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Review

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On the Measurement of Solubility

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Supporting Information

ABSTRACT: The focus of this contribution is on the understanding of solubility that is a prerequisite to any meaningful measurement, reporting, and interpretation of solubility data. A brief reprise of the thermodynamics of solubility is followed by a summary of 'excess solvent' and 'excess solid' methods of measurement in common usage. Case studies illustrate how temperature, polymorph, water, and impurities can change the measured solubility by factors of 2 or more. The interplay between these factors and the method of measurement is explored, drawing on the differing academic, industrial, and geographical perspectives of the authors.

1. INTRODUCTION

Solubility data are essential for the design and optimisation of many experimental studies, including chemical analysis, salt and polymorph screening, organic process development, and crystallisation. In the fine chemicals industries, typical solvents include a range of organic liquids and their mixtures with each other and with water. Solutes are typically organic molecules and their salts. Variable solubility data for different batches of a compound are commonplace, and in some cases are considered unsurprising. Discussions on how to measure solubility typically focus on the relative merits of different analytical methods, for example gravimetric, HPLC, NMR, or turbidity.

The focus of this contribution is on the understanding of solubility that is a prerequisite to any meaningful measurement, reporting, and interpretation of solubility data. A brief reprise of the thermodynamics of solubility is followed by a summary of 'excess solvent' and 'excess solid' methods of measurement in common usage. Case studies illustrate how temperature, polymorph, water, and impurities can change the measured solubility by factors of 2 or more. The interplay between these factors and the method of measurement is explored, drawing on the differing academic, industrial and geographical perspectives of the authors.

1.1. Theory. Solubility is a measurement of the equilibrium state between a solid and liquid phase (Figure 1):

There are several assumptions in this simple picture. For reproducible solubility measurements, the temperature and composition of the system must be constant. Less obvious, but just as important, is that the solid form (polymorph, hydrate/solvate, salt, cocrystal) should also be constant. The measurements should all be made at equilibrium. If the solute can dissociate, then the extent of this dissociation should be constant.

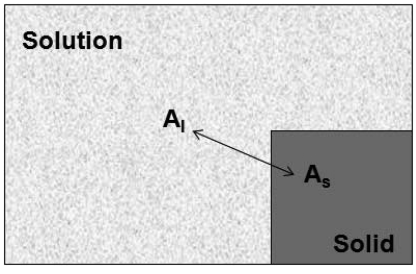

Figure 1. Solubility equilibrium.

Applying the phase rule to solid/liquid systems[1] has much to offer here. At a constant temperature, solubility is a constant in any system at equilibrium that contains only two components. Many solubility measurements, either knowingly or unknowingly, contain a third component, often water or an impurity. Under certain circumstances, this third component can have a dramatic impact on the 'solubility' that is reported.

1.2. Methods of Measurement. Adding solvent gradually until all the solid dissolves is common practice in process development. A variant of this technique is to increase the temperature until all the solid dissolves. If the human eye is replaced by a light source and a detector, this method can be automated.[2,3] In the past decade many new laboratory devices based on this technique have become available, working at ever-decreasing scales.[4,5] These methods are referred to as 'turbidity', 'clear point', or by the proprietary names of the equipment used. The methods assume that the equilibrium between solid and liquid is re-established rapidly as temperature or solvent volume increases. The results are usually quoted as 'mass of solute per volume of solvent', or sometimes as 'relative volumes'. The measurement is characterised by the detection of a single liquid phase containing 'excess solvent'.

Alternatively, equilibrium is established between a solution and 'excess solid', the solution is sampled and the solution composition is determined. This analysis can be performed separately using classical derivatisation/titration techniques,[6] gravimetric methods,[7−9] HPLC,[10−12] NMR, UV−vis spectroscopy,[13] or other techniques. A variant of this method is to filter, dry, and weigh the solid that has not dissolved, and complete

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the solute mass balance to determine the amount dissolved. The results are usually quoted as 'mass of solute per volume of solution'. At high concentrations, there will be significant differences between the solubility in 'g/L (grams/litre) of solvent' and in 'g/L of solution'. As a crude estimate, at a solubility of 100 g/L of solvent, the additional volume due to the solute will be ~70 mL (7%), using a typical solute density of 1.4 g/mL and neglecting any volume change on dissolution.

