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Research Article

The Metastability and Nucleation Thresholds of Ibuprofen in Ethanol and Water-Ethanol Mixtures

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To investigate the crystallization of ibuprofen [((*RS*)-2-(4-(2-methylpropyl) phenyl) propanoic acid)] from ethanol and water-ethanol mixtures it is necessary to know the nucleation limits of its solutions. In the absence of crystals, nucleation will seldom occur below the PNT (primary nucleation threshold). If crystals are present, nucleation will seldom occur until below the lower SNT (secondary nucleation threshold). Below the SNT, crystals will still grow with negligible nucleation. PNT and SNT values (expressed as relative supersaturation σ) have been measured at 10, 25, and 40°C for ibuprofen in ethanol and in a range of mixtures of different ethanol (E)/water (W) ratios. The induction times were determined from observing the times to nucleate for a range of different supersaturated solutions at a given temperature and E/W ratio. As expected, lowering the supersaturation leads to longer induction times. In ethanol, the SNT values are small and thus the secondary metastable zone width (MSZW) is relatively narrow with a 1 h SNT relative supersaturation typically about $\sigma \sim 0.05$. The 1 h PNT values are much larger with values for σ around 0.3. In aqueous ethanolic mixtures at 25°C, both the PNT and SNT decrease as the water content increases.

1. Introduction

Crystallization is a key separation and purification process used in the pharmaceutical and related industries. About 70% of solid products are produced in crystal form [1, 2]. The quality of the crystals, such as size and shape, and the progress of the operation are generally considered to be better when crystallization is undertaken inside the MSZ (metastable zone) below the SNT [3–6] (secondary nucleation threshold). The upper limit of the primary nucleation MSZ is the primary nucleation threshold (PNT), while that for the secondary nucleation is the SNT. Experimental determination of the MSZ is time consuming and prone to investigational errors [7]. Two standard approaches [1] are used to determine the MSZ. In the polythermal method, the solution is cooled at a constant rate until nucleation is detected and calculations are then carried out to determine the NT (nucleation threshold) boundary. For the isothermal method, a constant supersaturation is maintained and timing continues until visible crystals are formed. The time between the generation of supersaturation and the formation of visible nuclei is defined as the induction time [8].

Here the metastability and nucleation thresholds of ibuprofen will be based on induction time measurements. These MSZ results have been used in the measurement of the nucleation kinetics and crystal growth kinetics for the ibuprofen crystallization system [9]. The most important benefit of this technique is the simplicity of the experimental method. There are no other comparable published data available for ibuprofen nucleation threshold measurements. This paper gives measurements of the MSZ using isothermal seeded and nonseeded batch crystallizations in ethanol and water-ethanol mixtures.

2. Experimental Section

2.1. Materials. Ibuprofen USP (CAS registry number 15687-27-1), purchased from Professional Compounding Chemists

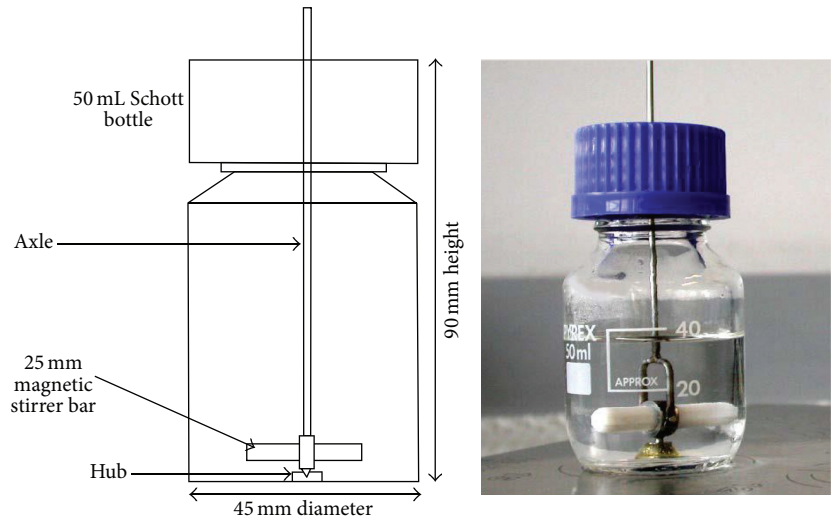

Figure 1: Stirred bottles for metastability experiments.

of Australia Pty Ltd. (Matraville, NSW), was a racemate of ((*RS*)-2-(4-(2-methylpropyl) phenyl) propanoic acid) with the empirical formula $C_{13}H_{18}O_2$ and molecular weight 206.27 g/mol. The melting point of this colourless, crystalline material is quoted as 75–77°C [10]. Ibuprofen is a widely used anti-inflammatory drug.

