxane - water	958.44	509.45	867.44	27
Ethanol - water	724.21	485.17	194.41	48
Polyethylene glycol 400 - water	394.82	-355.28	388.89	40
Propylene glycol - water	37.03	319.49	-	24
Ethanol - ethyl acetate	382.987	125.663	214.579	13

Table 5. The constants of the Jouyban-Acree model for a number of solvent systems, data taken from (Jouyban and Acree, 2007; Jouyban, 2008)

- iv. in the trained versions of the Jouyban-Acree model, we assumed the extent of the solute-solvent interactions are the same, however, it is not the case since various solutes possess different functional groups leading to various extent of the solute-solvent

interactions. To cover this point, the deviated solubilities from the trained versions of the Jouyban-Acree model were correlated using available solubility data sets in ethanol – water and dioxane – water mixtures at various temperatures and the following equations are obtained:

$$\begin{aligned} \log S_{m,T} = & f_1 \log S_{1,T} + f_2 \log S_{2,T} \\ & + \left(\frac{f_1 f_2}{T} \right) \{ 558.45 + 358.60E + 22.01S - 352.97A + 130.48B - 297.10V \} \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)}{T} \right) \{ 45.67 - 165.77E - 321.55S + 479.48A - 409.51B + 827.63V \} \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T} \right) \{ -493.81 - 341.32E + 866.22S - 36.17A + 173.41B - 555.48V \} \end{aligned} \quad (21)$$

and

$$\begin{aligned} \log S_{m,T} = & f_1 \log S_{1,T} + f_2 \log S_{2,T} \\ & + \left(\frac{f_1 f_2}{T} \right) \{ 648.01 - 404.99E + 428.69 + 340.99A - 59.03B - 56.94V \} \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)}{T} \right) \{ -135.95 - 41.11E - 192.19S + 237.81A + 363.87B + 310.30V \} \\ & + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T} \right) \{ -1102.49 - 667.02E + 2070.16S + 421.15A - 924.73B - 271.54V \} \end{aligned} \quad (22)$$

The mean percentage deviation values for ethanol and dioxane were 34 and 22 %, respectively (Jouyban et al., 2009).

- v. a generalized version of the Jouyban-Acree model was proposed using its combination with the Abraham solvation parameters where the model constants of the Jouyban-Acree model were correlated with the functions of the Abraham solvent coefficients and the solute parameters as:

The mean percentage deviation of this model was 42 % for 152 data sets which was significantly less than that of the log-linear model (78 %). Figure 5 shows the relative frequency of the individual percentage deviations of the predicted solubilities using equations 23 and 16 (log-linear) in which the error distribution of equation 23 is better than that of the log-linear model. It should be noted that the Jouyban-Acree model requires two experimental data points, i.e. $S_{1,T}$ and $S_{2,T}$, whereas the log-linear model needs just aqueous solubility of the drug as input data. The main advantage of equation 23 is that it could be used to predict the solubility in mixed solvents where the Abraham solvent parameters (i.e. c, e, s, a, b and v) are available. Table 6 listed these parameters for a number of more common solvents in the pharmaceutical industry. Unfortunately these parameters are not available for a number of more common pharmaceutical cosolvents, such as propylene glycol and polyethylene glycols, and this is a disadvantage for this model.

