

Crystallization Kinetics of Ibuprofen from Ethanol and Aqueous Ethanol

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Ibuprofen [2-(4-isobutyl-phenyl)-propionic acid] is a common analgesic pharmaceutical. It is substantially insoluble in water but quite soluble in organic solvents. Ibuprofen here has been crystallized from ethanol and aqueous ethanol. Batch experiments were undertaken from 10 to 40 °C to measure the solubility, the width of the metastable zone and the growth kinetics. The solubility in ethanol varies markedly with temperature. Generally solubilities fall as the water content increases for aqueous ethanol. At 40 °C, saturated solutions with solvent water contents from 35 to 65 % w/w show a phase separation into two liquid layers. The metastable zone width for primary nucleation is substantial, but is much narrower for secondary nucleation. None the less, growth rates in this narrow secondary metastable zone are still significant and this region, with care, can be used for non-nucleating seeded batch crystallizations. Crystal growth rates were found to be first order with supersaturation, with growth rate constants increasing with temperature [activation energy = 23.4 (±50%) kJ/mol] and within the accuracy of measurement not changing with the solvent water content.

1. Introduction

Ibuprofen [2-(4-isobutyl-phenyl) propionic acid] is a widely used NSAID anti-inflammatory drug, with the formula C₁₃H₁₈O₂, molecular weight 206.27 and melting point 75 – 77 °C (O'Neil *et al.*, 2006). It is insoluble in water but soluble in many organics (Gracin and Rasmuson, 2002; Garzon and Martinez, 2004). It may be purified by crystallization. Crystallization from ethanol and aqueous ethanol will be considered here. The solubility of ibuprofen in ethanol varies substantially with temperature (Gracin and Rasmuson, 2002) so supersaturation may be generated by cooling solutions. The chemical structure of ibuprofen is shown in Figure 1. Two isomers [R(+) and S(-)] are possible depending on the location of the groups about the location indicated by an asterisk on Figure 1. The S(-) form is pharmaceutically active. All experiments were undertaken with racemic ibuprofen. Figure 2 illustrates crystals grown in this study. The primary data required for the design of crystallizers is,

1. Solubility and phase information.

2. Nucleation thresholds and metastable zones.
3. Growth rate kinetics and effect of operating conditions
4. Nucleation rates (primarily secondary nucleation).

The first three will be considered here in turn.

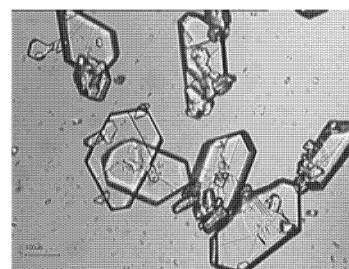
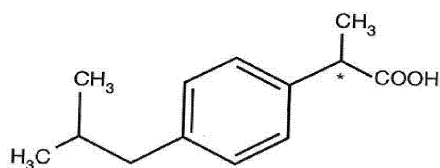


Figure 1: The chemical structure of ibuprofen. The asterisk (*) indicates the atom where arrangement of the CH_3 and COOH entities give the *R* and *S* isomers (Lerdkanchanaporn and Dollimore, 1997). Figure 2: Ibuprofen crystals grown in this study. The scale bar is 100 μm .

2. Solubility

The solubilities of racemic ibuprofen in absolute ethanol and in aqueous ethanol mixtures were measured at temperatures from 10 to 40 °C, the expected practical temperature range. The solubility studies were carried out by the dissolution of excess ibuprofen crystals in stirred Schott bottles kept in a constant temperature bath. The ibuprofen concentration of the clear supernatant at equilibrium, after settling, was determined by vacuum drying. An allowance was made for the small amount of sublimation from dried ibuprofen. Further details are given by Rashid (2011).