2.2. Method. A number of 50 mL stirred Schott bottles (Figure 1) with 40 mL of ibuprofen solutions (in ethanol or water-ethanol mixtures) of different known supersaturations were prepared at a warmer temperature (10°C above the test temperature to dissolve ghost nuclei). These were then placed in a constant temperature bath. They were stirred at 250 rpm with a 25 mm Teflon coated magnetic stirrer suspended 5 mm from the bottom of the bottle to avoid crushing seed crystals. The bottles were observed at time intervals to ascertain if they had nucleated, that is, had a white background in the solution distinct from the added larger seed crystals for secondary nucleation (though this was sometimes hard to detect). Further details are given by Rashid [11]. For the secondary nucleation tests a small amount (~0.1 g) of large ibuprofen seed crystal was added to each bottle after it had reached test temperature. At later times, the bottles were inspected by the naked eye to see if they had nucleated. For secondary nucleation, time was measured from the moment of seed addition. Primary nucleation data were obtained in the same way without adding any seed crystals and time was measured from the moment the warmed bottles were added to the bath, which corresponds to a slight overestimate of the nucleation time allowing for the time the bottle cools to the operating temperature (~10 min).

2.3. Detection of Nucleation. A conventional visual inspection method, in which a solution is visually observed at time intervals until it nucleates, was the detection method used in these nucleation threshold experiments. This technique had been extensively used in other crystallization studies [12, 13]. Solutions were inspected at suitable time intervals, with a maximum observation time of 10 h. As it was sometimes hard to detect the onset of nucleation, recorded times were taken as the latest time *definitely* before nucleation and the earliest time when nuclei were *definitely* present in the solution. The true induction time must therefore lie in the time interval between the two. Both times are given in the results and both were used for later regressions.

3. Results and Discussions

3.1. SNT (Secondary Nucleation Threshold) Results. The SNT results for the three temperatures with ethanol alone (no water) are shown in Figure 2. Duplicate tests were undertaken at each temperature. The supersaturation results are shown as the relative supersaturation σ (= $(I/E)/(I^*/E) - 1$, where I is ibuprofen, I^* is its solubility value, and E is ethanol) as this brings the values for different conditions closer together. Horizontal lines join the earliest and latest detection times.

As expected, the lower the supersaturation the longer the time to nucleate. There is also a considerable amount of scatter in the results. This is expected as nucleation is considered to be a random process [1] and further the time estimates rely on the subjective visual detection of the nuclei. It is expected that nuclei form by collision nucleation [1].

The width of the MSZ (MSZW) is small ($\sigma < 0.1$) and thus the SNT is relatively close to the solubility curve. There is no significant effect of temperature, though the 25°C data appear to be lower than the other two sets (10°C and 40°C) which overlap. A common curve (no effect of temperature) was fitted as

$$\sigma_{\mathrm{SNT}} = 0.02\,(\pm 0.01) + 0.07\,(\pm 0.01) * \exp\left\{-\frac{t}{2.1\,(\pm 0.3)}\right\}, \quad (1)$$

where σ is the relative supersaturation (in I/E mass units) and t is the time (in h) to nucleate. The uncertainties are the

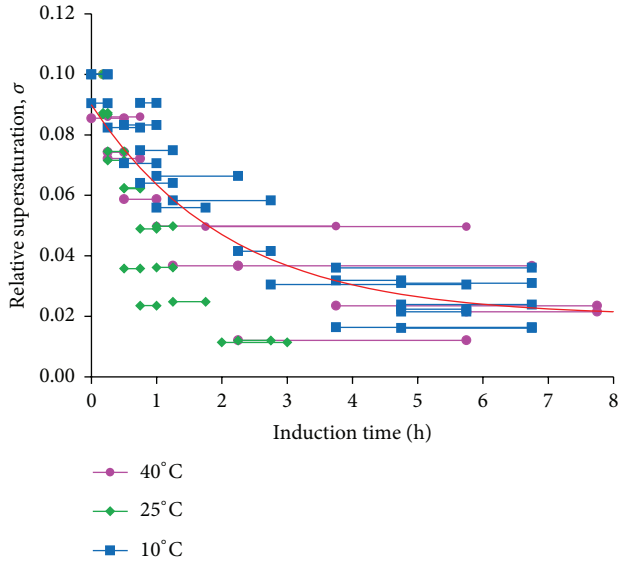

Figure 2: SNT in ethanol at 10, 25, and 40°C. The curve represents the exponential of best fit (1) to all the data. In the graph the points represent the induction time range between the latest time before nucleation was definitely observed and the earliest time after nucleation definitely was observed. Nucleation must have occurred somewhere between these two times.