$$\begin{aligned}
\log S_{m,T} = & f_1 \log S_{1,T} + f_2 \log S_{2,T} \\
& + \left(\frac{f_1 f_2}{T} \right) \left\{ \begin{aligned} & 1639.07 - 561.01 \left[(c_1 - c_2)^2 \right] - 1344.81 \left[E(e_1 - e_2)^2 \right] - 18.22 \left[S(s_1 - s_2)^2 \right] \\ & - 3.65 \left[A(a_1 - a_2)^2 \right] + 0.86 \left[B(b_1 - b_2)^2 \right] + 4.40 \left[V(v_1 - v_2)^2 \right] \end{aligned} \right\} \\
& + \left(\frac{f_1 f_2 (f_1 - f_2)}{T} \right) \left\{ \begin{aligned} & -1054.03 + 1043.54 \left[(c_1 - c_2)^2 \right] + 359.47 \left[E(e_1 - e_2)^2 \right] - 1.20 \left[S(s_1 - s_2)^2 \right] \\ & + 30.26 \left[A(a_1 - a_2)^2 \right] - 2.66 \left[B(b_1 - b_2)^2 \right] - 0.16 \left[V(v_1 - v_2)^2 \right] \end{aligned} \right\} \quad (23) \\
& + \left(\frac{f_1 f_2 (f_1 - f_2)^2}{T} \right) \left\{ \begin{aligned} & 2895.07 - 1913.07 \left[(c_1 - c_2)^2 \right] - 901.29 \left[E(e_1 - e_2)^2 \right] - 10.87 \left[S(s_1 - s_2)^2 \right] \\ & + 24.62 \left[A(a_1 - a_2)^2 \right] + 9.79 \left[B(b_1 - b_2)^2 \right] - 24.38 \left[V(v_1 - v_2)^2 \right] \end{aligned} \right\}
\end{aligned}$$

In addition to the above discussed models to predict the solubility of drugs in solvent mixtures, there are some models derived from molecular thermodynamic approaches. These models require relatively complex computations and did not attract more attention in the pharmaceutical area. These models provide comparable prediction accuracies with the above discussed models. As an example, the prediction error of a method based on statistical mechanical fluctuation solution theory varied 0.3-58 % (Ellegaard et al., 2010) whereas the corresponding value for the common models in the pharmaceutical area varied between 8 to 19 % (Jouyban-Gharamaleki et al., 1999).

