SOLUBILITY: IMPORTANCE, MEASUREMENTS AND APPLICATIONS

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The solubility of a compound in organic solvents or water is equally important for screen design and later for process development. For designing a screen, for instance around cooling crystallization, you need to select solvents that have sufficient **solubility** and that have a high dependency of solubility on temperature. In addition, a selection of solvents and mixtures that spans the range of possible chemical functionalities will maximize the chances of finding new, interesting and developable solid forms. This white paper covers two dynamic methods for effective and reproducible solubility data generation: the **temperature variation** and **solvent addition methods**. These methods can be easily applied by making use of the turbidity probes integrated in the ***Crystal16*** and particle viewer cameras of the ***Crystalline*** instruments.

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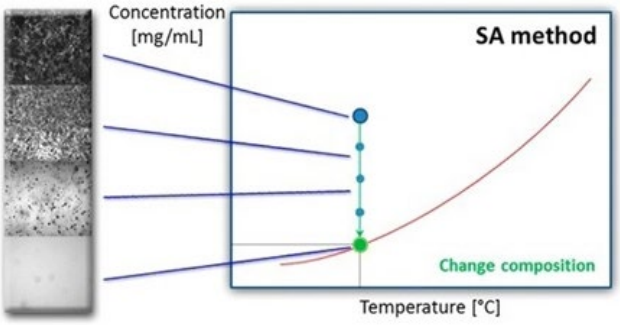


Technobis CRYSTALLIZATION SYSTEMS

1. Introduction

Solubility is defined as the equilibrium amount of a crystalline compound that can be dissolved in a specific solvent system at the given process conditions, of which the temperature is often the most influential parameter. For many compounds, the solubility increases with temperature. An example is given in Figure 1a for the binary system isonicotinamide (INA) in ethanol, where the INA solubility increases with the temperature T. A compound may have considerably different solubility depending on the investigated solvent/solvent system (see Figure 1b). Additionally in Figure 1c is shown how the solubility of different compounds: 4-hydroxybenzoic acid (HBA), niflumic acid (NIF) and isonicotinamide (INA) may be totally different in a specific solvent (e.g. 1,4-dioxane).

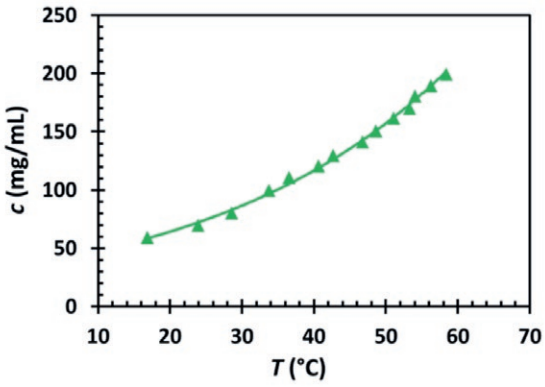
Solubility data are used to take critical decisions from the earliest stages of drug discovery, throughout the entire process development and up to formulation. For many products, crystallization is used for purification as well as particle formation. In crystallization of active ingredients (AI), the solubility curve helps to choose a suitable crystallization process (e.g. cooling or evaporative crystallization) and determines the yield. Therefore, knowledge of the solubility is essential for the design of the crystallization process.

Measuring the solubility requires accurate control of temperature and composition in liquid and solid phase, preferably with the capability to generate a vast amount of data in a short period of time. The ***Crystal16*** and ***Crystalline*** provide the ideal tools to efficiently gather and analyse solubility data.

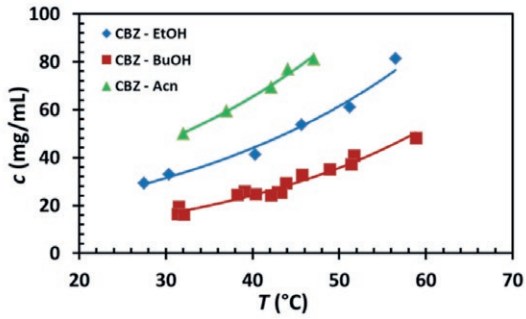
Measuring the solubility requires accurate control of temperature and sharp observation of the phase transition, i.e. full dissolution of the solid phase, combined with information regarding the composition of the system. Since generally a reproducible solubility dataset over a temperature or compositional range is required, many data points need to be determined separately. This can be labor intensive and time consuming. ***Crystal16*** and ***Crystalline*** instruments offer invaluable tools to automate the execution of solubility measurements in quick, controllable and reproducible manner.