95% confidence intervals on the parameters. Equation (1) is the line drawn on Figure 2. This curve fits an estimated 95% of the experimental data within ±0.025 supersaturation units. For convenience, 1 h nucleation induction time has been used in the later analysis as a value at this time is considered comparable with the expected growth kinetics. The 1 h SNT values as relative supersaturations from the separately fitted exponentials for the three temperatures are $\sigma = 0.071$, 0.052, and 0.057 for 10, 25, and 40°C (average = 0.060). In $\Delta I/E$ w/w units the corresponding supersaturation values are 0.040, 0.050, and 0.120.

3.2. PNT (Primary Nucleation Threshold) Results. The PNT values for absolute ethanol are shown in Figure 3 for the three temperatures. Note that the lowest temperature here is 15°C rather than 10°C used for SNT. The main point to note is that the PNT supersaturation values are considerably larger than those for SNT (approximately 6 times larger). Again there appears to be little effect of temperature on the results when expressed as relative supersaturation.

All the data was again fitted by an exponential as

$$\sigma_{\mathrm{PNT}} = 0.16\,(\pm 0.04) + 0.39\,(\pm 0.05) * \exp\left\{\frac{t}{1.0\,(\pm 0.3)}\right\}. \quad (2)$$

This relation fits an estimated 95% of the experimental results within ±0.15 relative supersaturation units. The 1 h PNT values are $\sigma = 0.32$, 0.32, and 0.30 at 15, 25, and 40°C (average = 0.31) and 0.24, 0.37, and 0.64 expressed as $\Delta I/E$ w/w. These are approximately 6 times larger than the SNT values.

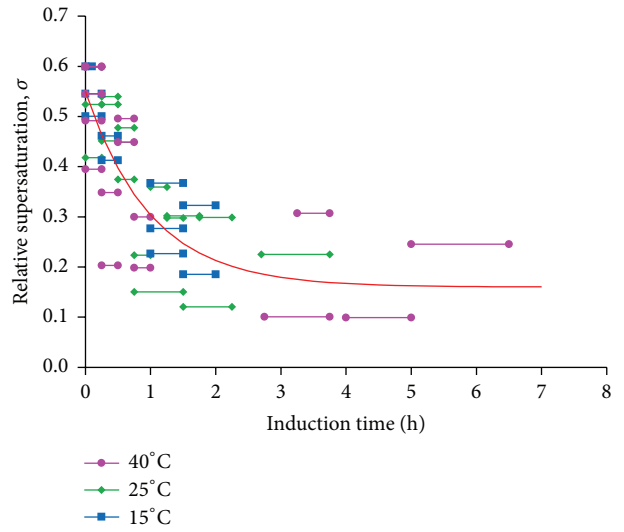

Figure 3: PNT in ethanol at three temperatures. The curve represents the line of fit (2).

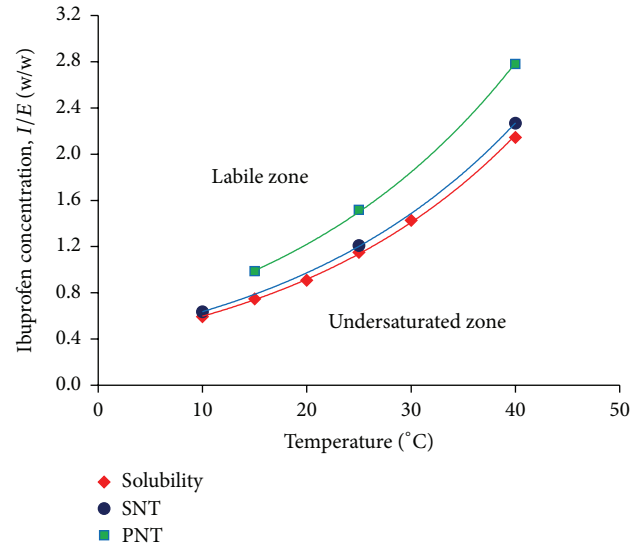

Figure 4: Phase diagram for ibuprofen in ethanol with superimposed SNT and PNT data.