At elevated temperatures, sampling can be difficult, and may be avoided by using probes to determine the solution concentration in situ. Attenuated total reflection (ATR) techniques such as FTIR[14] and UV−vis[15] are not affected by the presence of solid. These techniques can also be automated, together with the necessary calibration routines. The units of measurement depend on how the calibration is performed.

Here the terms 'excess solvent' and 'excess solid' are used to distinguish between these two approaches.

2. CASE STUDIES

Five case studies illustrate the effects of temperature, polymorph, water, and an impurity on solubility and its measurement.

2.1. Temperature. Figure 2 shows data from a recent experimental determination of the solubility of fumaric acid in

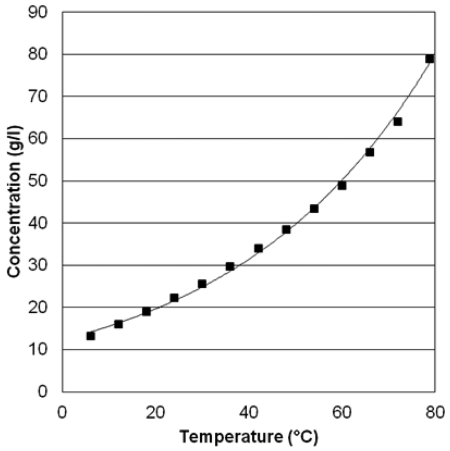

Figure 2. Solubility of fumaric acid in *n*-propanol as a function of temperature.

n-propanol.[16] An 'excess solvent' method was used, and temperature was reported with an accuracy of ±0.05 °C. Solubility data were measured at 13 temperatures ranging from 6.0 to 78.8 °C, and reported as mole fractions as a function of absolute temperature. Figure 2 shows these data converted to g/L of solvent, using an approximated solvent density of 0.80 g/L, with the temperature converted to °C.

The line in Figure 2 is an exponential fit using eq 1[17]

$$s = a \cdot \exp(b \cdot T) \quad (1)$$

The fit is good, with $R^2 = 0.996$. 's' is the solubility in grams per litre of solvent, and T is the temperature in °C. 'a' is the extrapolated solubility at 0 °C in g/L (12.31g/L in this case). 'b' is related to the solubility doubling temperature, ΔT_{sd}, by eq 2[17]

$$b = 0.693/\Delta T_{sd} \quad (2)$$

Here $b = 0.0234\ °C^{-1}$; hence, $\Delta T_{sd} = 30$ °C. As can be seen by inspection of Figure 2, any temperature increase of 30 °C corresponds to a doubling of the solubility.

Moreover, $100b$ is the % change in solubility for each 1 °C temperature change: 2.3% in this case (see Supporting Information for further details). Using the process heuristic that 'on average, $\Delta T_{sd} \approx 20$ °C (Black's rule),[17] the average change is 3.5% for every 1 °C change in temperature.

It follows that the common practice of quoting solubility to the nearest 1 °C introduces an average error in measured solubility of 3.5%, which may be significant. 'Excess solvent' methods are typically isothermal, which makes accurate temperature determination easier. For example, in selected literature studies, the accuracy in temperature is quoted to ±0.1 °C,[9,13] ± 0.05 °C,[8,16] or ±0.02 °C.[6]

When comparing data between different experimental set-ups, whether in the next fume cupboard or on another continent, there will be an additional source of error due to different thermocouple calibrations. It is unusual to find a description of a temperature calibration check associated with the measurement of solubility data.[9] When scaling up to kilo lab, pilot plant, and production scale, increased uncertainties in temperature measurement must be considered. This can be particularly important when specifying seeding temperatures.

These considerations expose the disadvantages of quoting solubility data measured 'at room temperature'. The meaning of 'room temperature' varies with time and place, and particularly with local climatic extremes and the extent to which laboratories are exposed to them.