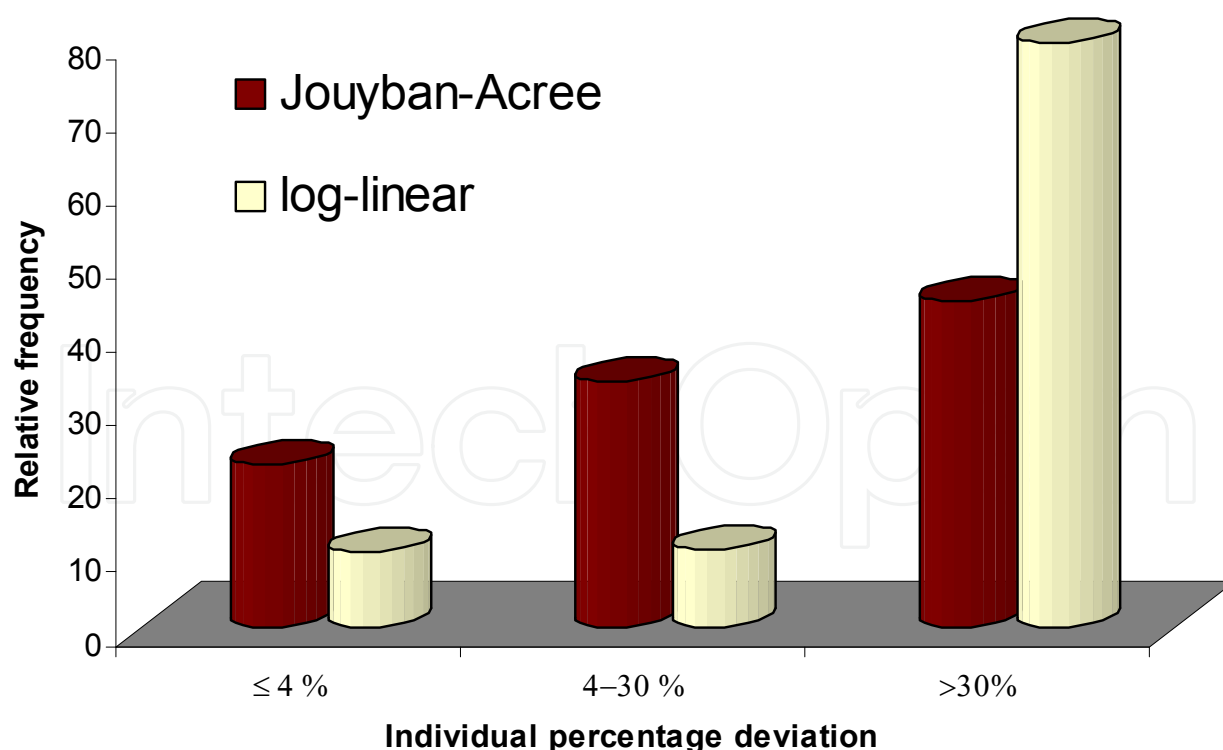


Fig. 5. The relative frequencies of the predicted solubilities in binary solvent mixtures using Jouyban-Acree and log-linear models

Solvent	c	e	s	a	b	v
Acetone	0.335	0.349	-0.231	-0.411	-4.793	3.963
Acetonitrile	0.413	0.077	0.326	-1.566	-4.391	3.364
Dimethyl formamide	-0.438	-0.099	0.670	0.878	-4.970	4.552
Dioxane	0.098	0.350	-0.083	-0.556	-4.826	4.172
Ethanol	0.208	-0.409	-0.959	0.186	-3.645	3.928
Ethylene glycol	0.243	0.695	-0.670	0.726	-2.399	2.670
Methanol	0.329	0.299	-0.671	0.080	-3.389	3.512
2-Propanol	0.063	0.320	-1.024	0.445	-3.824	4.067
Water	-0.994	0.577	2.549	3.813	4.841	-0.869

Table 6. The Abraham solvent parameters of a number of common solvents (data taken from Stovall et al., 2005a; 2005b)

3.5 Solubility in the presence of surfactants

Equation 24 is one of the equations used for the solubility calculation in presence of surfactant (Rangel-Yagui et al., 2005):

$$\chi = \frac{(S_T - S_W)}{(C_{Surfactant} - cmc)}$$

(24)

where χ is the ratio of the concentration of the drug in micelles to the concentration of the micellar surfactant molecules, S_T is the total drug solubility in the solution, S_W is the aqueous solubility of the drug, $C_{Surfactant}$ is the molar concentration of the surfactant in the solution, and cmc is the critical micelle concentration. Another equation is (Rangel-Yagui et al., 2005):

$$K = \frac{S_T - S_W}{S_W}$$

(25)

where K is the micelle-water partition coefficient of the drug. However, these equations require at least two other experimental data as input for total solubility prediction of the drug in micellar solutions. Abraham et al. (1995) have proposed two models for prediction of K for different solutes in the presence of sodium dodecylsulfate (SDS) as:

$$\log K_x = 1.201 + 0.542E - 0.400S - 0.133A - 1.580B + 2.793V$$
$$R = 0.9849 \quad , \quad N = 132 \quad , \quad \text{standard deviation} = 0.171$$

(26)

and

$$\begin{aligned}\log K_x &= 1.129 + 0.504 \log P + 1.216V \\ R &= 0.9755, \quad N = 132, \quad \text{standard deviation} = 0.215\end{aligned}\quad (27)$$

where K_x is the definition of K of equation 25 in mole fraction unit (Abraham et al., 1995). Ghasemi and coworkers have developed a MLR model for micellar solubility prediction in the presence of SDS for a diverse set of compounds:

$$\begin{aligned}\log K_S &= -0.638 + 0.001E_b + 0.384MR - 0.112LUMO + 0.570C \log P - 0.001RepE \\ R^2 &= 0.9679, \quad N = 62, \quad RMSEP = 0.124\end{aligned}\quad (28)$$