Figure 4 shows the 1 h SNT and PNT values superimposed on the solubility diagram for ibuprofen in ethanol [14]. The metastable zones lie between the nucleation threshold and the solubility curve. The narrowness of the SNT metastable zone is clear.

4. Nucleation Thresholds in Water-Ethanol Mixtures

Nucleation threshold experiments were undertaken at 10, 25, and 40°C. Water-ethanol mixtures ranged from $X_W = W/(E + W) = 0.2$ to 0.6 w/w. Note that only $X_W = 0.2$ was studied at 40°C as phase separation into two liquid phases was observed in high water-ethanol content mixtures [14].

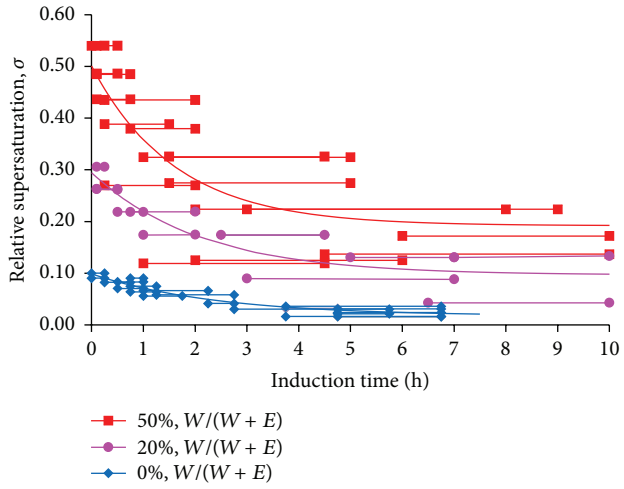

Figure 5: SNT in water-ethanol mixtures at 10°C for three different water concentrations. A best-fit exponential curve is drawn for each concentration.

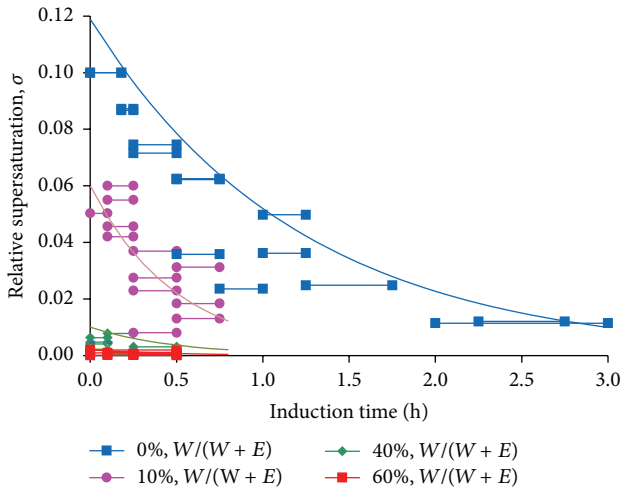

Figure 6: SNT in water-ethanol mixtures at 25°C for four different water concentrations. An exponential curve is drawn for each concentration.

4.1. SNT Results. Figure 5 shows the SNT results for three different water content solutions at 10°C, Figure 6 for four different solutions at 25°C, and Figure 7 for two different water contents at 40°C.

Again the induction time increases as the supersaturation is lowered. The results for each set of data may again be approximated by a negative exponential. For the 25°C results (Figure 6) the initial solutions had a slightly higher supersaturation than intended and all samples nucleated within an hour, so this data is over a reduced induction time range. The fitted exponentials have been used to give extrapolated estimated 1 h results for later comparison.

The estimated 1 h SNT values for all runs are summarized in Table 1 and are plotted against water content in Figure 8.

The measured SNT values as relative supersaturation increase with increasing water content at 10°C but decrease

Table 1: One h σ_{SNT} values from all experiments.