If the solubility has been measured at one temperature only, the solubility at other temperatures can be estimated using $\Delta T_{sd} \approx 20$ °C, and this estimate can be used to design further solubility experiments. If the solubility has been measured at two temperatures, ΔT_{sd} for the system can be estimated. For three or more data points, a plot such as Figure 2 shows how well the data follow eq 1 and identifies potential outliers. Four data points spanning the required temperature range and a good data fit may suffice to the design a successful cooling crystallisation process.[18] If more data points are available, curve fitting using eq 1, which has only two parameters, may highlight outliers. For racemic tartaric acid monohydrate in water, analysis of eight measurements from the literature suggested that the two data points at elevated temperatures were data for the anhydrous form.[19] Introducing a third parameter would have given a better data fit and concealed the significance of these data. In most cases, two parameters are sufficient,[17] and where this is not the case, the data should be verified.

2.2. Polymorph. Figure 3 (left) shows in-house data comparing the solubility of the same batch of a pharmaceutical development compound in the process solvent measured using two different techniques. The 'excess solid' data (filled triangles) were measured using a calibrated ATR-UV/vis probe in a vessel equipped with an overhead stirrer. The four 'excess solvent' measurements (open squares) were determined by adding different solute/solvent compositions to four HPLC vials, placing the four vials in a 'Crystal16' apparatus, agitating using magnetic fleas, and heating until all the solid had dissolved, as detected by in situ light scattering. The differences between the two data sets were too large to be due to differences in heating rates, equilibration times, or temperature calibration.

A new polymorph, 'Form B' was discovered in later studies. Figure 3 (right) shows solubility data for Form B (filled

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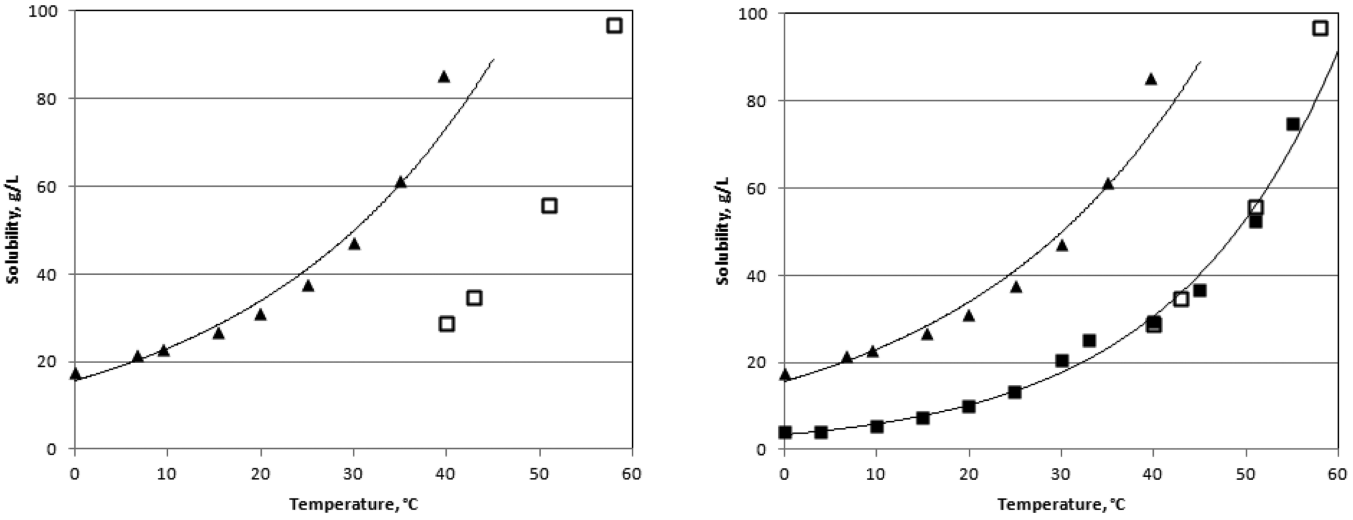

Figure 3. (Left) Solubilities measured by 'excess solid' method (filled triangles), and by 'excess solvent' method (open squares). (Right) With additional 'excess solid' data for Form B (filled squares). Lines are fitted using eq 1.

squares), measured using the same 'excess solid' method as previously. The data are very different from the solubility data measured by the same method for 'Form A' (filled triangles). However, the data are consistent with the solubility data measured by the 'excess solvent' method (open squares), using Form A as the starting material.