Figure 1: Temperature dependent solubility curves

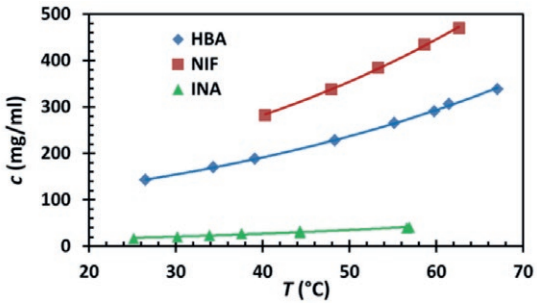
A **Isonicotinamide (INA) in ethanol**



B **Carbamazepine (CBZ) in ethanol (EtOH), butanol (BuOH) and acetonitrile (Acn)**



C **HBF, NIF and INA in 1,4-dioxane**



Data collected with the use of the Crystal16

2. Measurement methods of solubility

Equilibrium Concentration vs Dynamic Methods

A widely accepted and accurate method for measuring the solubility is through equilibration of a suspension, followed by an assessment of the solution composition, from which the solution concentration can be determined. The method requires sampling followed by filtration to remove the solids and measurement of the concentration using for example, a gravimetric, spectroscopy or a chromatographic method like HPLC (see Figure 2a). However, this Equilibrium Concentration (EqC) method is laborious and time consuming.

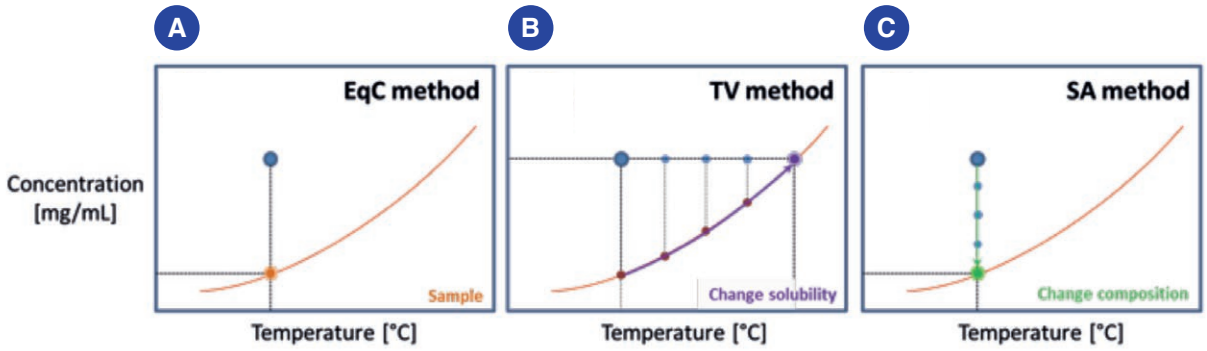
Two other methods are available and easily accessible: the Temperature Variation (TV) method and the Solvent Addition (SA) method, in which respectively the temperature of the suspension and the composition of the suspension are gradually changed until all crystals are dissolved.

The point in the concentration-temperature diagram at which the suspension turns into a clear solution is called the clear point. A clear point temperature can be determined using the TV method. Figure 2b shows the principle of a Temperature Variation (TV) measurement, in which crystals in a suspension dissolve upon heating. At a specific temperature, the clear point temperature, crystals are not detected anymore. The SA method can be used to determine a clear point composition at a constant temperature. Figure 2c shows the principle of a Solvent Addition (SA) measurement [1], in which the crystals in a suspension are dissolved upon dilution.

The clear point can be assumed to be equal to the solubility if the heating or addition rate is chosen sufficiently small [2]. Compared to the equilibrium concentration method, these dynamic methods are beneficial since they are much less labour intensive, much faster and have less risk of human error due to fewer required operations (no sampling or filtration). Apart from the heating or addition rate and the accuracy of the clear point determination, the error in the solubility measurements depends on the chemical system. For example, if crowning occurs, i.e. crystallization on the wall of the measurement vessel above the liquid level, the measured solubility deviates from the actual value, since part of the solid phase is not dissolved.