where K_S is the micellar solubility, E_b is bending energy, MR is molar refractivity, $LUMO$ is the lowest unoccupied molecular orbital, $C \log P$ is logarithm of calculated partition coefficient and $RepE$ is the repulsion energy (Ghasemi et al., 2008). In other work, they have proposed a QSPR model for micellar solubility prediction for a diverse set of compounds in presence of cetyltrimethylammonium bromide (CTAB) as:

$$\begin{aligned}\log K_S &= -1.1522 + 0.0070MP + 0.8089 \log P - 0.1262DPLL \\ R^2 &= 0.9624, \quad N = 40, \quad RMSEP = 0.169\end{aligned}\quad (29)$$

where MP is melting point of the solute, and $DPLL$ is the dipole length of the solute (Ghasemi et al., 2009).

However, as mentioned above, at least intrinsic solubility is required for total solubility prediction in the presence of a surfactant and they cannot be used as *ab initio* QSPR models for solubility prediction.

3.6 Solubility in the presence of complexing agents

In most of the cases, by adding complexing agents (e.g. cyclodextrins) to the solution, the solubility of a specific ligand (i.e. drug) is enhanced. But this enhancement could have different types as illustrated in Figure 6.

As has been seen, different kinds of drugs show different behaviours. But except for one condition, in the smaller amounts of complexing agent, the solubility changes are the same for other types. This common part of the curves is considered as a straight line with a slope of:

$$\begin{aligned}\text{Slope} &= \frac{K_{1:1}S_0}{1 + K_{1:1}S_0} \\ K_{1:1} &= \frac{[Host.Ligand]}{[Host] \cdot [Ligand]}\end{aligned}\quad (30)$$

where $K_{1:1}$ is the complex formation coefficient, $[Host.Ligand]$ is the concentration of the formed complex between drug and complexing agent, $[Host]$ is the concentration of the complexing agent, and $[Ligand]$ is the concentration of the drug (Sinko and Martin, 2006; Brewster and Loftsson, 2007). To correlate solubility value in presence of a complexing agent in this part of the solubility curve, one can use the following equation:

$$S_{Total}^{Complex} = S_0 + \text{Slope} \cdot C_{Host}\quad (31)$$

where $S_{Total}^{Complex}$ is the total solubility amount in the presence of a complexing agent, S_0 is the intrinsic solubility, $Slope$ is the slope of the first part of solubility curve versus complexing agent concentrations, and C_{Host} is the concentration of the complexing agent (Sinko and Martin, 2006; Brewster and Loftsson, 2007).

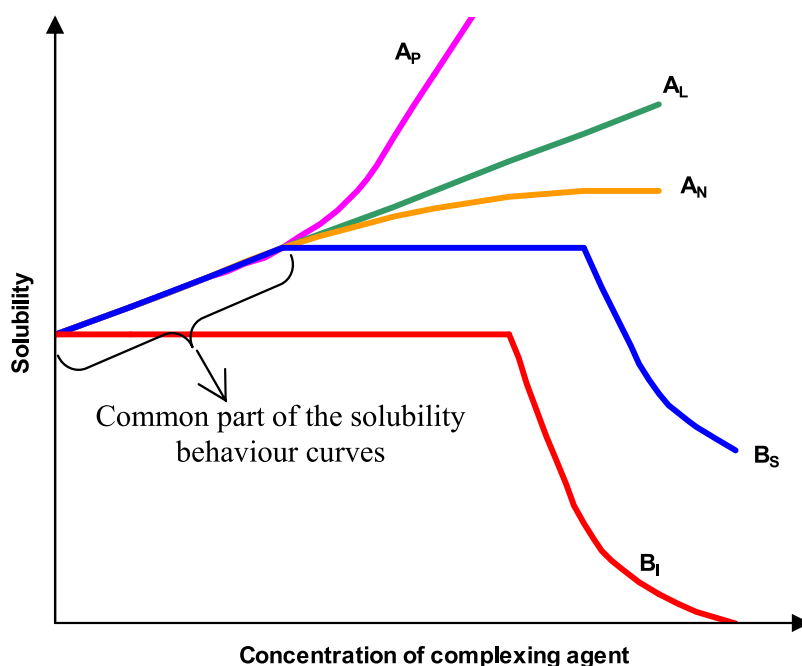


Fig. 6. Possible different solubility behaviours in the presence of complexing agent.