X_W	Temperature, °C		
	10	25	40
0	0.071	0.052	0.057
0.2	0.220	0.008	0.021
0.4	—	0.0014	—
0.5	0.358	—	—
0.6	—	0.0003	—

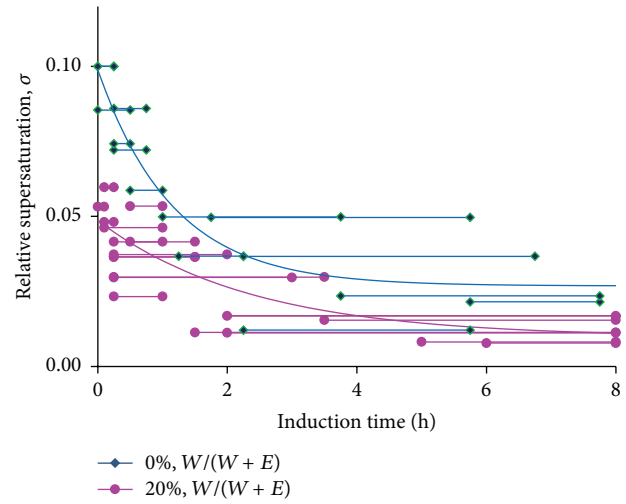

Figure 7: SNT in water-ethanol mixtures at 40°C for two different water concentrations. An exponential curve is drawn through the 20% data and compared with the previous curve for pure ethanol.

at 25 and 40°C. The reason for this different temperature trend is not known. The data may be fitted by exponentials, the straight lines on the log-linear plot of Figure 8 giving the following correlations (with parameter uncertainties) for the effect of water content (as mass fraction) on the 1 h SNT values:

$$\sigma_{SNT} = 0.07\,(\pm 0.09) * \exp\left\{\frac{X_W}{0.31\,(\pm 0.3)}\right\} \quad \text{for } 10^{\circ}\text{C},$$

$$\sigma_{SNT} = 0.060\,(\pm 0.005) * \exp\left\{\frac{-X_W}{0.15\,(\pm 0.04)}\right\} \quad \text{for combined 25 and } 40^{\circ}\text{C data.} \tag{3}$$

These equations summarise all the SNT results.

4.2. PNT Results. The PNT values for various water ethanol mixtures are shown in Figures 9, 10, and 11 for the three temperatures. Note that the lowest temperature here is 15°C (Figure 9) rather than 10°C used for the SNT (Figure 5). Again the induction time decreases as the supersaturation is increased. As was found for ethanol alone, the PNT supersaturation values are considerably larger than those for SNT (still approximately 6 times larger). Also the scatter of results is correspondingly larger.

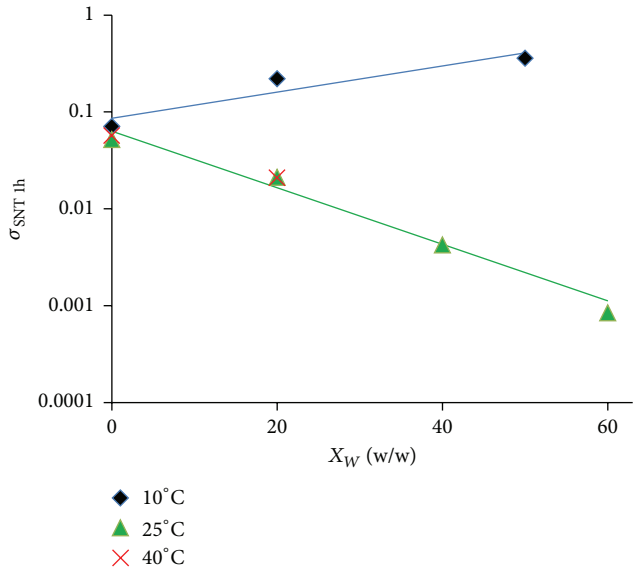

Figure 8: Effect of water concentration on the 1 h SNT values.

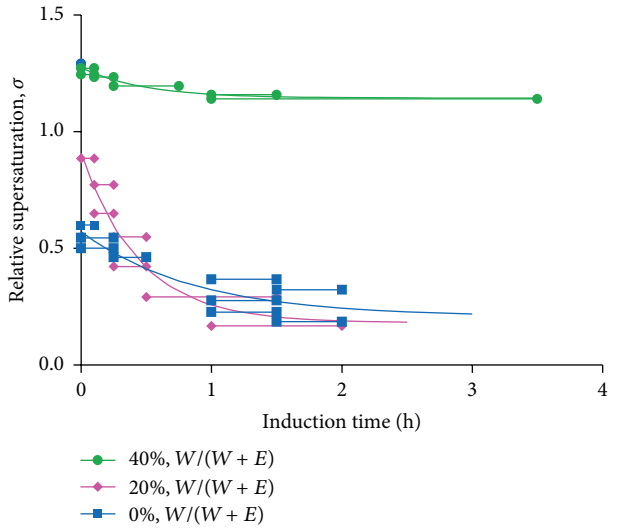

Figure 9: PNT in water-ethanol mixtures at 15°C. The best fit exponential curve is drawn for each concentration.