Moreover, the Temperature Variation (TV) and the Solvent Addition (SA) methods showed to give reliable and reproducible data in short time for a considerable amount of systems and reflected in the high number of scientific articles published per year.

Figure 2: Three different methods of determining the solubility of a compound from a suspension with composition (•)



(a) The orange dot represents the concentration of the liquid sampled from the suspension in the traditional EqC method.
(b) The purple arrow shows how the solubility of the system is changed through temperature until it corresponds to the overall concentration in the TV method.
(c) The green arrow depicts the change in composition of the system through in the SA method.

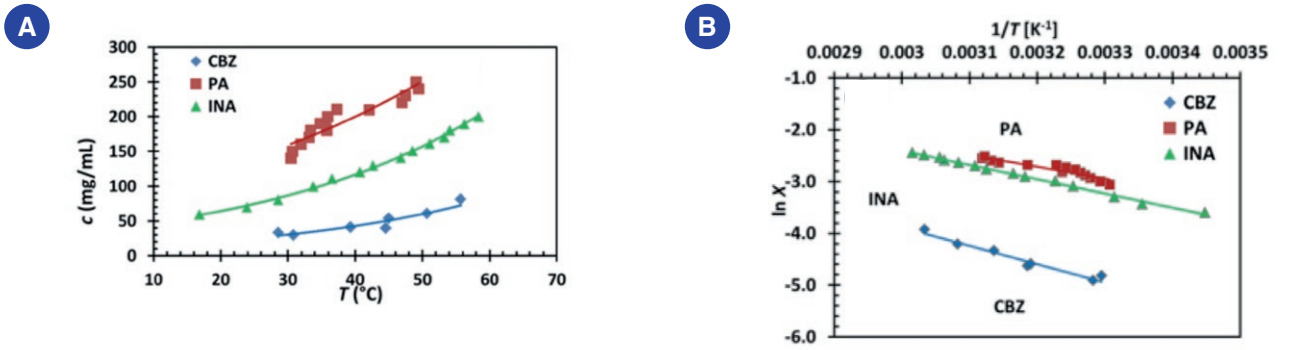
3. Dynamic measurement methods of solubility and their applications

3.1 Temperature Variation (TV) method

The TV method is the most suitable method for **determining the temperature dependent solubility** line of a compound in a solvent. Upon heating a suspension of known composition, the temperature at which all crystals are dissolved marks a point on the solubility line. After a recrystallization step through cooling, the measurement can be repeated. An additional benefit of these cyclic measurements is that during the cooling stage the temperature at which the first crystals reappear can be recorded as the cloud point. The collection of cloud points give the metastable zone width (MSZW), which is used to determine the operation range of the process and indicates the tendency towards primary nucleation. The temperature range in which the solubility and MSZW can be measured is limited by the melting and boiling points of the solvent, as well as the decomposition temperature of the compounds involved. Additionally, for efficient data generation, it is required that the MSZ is narrow enough for recrystallization to occur in the cooling stage. With the ***Crystal16***, one can perform 16 solubility measurements at 1 mL scale. Measuring multiple samples simultaneously gives a dataset of saturation temperatures at different concentrations that represent the solubility line, as illustrated in Figure 3a for the compounds carbamazepine (CBZ), picolinamide (PA) and isonicotinamide (INA) in ethanol. The solubility information of the model compounds can then be used to construct the corresponding Van 't Hoff plot (see Figure 3b) to interpolate their solubilities at any given temperature. The Van 't Hoff plot is a linear fitting of lnx to 1/T, where x is molar fraction of the solute and T (K) is the corresponding saturation temperature:

$$\ln x = -\frac{\Delta H}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)$$

Figure 3: (a) Solubility curves of CBZ, PA and INA in ethanol and (b) their corresponding van 't Hoff plots.