Again, like the pH and surfactant effects, one must have intrinsic solubility and $Slope$ (or $K_{1:1}$) for solubility prediction in presence of complexing agents. However some QSPR models have been developed for prediction of $Slope$ (or $K_{1:1}$). But most of them only considered the effect of complexing agent on the solubility enhancement (i.e. $Slope$). Demian (2000) has proposed equation 32 for the correlation of the $Slope$ of the above mentioned equation for aromatics and terpenes with hydroxypropyl- β -cyclodextrin:

$$\begin{aligned} Slope &= 2.86 - 0.11 \times Sterimoll - 0.34 \times \log P \\ R &= 0.788, \quad N = 19, \quad \text{standard error} = 0.336 \end{aligned} \quad (32)$$

where $Sterimoll$ is a steric parameter which is calculated by ChemOffice software (Demian, 2000). Choi et al. (2006) have developed a QSPR model for the correlation of the $Slope$ for A_L type solubility curves between drugs and $\alpha/\beta/\gamma$ -cyclodextrines as following:

$$\begin{aligned} Slope &= -0.012E_{h-g} + 0.102E_{np_h-g} + 0.328E_{np_g-g} + 0.305 \\ R^2 &= 0.913, \quad N = 63, \quad \text{standard error} = 0.028 \end{aligned} \quad (33)$$

where E_{h-g} is the interaction energy between host and guest, E_{np_h-g} is the difference between nonpolar components of free energy of solvation of the host-guest complex and those of individual host and guest molecules, E_{np_g-g} is the difference between nonpolar components of free energy of solvation of the guest-guest dimer and those of individual guest molecule (Choi et al., 2006). These energy values are calculated after a Monte Carlo docking

simulation between each drug and related complexing agent. Trapani et al. (2005) have developed a QSPR model for the correlation of the ratio of the total versus intrinsic solubilities of 25 drugs in the presence of 2-hydroxypropyl- β -cyclodextrin as following:

$$\log \frac{S_{Total}^{Complex}}{S_0} = 3.766 + 0.182CMR - 0.150C \log P - 0.00683TPSA - 0.0844\delta_{tot} \quad (34)$$

$$R^2 = 0.793, \quad N = 25, \quad Q^2 = 0.711$$

and

$$\log \frac{S_{Total}^{Complex}}{S_0} = 1.827 - 0.00508MW + 0.0122MV - 0.179C \log P - 0.00547TPSA \quad (35)$$

$$R^2 = 0.763, \quad N = 25, \quad Q^2 = 0.605$$

where *CMR* is calculated molecular refractivity, *TPSA* is total polar surface area, δ_{tot} total solubility parameter, *MW* is molecular weight, and *MV* is molecular volume. Equation 34 was derived using a MLR method and equation 35 was derived using a PLS method (Trapani et al., 2005).

However, as mentioned earlier, none of these models can be applied directly for solubility prediction in the presence of complexing agents and intrinsic solubility is required for all of them.

3.7 Available software

There is almost a large number of software for solubility prediction. A thorough review of these software was provided in an article (Jouyban et al., 2008). In this chapter, more useful solubility prediction applications and those which are newly developed or related with drug design and development is discussed.

ACD/Solubility DB predicts aqueous solubility at different pH with an accuracy of average error of 0.47 ± 0.67 (in decimal logarithm) for solubility prediction of 1125 compounds (ACD/Labs).