The solubility data for both polymorphs using the 'excess solid' method are fitted well using eq 1; R^2 = 0.97 (Form A) and 0.99 (Form B). The solubility doubling temperatures (ΔT_{sd}) are significantly different at 18.0 °C for Form A and 12.6 °C for Form B. The solubility ratio increases from 2.9 at 40 °C to 4.6 at 0 °C, large but not unprecedented differences in solubilities for polymorphs.[20]

This suggests an explanation for the 'excess solvent' solubility data measured using Form A as the starting material. Form A could have converted to Form B before the material has dissolved. The grinding action of the magnetic fleas may explain how this transformation occurred during the 'excess solvent' measurements but did not occur during the 'excess solid' measurements.

However, it is difficult to test this hypothesis directly because, in the 'excess solvent' method, *the solid disappears*. Furthermore, the transformation of Form A to Form B does not have to be complete. The outcome of 'excess solvent' measurements on other batches of Form A is difficult to predict, being at the mercy of the transformation kinetics. One advantage of 'excess solid' methods is that the solid can be checked, for example by powder X-ray diffraction, after the solubility measurement.

2.3. Water. Figure 4 shows data from the literature[17] illustrating the effect of low levels (up to 3.2%) of water on the solubility of a pharmaceutical development compound in ethyl acetate, measured using an 'excess solid' method.

Fitting the data using eq 1 reflects the scatter in the data, with R^2 values of 0.99, 0.90, 0.86, and 0.85 as the water level increases. Using the relationship between b and the solubility doubling temperature shows that this parameter is relatively constant as the water level increases (19, 23, 24, and 20 °C, respectively). The other parameter, a, which is the extrapolated solublity at 0 °C, trebles (0.96, 1.71, 2.65, and 2.85 g/L) as the water level increases. This demonstrates that careful control of water level is necessary. This is a common phenomenon,

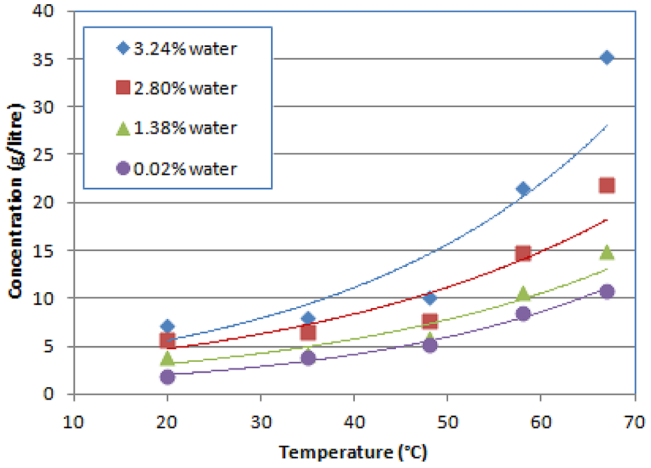

Figure 4. Example of solubility as a function of temperature and water content. Lines are data fits using eq 1.

particularly in hydrophobic solvents such as ethyl acetate where the water is highly active.

Three different potential sources of water must be controlled. If the solid contains low levels of water, the amount of water in the system will increase as more solid is added, and the amount of water that partitions to the liquid phase may also increase. If, as was the case here, the preceding process step was separation of an aqueous layer, then distillation may be required to remove remaining water. Water can also be absorbed by the solvent, either before or during the experiment. In these experiments the quoted water level for each system was determined using Karl Fischer analysis, giving data expressed as % by weight.

Where solubility is very sensitive to water levels, the differences between '% by weight' and '% by volume' can be significant. When preparing solvent mixtures by volume, significant differences have been observed between measuring the volume of each solvent separately and increasing the total solvent volume from, say, 95 to 100 mL by adding water to a measuring cylinder.