The solubilities of ibuprofen in ethanol are plotted in Figure 3. Ibuprofen solubility increases dramatically with temperature. The data may be correlated by $\text{I}^*/\text{E} = 0.497 (\pm 0.008) + 0.001026 (\pm 0.000012) \text{T}^2$, where I^*/E is the solubility as mass ratio of ibuprofen to ethanol and T is the temperature in °C. The values in brackets are the 95% uncertainty on the parameters. This correlation fits 95% of the data within $\pm 0.03 \text{ I}^*/\text{E}$ units and is believed to predict the true solubility within $\pm 1\%$.

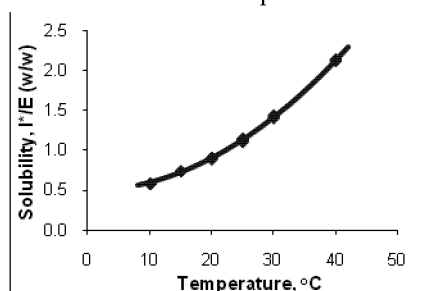


Figure 3: Solubility of ibuprofen in absolute ethanol.

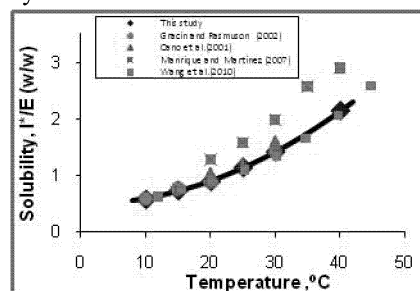


Figure 4: Comparison with published solubilities.

Published solubility data for ibuprofen in absolute ethanol are available and these are shown on Figure 4. Our results are in good agreement with Gracin and Rasmuson (2002) and most of the data of Wang *et al.* (2010), but lie somewhat below the results of Cano *et al.*, (2001) and considerably below the data of Manrique and Martinez (2007). Figure 5 shows the solubility of ibuprofen in aqueous ethanol against water content [$X_W = W/(E+W)$, w/w] at 10, 25 and 40 °C. Initially adding water increases the solubility at 25 and 40 °C, but then it decreases. At 40 °C solutions with $35 < X_W < 65$ % show two immiscible liquid phases behaviour, as reported by Manrique and Martinez (2007). Figure 5 also illustrates the two phase region for undersaturated solutions at 40 °C.

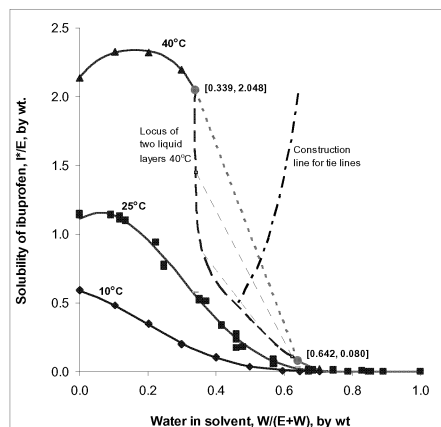


Figure 5: Solubility of ibuprofen in aqueous ethanol mixtures at 10, 25 and 40 °C.

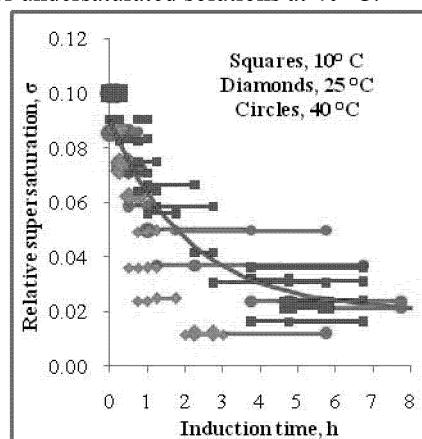


Figure 6: SNT in ethanol at 10, 25 and 40 °C.

For aqueous ethanol, three Yalkowsky papers (Machatha *et al.*, 2004, Machatha and Yalkowsky, 2005, Millard *et al.*, 2002) mention eight solubility data values amongst the over 200 materials they consider, but they do not appear to have published the actual values.