ACD/DMSO Solubility predicts whether a compound is soluble (a result of 1) or insoluble (a result of 0) in DMSO. Using a hybrid model of logistic regression with PLS method, its predictive model was trained with solubility related physicochemical parameters, and considering the effects of charged groups, atom chains, and ring scaffolds. It provides 30% high reliability, 70% moderate reliability and <1% low reliability in prediction, with an overall accuracy of 82% in correct prediction (Japertas et al.).

Simulations plus' ADMET predictor™, predicts aqueous solubility using 2D and 3D descriptors as input data with average error of 0.432 and 0.423 in logarithm scale for 2817 and 711 number of compounds in train and test sets, respectively (ADMET Predictor™). It can also predict the solubility in biorelevant medium of the fasted state simulated gastric fluid (FaSSGF), the fasted state simulated intestinal fluid (FaSSIF), and the fed state simulated intestinal fluid (FeSSIF). Its average errors in logarithm scale for FaSSGF are 0.510 and 0.470 for 137 and 20 compounds, respectively. Its average errors in logarithm scale for FaSSIF are 0.469 and 0.417 for 141 and 16 compounds, respectively. Its average errors in logarithm scale for FeSSIF are 0.424 and 0.409 for 136 and 21 compounds, respectively. These predictive tools are designed using 2D descriptors as inputs and ADMET Modeler's ANNE

methodology for modelling (ADMET Predictor™). This package also can predict possibility of supersaturation in water. It calculates ratio of kinetic solubility versus intrinsic solubility and if the result is higher than 1.3, then the answer to possibility of supersaturation is true. It classified 95 and 23 out of 97 and 24 compounds correctly as train and test sets (ADMET Predictor™).

Finally, Solvomix is a recently developed free software available via Handbook of Solubility Data for Pharmaceuticals as a tool for prediction of solubility in monosolvents and mixtures of solvents. It uses GSE and Abraham models for the prediction of solubility in monosolvents and trained versions of log-linear model of Yalkowsky and Jouyban-Acree model for solubility prediction in mixtures of solvents (Jouyban, 2009).

4. Conclusion

Although preparation of a drug solution is a simple procedure, the associated problems are still a challenging subject in the pharmaceutical area. Brief review of its importance, various experimental and computational methods to determine the solubility and a number of more common methods to alter the solubility are discussed in this chapter. A comprehensive compilation of aqueous solubility data of chemical/pharmaceutical compounds is available from a reference work of Yalkowsky et al. 2010. The solubility data of pharmaceuticals in organic mono-solvents and also aqueous and non-aqueous solvent mixtures are compiled in a recent work (Jouyban, 2009).

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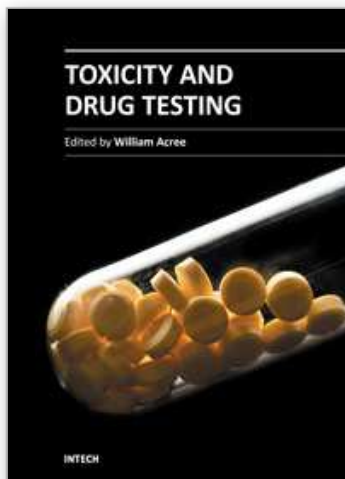
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Modern drug design and testing involves experimental in vivo and in vitro measurement of the drug candidate's ADMET (adsorption, distribution, metabolism, elimination and toxicity) properties in the early stages of drug discovery. Only a small percentage of the proposed drug candidates receive government approval and reach the market place. Unfavorable pharmacokinetic properties, poor bioavailability and efficacy, low solubility, adverse side effects and toxicity concerns account for many of the drug failures encountered in the pharmaceutical industry. Authors from several countries have contributed chapters detailing regulatory policies, pharmaceutical concerns and clinical practices in their respective countries with the expectation that the open exchange of scientific results and ideas presented in this book will lead to improved pharmaceutical products.

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