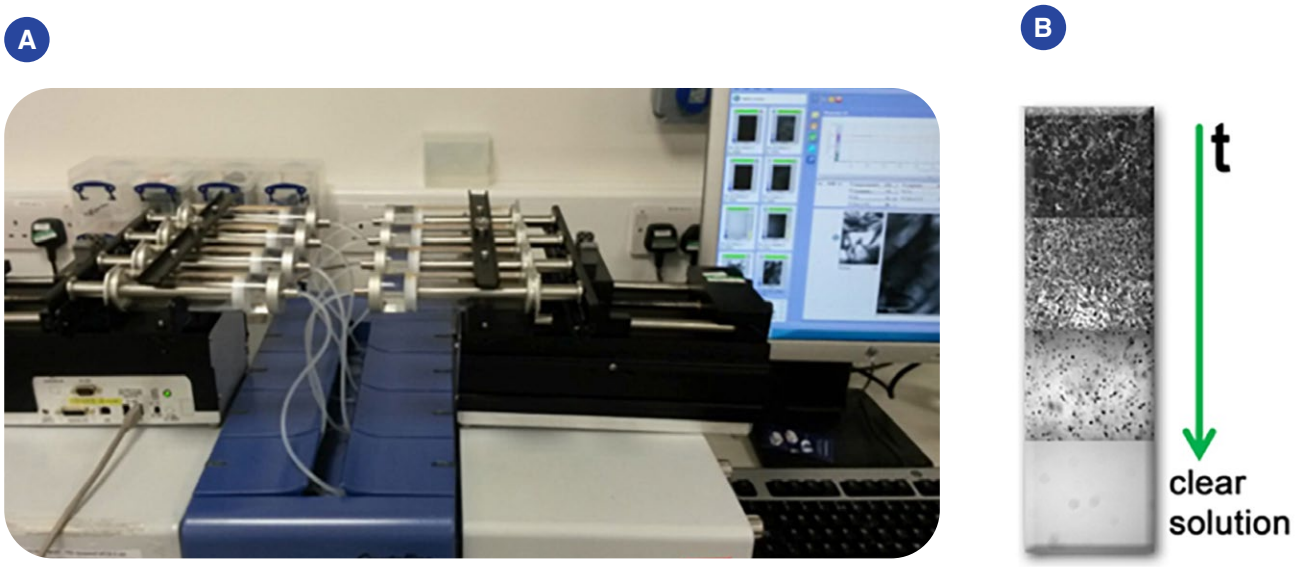
3.2 Solvent Addition (SA) method

When **solubility data is required at constant temperature**, which is often the case in multicomponent mixtures, SA is the method of choice. Additionally, the method is very useful for systems in which the solubility is not strongly dependent on temperature or where the MSZ is wide. However, the MSZW is not measured in this method. In the solvent addition method, the temperature is kept constant. Upon dilution of a suspension of known composition by the addition of solvent, a clear point is detected when the equilibrium concentration is reached. Figure 2c schematically shows this for a binary system. The clear point can be detected by a decrease in solution concentration (measured using e.g. in-situ FTIR) or by the disappearing of crystals. The latter is shown in Figure 4, where a ***Crystalline*** instrument is used to monitor the suspension by using the particle viewer cameras. The cameras take pictures at regular intervals and the clear point is determined as the first picture without crystals. Therefore, a shorter time between pictures increases the accuracy of the clear point. The most important parameter in the SA method is the addition rate. It must be chosen low enough for the dissolution to occur in time. Using a too high addition rate yields lower solubility data than the actual one. In the ***Crystalline***, eight measurements may be conducted simultaneously. Solvent is added to the vials over time using the syringe pumps as in Figure 4a. The cameras of the ***Crystalline*** clearly capture the thinning of the suspension upon the addition of solvent, until no crystals are detected anymore (see Figure 4b). The saturation concentration, c*, may be calculated by dividing the initial mass of crystals, mcryst,0 by the solvent volume at the time of the clear point, according to:

$$c^* = \frac{m_{cryst,0}}{V_0 + R_a \cdot t_{clear}}$$

where Ra is the addition rate and tclear is the time at which the clear point was determined.

Figure 4: (a) Solvent addition using the Crystalline with 8 syringes attached. Each syringe can contain a different solvent composition. (b) The cameras of the Crystalline register the disappearance of the crystals as solvent is added over time. Picture courtesy of Vaclav Svoboda, CMAC, University of Strathclyde.