The solubility doubling temperatures at the four water levels are all in the range 19–24 °C consistent with 'Black's Rule'.[17]

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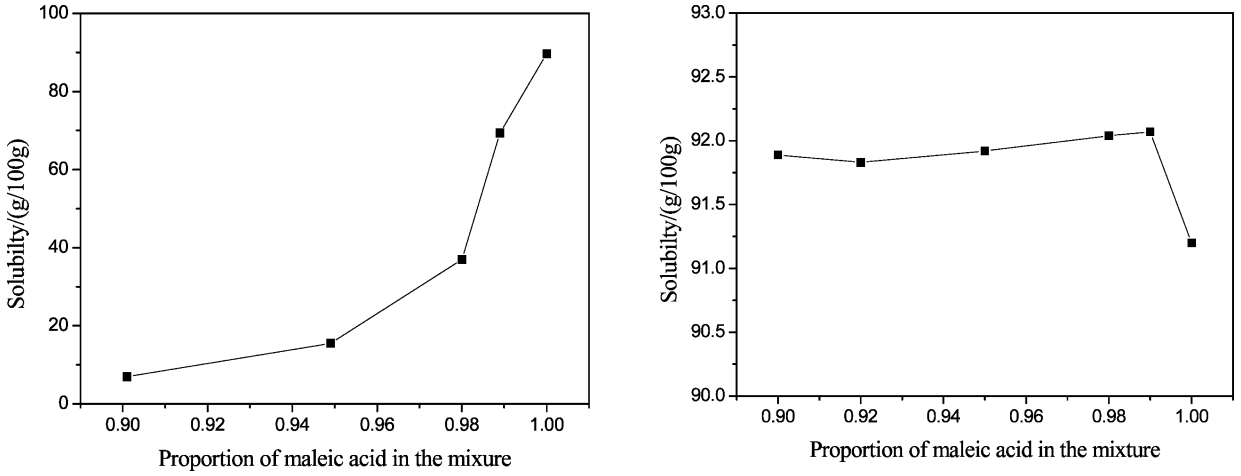

Figure 5. Measured 'solubility' of maleic acid/fumaric acid mixtures, using an 'excess solvent' method (left) and an 'excess solid' method (right).

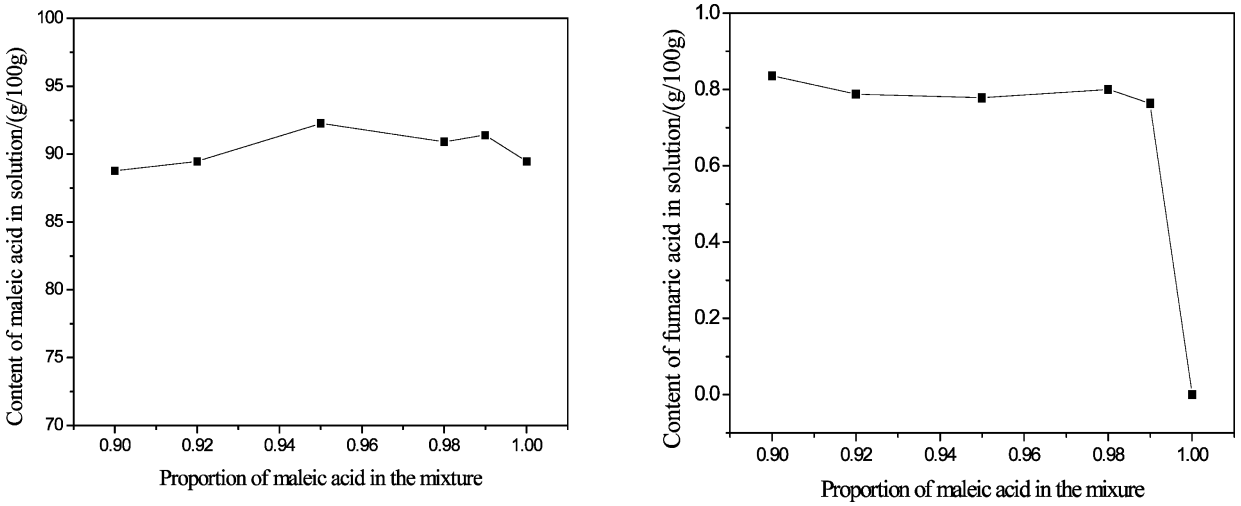

Figure 6. HPLC analysis of the solute from the 'excess solid' experiments: maleic acid (left) and fumaric acid (right).