3. Metastable Zone

The metastable zone (**MSZ**) is the region above the solubility curve where growth can occur without nucleation. The metastable zone width (**MSZW**) is determined here under isothermal conditions using the induction time procedure which measures the time to nucleate for isothermal supersaturated solutions. In the absence of crystals, nucleation will not occur below the **PNT** (Primary Nucleation Threshold); if crystals are present, below the lower **SNT** (Secondary Nucleation Threshold). Solutions of various supersaturations (with and without added crystal) were held in stirred Schott bottles in a constant temperature bath and observed until nucleation was seen. The onset of nucleation is hard to decide so the induction time results are given as two times, the latest time when there definitely were no nuclei and the earliest time when there definitely were. The actual nucleation time lies between the two.

Figure 6 shows the induction time results for secondary nucleation (i.e. with crystals present) in ethanol at three temperatures. Supersaturation is given here as the relative supersaturation by wt., $\sigma = (I/E)/(I^*/E) - 1$. For comparison purposes the SNT will be chosen as the relative supersaturation at a 1 h induction time. This is considered a time relevant to ibuprofen crystallization. For absolute ethanol, the relative 1 h SNT supersaturations range from 0.03 to 0.08, which are quite small. Figure 7 shows the threshold results (now in $\Delta I/E$ units) superimposed on the solubility diagram. The secondary **MSZW** is narrow and the primary large. The results for aqueous ethanol at 25°C are shown in Figure 8. The results at other temperatures are similar (Rashid, 2011).

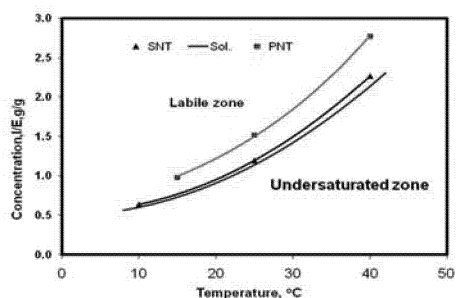


Figure 7: Solubility diagram for ibuprofen in ethanol with SNT and PNT curves.

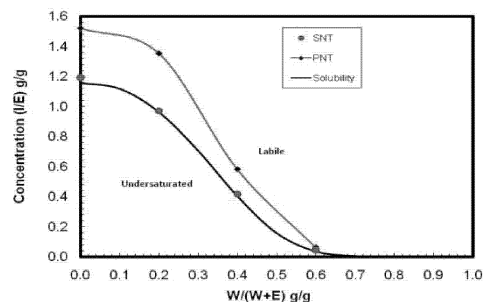


Figure 8: SNT and PNT values in aqueous ethanol mixtures at 25°C.

4. Growth Rate

Seeded non-nucleating batch crystallizations in a 1 L well stirred crystallizer were carried out at 10, 25 and 40 °C. Though the **MZW** for secondary nucleation is quite small, typically corresponding to a subcooling of about 1°C, growth at significant rates can still occur in this zone. Special **SPG** (size proportional growth, where the crystal size is directly proportional to the growth rate) seed was prepared and used. This material is convenient to show **GRD** (growth rate dispersion effects). Solution samples were taken at suitable time intervals during the batch for analysis to give the supersaturation and solids sizing to give the size distributions. Figure 9 shows the size distributions (plotted on a log size scale) for one run.

Apart from the seed (the left most size distribution in Figure 9) the other size distributions have a similar shape (within measurement errors) on a log size scale. This behaviour illustrates that ibuprofen growth exhibits GRD and has a log normal distribution of growth rates with a spread $CV_G = 0.5$.

Figure 10 shows the increase in crystal size (here taken as the volume median size) and the drop in supersaturation during a run. From this data, the growth rate kinetics can be determined (Rashid, 2011; Rashid et al., 2010). A first order relation (Figure 11) was obtained as $G = k_G s$, where G is the growth rate of the volume median sized crystals (in $\mu\text{m}/\text{min}$), s is the supersaturation (as $\Delta I/E$) and k_G is the growth rate constant (as $\mu\text{m}/\text{min}/\text{unit of } s$).