3.3 Applying TV and SA methods in Co-crystal Screening

TV and SA methods may be widely applied from early stage discovery to process development and formulation. The abovementioned **TV** and **SA methods** are also suitable for **co-crystal screening**. The physio-chemical properties of active pharmaceutical ingredients (APIs), such as shelf life, dissolution rate and bioavailability, can be improved by the means of co-crystallization, provided that a suitable co-former is chosen. Traditional methods of screening for co-crystals systems include liquid-assisted grinding and solution crystallization, usually with stoichiometric ratio of APIs and the candidate co-formers. Using these methods, it is believed that significant amounts of co-crystals can be missed since the compositions used do not necessarily lie in the co-crystal region of a solvent-API-co-former ternary phase diagram.

ter Horst et al. has reported a method based on pseudo-binary phase-diagrams, constructed by the **TV method**, to look for new co-crystal systems [3]. The essence of the method is that a suitable composition for co-crystal formation would be close to the relative solubilities of the API and the co-former in the corresponding solvent [4]. The ***Crystal16*** is used to measure the solubilities of all relevant compounds as well as to construct the pseudo-binary phase diagram of the candidate systems.

In the following example, carbamazepine (CBZ) is used as the model compound and its tendency to form co-crystals has been investigated with two different co-formers, picolinamide (PA) and isonicotinamide (INA) in ethanol.

The obtained solubility information of the pure component (see Figure 3) is used to construct the pseudo-binary phase diagrams for the model systems. The compositions of each sample in the diagram are determined based on the following equation:

$$\frac{x_B}{x_B^*(T)} = 1 - \frac{x_A}{x_A^*(T)}$$

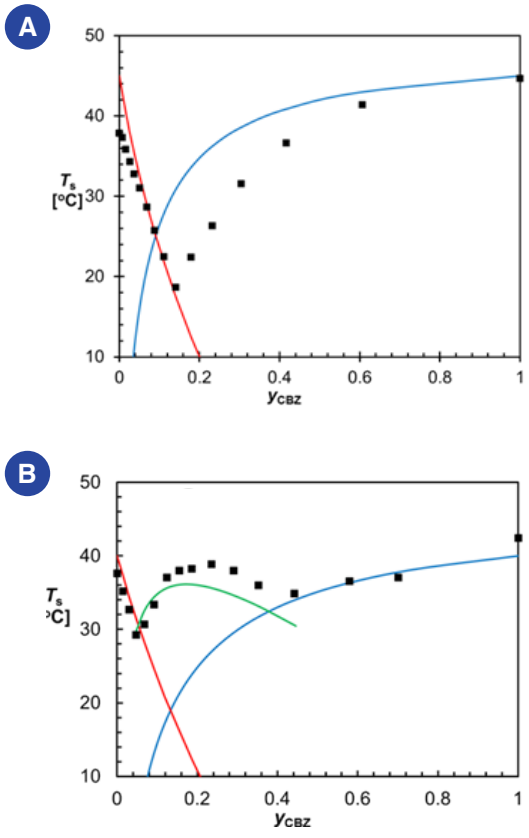
Here x is molar fraction of the compound (A) and the co-former (B) in each sample while x* is the molar solubility at temperature T. The saturation temperatures Ts of each sample are measured with the ***Crystal16*** and plotted against the solvent-excluded mole fraction yCBZ = χCBZ /(χCBZ + χco-former).

In the phase diagram of CBZ-PA system, only one eutectic point can be found which indicates that no co-crystals can be formed between the two model compounds. The solubility of PA, however, seems to be increased by the present of CBZ, based on the reduced Ts in region where yCBZ is 0.2 - 0.7.

In the phase diagram of CBZ-INA system, clearly more stable crystals are formed in the region 0.1 ≤ yCBZ ≤ 0.5. It is likely that this stable crystal is the co-crystal between CBZ and INA and that the region where Ts is significantly increased is the co-crystal zone. Further experiments can be performed to form single crystals of this system for crystal structure determination.