In this system, a temperature increase of 1 °C has a similar effect on the solubility to the addition of 0.1% water.

2.4. Impurity. Maleic acid and fumaric acid are geometric isomers of 2-butenedioic acid. Maleic acid forms an intramolecular hydrogen bond, whereas fumaric acid cannot. The respective solubilities in water at 30 °C are 91.2 g/100 g and 0.8 g/100 g.[16,21] The energy associated with the intramolecular hydrogen bond will be of the order of 10 kJ/mol, sufficient to account for the 125-fold difference in solubility.

To illustrate the effect of a less soluble contaminant, the aqueous solubilities of maleic acid samples contaminated with up to 10% of fumaric acid were measured by 'excess solvent' and 'excess solid' methods at 30 °C. The 'excess solvent' method detected the disappearance of the solid by measuring the intensity of a laser beam transmitted through the sample.[16] As can be seen from the data in Figure 5, the 'solubility' as measured by the 'excess solvent' method varies from 8 to 92 g/100 g water.

In the 'excess solid' experiments, samples of solution were withdrawn after equilibration and analysed both gravimetrically (Figure 5, right) and by HPLC (Figure 6). Note the differences in scales of the vertical axes.

For pure maleic acid, the measured solubilities are consistent with the literature value of 91.2 g/100 g. In all other cases, the total solubility of ~92 g/100 g is consistent with ~91 g/100 g of maleic acid and ~0.8 g of fumaric acid—also consistent with the literature values. The equilibrium between solid and dissolved maleic acid is not affected significantly by the presence of fumaric acid, and vice versa.

The observations in the 'excess solvent' method may be understood qualitatively by reference to a schematic ternary phase diagram (Figure 7). The 'excess solvent' method starts from point M, and as solvent is added, the system composition moves along the line towards L. At point S all of the more soluble component (here maleic acid) has dissolved, but there is still some undissolved fumaric acid. The laser beam then detects the disappearance of solid fumaric acid.

This approach can also be used to quantify the effect. Consider the dissolution of a mixture of 10 g of fumaric acid and 90 g of maleic acid in water. When 100 g of water has been added, all the maleic acid will dissolve (point S). However, only 0.8 g of fumaric acid will dissolve, leaving 9.2 g in suspension. In order to obtain a clear solution, a total of 1250 g of water will be necessary to dissolve 10 g of fumaric acid (point C). The measured 'solubility' is then 100 g solid in 1250 g water, or 8 g/100 g. The results of similar calculations at other fumaric acid levels are shown in Figure 8, which shows good agreement with Figure 5 (left).

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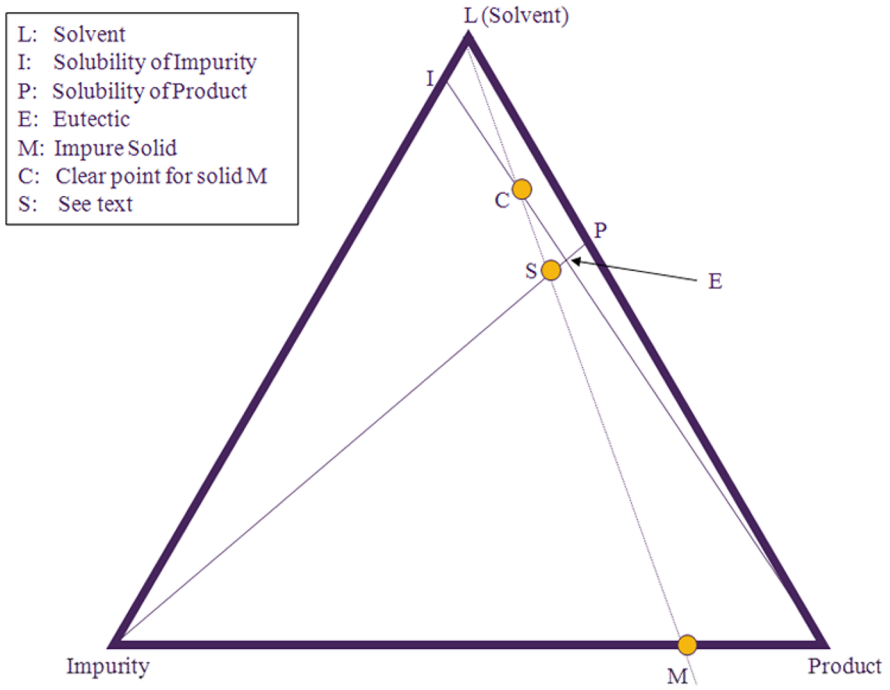