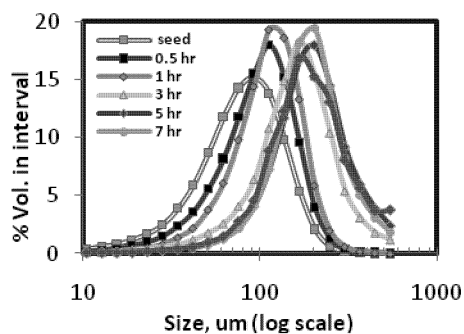


Figure 9: Size distributions of samples during a crystallization run.

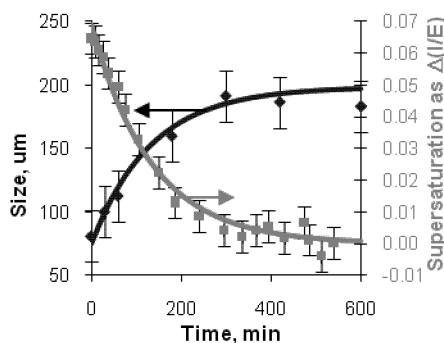


Figure 10: Supersaturation and size results for one run.

Figure 12 shows the measured dependence of k_G on temperature (T , °C) for absolute ethanol which can be correlated by $k_G = 4.8 (\pm 20\%) \cdot \exp(T/29 (\pm 35\%))$ where the values in brackets are the 95% uncertainties on the parameters. This corresponds to an activation energy of 23.4 ($\pm 50\%$) kJ/mole, which is a doubling in growth rate for approximately every 20°C temperature change. Within the accuracy of measurement k_G does not change with the water content of the solution.

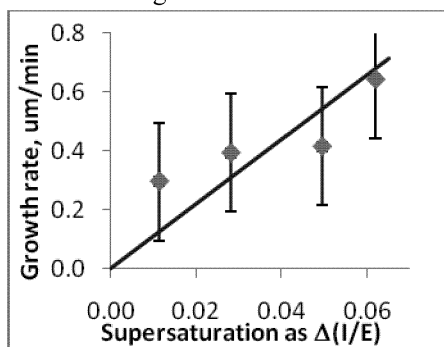


Figure 11: Growth rate vs. supersaturation for one run.

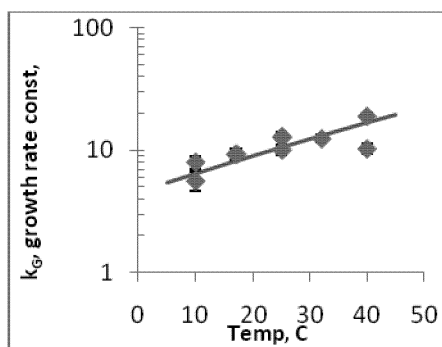


Figure 12: k_G (as $\mu\text{m}/\text{min}/\text{unit } \Delta I/E$) for ibuprofen in ethanol at various temperatures.

5. Conclusions

1. The solubility, metastable limits and the growth rate kinetics have been measured for ibuprofen crystallizing from ethanol and aqueous ethanol.
2. The solubility increases greatly with temperature. A small amount of water can increase the solubility of ibuprofen (salt in) but generally water will decrease the solubility (salt out).
3. At 40 °C, saturated solutions with solvent water contents from 35 to 65 % w/w show a phase separation into two liquid layers.
4. Cooling, evaporation of ethanol or adding water to an ethanolic solution can promote supersaturation for crystallization.

5. The secondary metastable zone is narrow, but with care, non-nucleating batch crystallizations can be carried out. The primary metastable zone is appreciable.
6. The growth rate dependence on supersaturation is first order and a correlation was obtained. The growth rate doubles for about every 20 °C temperature rise.
7. This data is sufficient to design well mixed non-nucleating batch crystallizers. With nucleation rates (now being measured) nucleating batch and continuous crystallizers can be designed.

Acknowledgement

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