As for the SNT data, the PNT values fall with increasing water content for 25 and 40°C but increase for 15°C. Exponential curves were fitted to each set of data and the estimated 1 h PNT values are summarized in Table 2.

These PNT results expressed as relative supersaturation are plotted against water content in Figure 12. The results may be fitted by

$$\sigma_{PNT} = 0.3\,(\pm 0.4) * \exp\left\{\frac{X_W}{0.3\,(\pm 0.5)}\right\} \quad \text{for } 15^{\circ}\text{C},$$

$$\sigma_{PNT} = 0.32\,(\pm 0.006) * \exp\left\{\frac{-X_W}{0.4\,(\pm 0.3)}\right\} \quad (4)$$

for combined 25 and 40°C data.

Table 2: One h σ_{PNT} values from all experiments.

X_W	Temperature, °C		
	15	25	40
0.0	0.30	0.32	0.30
0.2	0.26	0.15	0.06
0.4	1.16	0.08	—
0.6	—	0.03	—

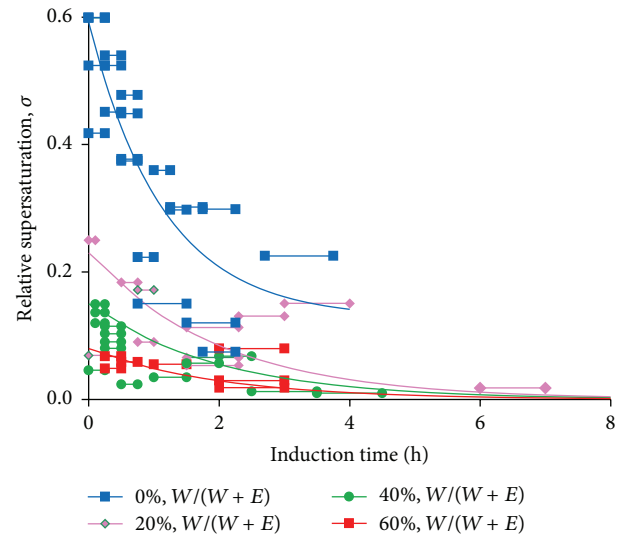

Figure 10: PNT in water-ethanol mixtures at 25°C. The best fit exponential curve is drawn for each concentration.

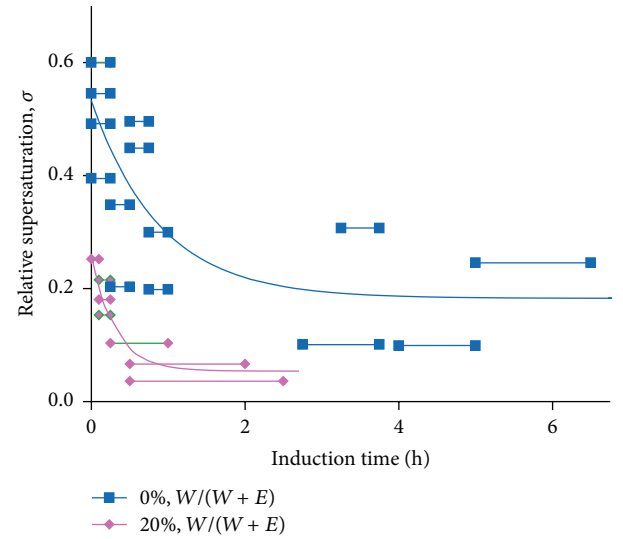

Figure 11: PNT in water-ethanol mixtures at 40°C. The best fit exponential curve is drawn for each concentration.

Figure 13 shows the solubility diagram for ibuprofen in aqueous ethanol at 25°C [14] with the estimated 1 h PNT and 1 h SNT data points superimposed. A curve has been drawn to indicate the position of the PNT line. The SNT line (not drawn) would be very close to the solubility line.