Figure 7. Schematic phase diagram for a ternary system solvent/product/impurity, where the impurity is much less soluble than the product.

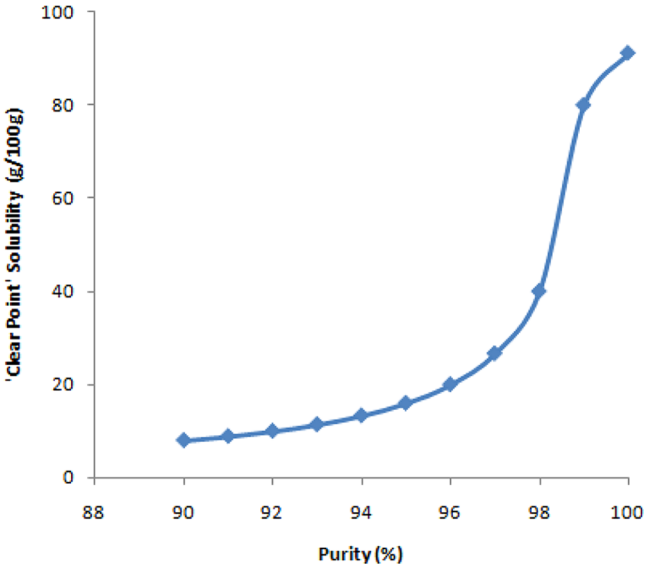

Figure 8. Simulation of 'excess solvent' solubility data for maleic acid contaminated with fumaric acid; compare with Figure 5 (left).

Figure 7 also reveals how low levels of maleic acid will affect solubility measurements of the less soluble fumaric acid. The impact is much lower; at levels up to 10%, the main effect is predicted to be that the solubility will be overestimated by the same amount, unless a selective analytical method such as HPLC is used to measure the concentration of solute.

In this system, the eutectic position is at ~0.8% fumaric acid. Any measurements on samples containing more than 0.8% fumaric acid will show this effect. Note that 'excess solid' methods may also be affected, if the system composition is between points C and S. The 'excess solid' in this case is pure fumaric acid, and the maleic acid is undersaturated, but this will only be revealed if the composition of the solid is checked.

This effect can be much more troublesome if the impurity has not been identified or its presence is not suspected. In this example, if the purity of maleic acid/fumaric acid mixtures were assessed by titration, samples of 'maleic acid' could easily contain 10% or more of fumaric acid. Insoluble impurities may also escape detection by analytical methods such as HPLC that require the analyte to dissolve.

This effect can occur in any system in which the impurity is much less soluble that the solute—more specifically, if the purity is less than the eutectic composition. This is particularly relevant to chiral systems in which the 'insoluble impurity' is the racemic compound. This type of behavior has also been reported for the chiral system dexclamol hydrochloride, in which the pure enantiomer is 5 times more soluble than the racemate. Even at levels below 2%, the opposite enantiomer affected the amount of water required to dissolve the entire sample.[22]

When forming salts or cocrystals, it is probable that the counterion/coformer will be much more soluble than the product. Phase diagrams of such systems show features similar to that of Figure 7 where the counterion/conformer is present in excess.[12,23] In such systems, measuring the solubility by a different method may also give very different results. Small changes in pH can also alter the solubility of ionizable compounds by orders of magnitude, but further discussion is beyond the scope of this paper.