In the example case introduced above, two model compounds systems have been screened using only the ***Crystal16***. The constuction of pseudo-binary phase diagrams requires the prior knowledge of the solubility of each compound involved. Theoretically, all results including the phase diagram of a certain API-co-former system can be generated within 48 hours. The present method provides a fast prelimenary screening for possible co-crystal systems, followed by further investigation such as single crystal X-ray Diffraction (SC-XRD), solid-state nuclear magnetic resonance (SS-NMR), solid-state infrared spectroscopy (IR), differential scanning calorimetry (DSC), etc.

Figure 5: The saturation temperature T_s [°C] as a function of the solvent-excluded mole fraction y_{CBZ} of CBZ with co-former PA (a) and INA (b)

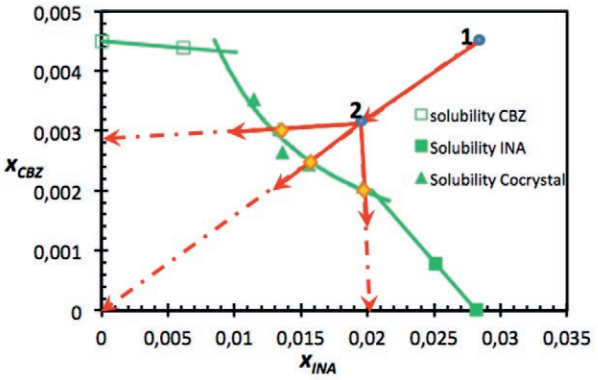


The saturation temperatures of the single-component API and co-former and the co-crystal predicted using the van 't Hoff parameters are shown as solid lines from the pure-component axes.

4. Summary

An effective method for solubility determination of complex systems such as co-crystals and defining well the co-crystal formation region is highly needed. The isothermal solubility of the co-crystal along the composition range, which provides information of the co-crystal formation region, can be determined easily by the SA method, starting from the pure component solubilities at the given temperature. An example of CBZ and INA is presented below. A starting point is generated by dissolving both components at their saturation concentration (point 1 in Figure 6). Although the solute excluded mole fraction of both components is not necessarily close to their stoichiometry ratio in the solid co-crystal, it is in most cases located in a region where co-crystals form, yielding a starting suspension. When solvent is added to dilute the system, eventually a clear point is registered. If the co-crystal solubility is drastically lower than that of the pure components, the volume to be added is considerable. In that case, consecutive measurements can be performed. A starting composition containing less of both pure components needs to be prepared (e.g. point 2 in Figure 6). From that point, under-saturated solutions of either compound can be added until a clear solution is obtained. This yields the other points on the solubility line. The solvent addition technique provides a fast way of determining the solubility of complex systems. Multiplexing and automation of this technique, as shown in Figure 4, and similar to the TV method in the ***Crystal16***, leads to efficient data generation.

Figure 6: Determining the phase diagram of the INA-CBZ co-crystal in ethanol using solvent addition



The mole fraction of CBZ (x_{CBZ}) is plotted versus the mole fraction of INA (x_{INA}). The green markers represent solubility data at T = 20°C. The SA methodology is represented by the blue dots (starting points), the red arrows (addition paths) and orange diamonds (selected clear points).

The use of automated clear-cloud point techniques, either through turbidity or camera analysis, has greatly intensified the acquisition of solubility data. The **clear-cloud point method for solubility determination** with the ***Crystal16*** and its integrated turbidity sensors enables scientist to easily obtain and reproduce their data, without too much effort when compared to the EqC method. The **solvent addition method** applied with the ***Crystalline*** and its particle viewer cameras is a popular technique for solubility determination at constant temperature and fast generation of isothermal phase diagrams. As a result, these methods are widely applied in many laboratories around the world both industry and academia. About 25 scientific articles are written each year where the use of ***Crystal16*** and ***Crystalline*** in such measurements is emphasized.

Next to multiplexing the principle of clear/cloud point measurements, automation of the instrument has led to an enhancement of the efficiency and a reduction of the labor costs for this analysis method, which should encourage the use of solubility data from the early stages of discovery to crystallization process development and up to formulation stage.

For more information on ***Solubility: Importance, Measurement and More*** please check our website for the ***webinar*** with the same title presented by Prof. dr. Joop ter Horst, our publications database or the references mentioned in this document.

If you are interested in a free demonstration or assessment write to us via the website or at ***info@crystallizationsystems.com***.

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