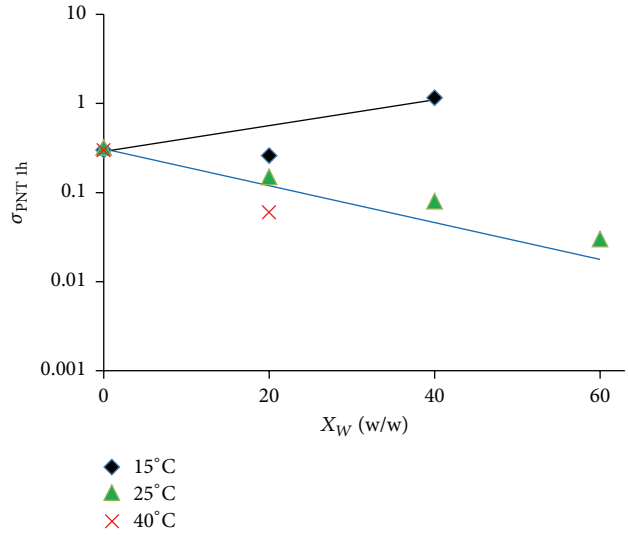

Figure 12: Effect of water content on the 1 h PNT values, on the same scale as for σ_{SNT} (Figure 8). The σ_{PNT} values are approximately six times larger than the σ_{SNT}.

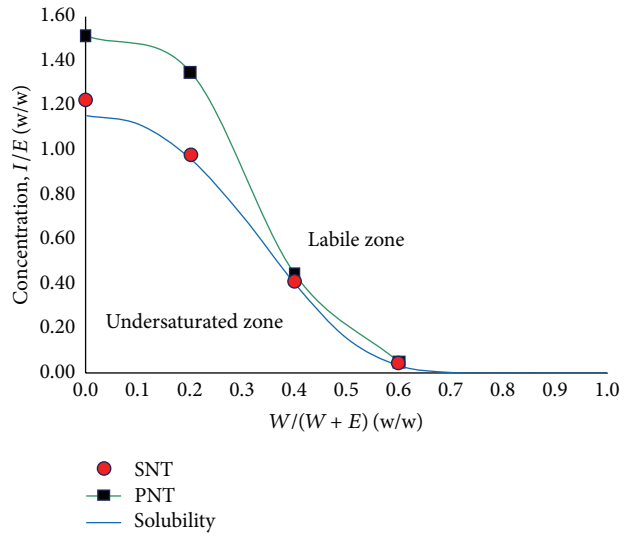

Figure 13: Phase diagram for ibuprofen in water-ethanol mixtures with superimposed SNT and PNT data at 25°C.

5. Conclusions

Nucleation thresholds for the crystallization of ibuprofen, estimated from the induction times for nucleation, are presented. Supersaturation is the experimental parameter with the greatest influence on the induction period, but it is also affected by the water content of the solvent and to a lesser extent by temperature.

PNT and SNT values were measured for ibuprofen in ethanol alone at three temperatures. For ethanol both the PNT and SNT appear to be little affected by temperature (from 10 to 40°C). The SNT values for ethanol are small and thus the metastable zone is relatively narrow. The 1 h values have been superimposed on the solubility phase diagram (Figure 4). The PNT values for ethanol are much larger than the SNT values by about a factor of 6.

In water-ethanol mixtures at 25 and 40°C both the SNT and PNT (expressed as relative supersaturation) decrease significantly as the water content increases. However, at a lower temperature, both increase significantly as the water content increases. The reason for this is not known. The SNT values at 25°C are close to the solubility curve (Figure 13) while the PNT values are significantly larger.

With the solubility results, this study has generated phase diagrams (Figures 4 and 13) with superimposed nucleation limits for ethanol and water-ethanol mixtures which will be useful for developing ibuprofen crystallization processes. The SNT results will be used in nucleation rate experiments to ensure that test conditions exceed the SNT and in growth rate experiments to ensure that the SNT is not exceeded so there is growth without nucleation.

Abbreviations, Subscripts, and Symbols

MSZW: Metastable zone width
PNT: Primary nucleation threshold
SNT: Secondary nucleation threshold
t: Time, h
C: I/E
C^*: Saturation value for C
E: Ethanol/mass of ethanol
I: Ibuprofen/mass of ibuprofen
W: Water/mass of water
X_W: $W/(E+W)$
σ: Relative supersaturation $(C - C^*)/C^*$, dimensionless.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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