2.5. Impurities and Polymorphs. Figure 9 shows the chemical structures of sulfamerazine, and a structurally related impurity. The effect of this impurity on the rate of the solution-mediated transformation between the metastable and stable polymorphs of sulfamerazine has been reported.[24] If the impurity is present at a level of 0.5% of the solute, the transformation in unseeded experiments was delayed by over 24 h—long enough to affect some solubility determinations. With reference to section 2.2 above, this is another mechanism by which low levels of impurity can influence the outcome of a solubility measurement, in this case by inhibiting the trans-

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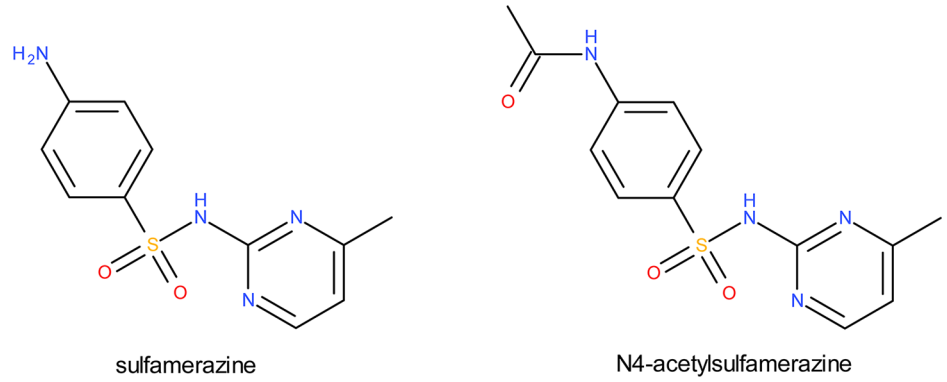

Figure 9. Sulfamerazine and a structurally related impurity.

formation to the most stable polymorph. In this case both 'excess solid' and 'excess solute' methods could be affected.

In a separate study[25] on the effect of solvents on this polymorphic transformation, it was noted that no transformation at all occurred in acetic acid—possibly because the impurity above was formed during the experiment. This highlights a potential disadvantage of leaving solubility experiments for long time scales—the levels of certain impurities may increase over time and influence the results either directly (by removing solute) or indirectly (by crystallising or inhibiting transformations).

How long is required for 'excess solid' methods to reach equilibrium? In previous studies, equilibration times from 6 h[8] up to 5 days[12] have been used. However, performing repeated analyses of solution concentration over time to reach a consistent value (within 1%)[13] may not detect polymorphic transformations. Given the added risks inherent in long-term experiments, equilibration overnight is a sensible compromise.

CONCLUSION

The case studies illustrate simple rules for measuring solubility data using either 'excess solid' or 'excess solvent' methods. Advantages of 'excess solvent' methods include speed, the potential to work at small scale, and ease of automation. Disadvantages include potential inaccuracies in temperature measurement, and the inability to check the composition and polymorph of the last solid to dissolve.

'Excess solid' methods are slower, more labour-intensive, and typically require more material. One advantage of these methods is that the chemical composition and physical form of the solid can be checked. This is recommended if the presence of new polymorphs or insoluble impurities is suspected. Equilibration overnight is recommended.

For both methods, the temperature must be measured and quoted to an appropriate accuracy. When using 'dry' solvents, test the water content at the end of the experiment. At the end of prolonged experiments, check for degradation of the solute with a chemically specific analytical method (HPLC, NMR).

The common observation that solubility varies from batch to batch is, in the experience of these authors, usually due to one of the factors mentioned above. More exotic explanations, such as partial solid solutions or complexation in solution, are only rarely justified.

ASSOCIATED CONTENT

Supporting Information

The derivation of the relationship between the parameter '*b*' in eq 1 and the percentage change in solubility. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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