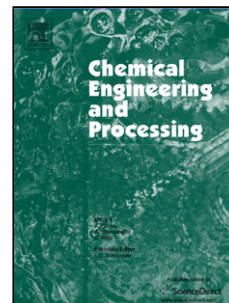Accepted Manuscript

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Effects of Water and Temperature on Reaction Mechanism and Crystal Properties in a Reactive Crystallization of Paracetamol

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Graphical abstract
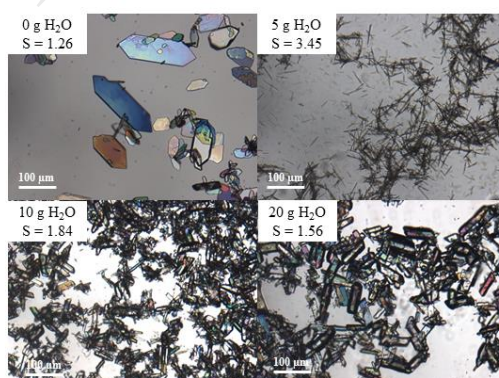
Highlights

- We treated the reactive crystallisation of paracetamol as a single process and optimized the solubility for crystallisation first, from which reaction stoichiometry was retrospectively determined.

- The effects of water and temperature on reaction kinetics and crystal properties were jointly investigated for the first time.

- Paracetamol form I particles with high purity were produced due to various amounts of water in reaction. 4'-acetoxyacetanilide was the main product in the reaction without water.

Abstract

By considering both reaction and crystallization of paracetamol as a single process for the purpose of continuous operation, the solubility for crystallization was firstly optimized, from which suitable concentrations of reagents for the reaction were then determined. The effects of water content and reaction temperature on reaction kinetics and mechanism as well as crystal properties were jointly investigated, for the first time, using chromatographic methods; paracetamol form I particles with high purity (99%) were produced with the presence of water, while 4'-acetoxyacetanilide was the main product in the absence of water.

1 Introduction

Paracetamol (Acetaminophen) is a widely used analgesic drug[1], traditionally manufactured by acetylating 4-aminophenol with a small stoichiometric excess of acetic anhydride in an aqueous medium [2-4]. Many variations in reaction have since been implemented to enhance productivity and product properties, for instance, Baron et al[5] dissolved 4-aminophenol in hot acetic acid, treated it with carbon, filtered it out, the filtrate was further treated with acetic anhydride at 85 °C; Young[6] added ammonium hydroxide to increase product purity; Ness and Warner[7] hydrogenated p-nitrophenol to p-aminophenol and concurrently acetylated the p-aminophenol to paracetamol; Caldeira[8] used phosphoric acid as the catalyst. Either a precipitation or crystallization step was then used to isolate paracetamol particles under limited control, affecting crystal properties [9-14], i.e. two separate unit operations are the norm for reactive crystallization. In this work, we treat the reactive crystallization as a single process for the purpose of continuous operation, we optimize solubility for crystallization as the first protocol, the concentrations of reactants that deliver the optimized solubility are retrospectively determined. By maintaining the targeted ratio of acetic acid to water in the reaction that optimizes the solubility, the effects of water and temperature on reaction kinetics, mechanism and crystal properties were jointly investigated; these are new from previous studies in this area. We demonstrate that by manipulate reaction conditions, we can achieve the control over crystal properties.

2 Experimental set up and procedures

2.1 Chemicals and analytical methods

4-Aminophenmol (Sigma Aldrich UK Ltd.; purity, ≥ 99 % HPLC grade; mp, 187.5 ℃; MW, 109.13 g mol^{-1}) was sourced in the form of light brown crystalline solid. Paracetamol (GlaxoSmithKline Pharmaceutical Company; purity, 99.8 %; mp, 169 ℃; MW, 151.16 g mol^{-1}) was purchased for the purpose of comparison with crystals produced. 4'-Acetoxyacetanilide (TCI AMERICA; purity, ≥ 99.0 % HPLC, Nitrogen; mp, 155 ℃; MW, 193.20 g mol^{-1}) was purchased for the identification and calibration of the intermediate product. Acetic anhydride (purity, 99+ % pure; density, 1.08 g cm^{-3}; MW, 102.09 g mol^{-1}) and methanol (purity, HPLC grade; density, 792 kg m^{-3}; MW, 32.04 g mol^{-1}) were also sourced. Distilled water (density, 1 g cm^{-3}; MW, 18.02 g mol^{-1}) was prepared in-house.

The purity of product particles was analyzed using the Agilent1100 Series HPLC System, and the chromatograph column was a reverse phase ZORBAX SB-C8 (4.6×150 mm; 5 μm packing). The UV detector was set at 243 nm and the mobile phase running throughout the system was a mixture of methanol and water with a mass ratio of 1:3. The mass spectrometry measurement was carried out at the School of Chemistry, the University of Edinburgh. The concentration of paracetamol was analyzed by a UV-Vis spectrophotometer (Hewlett-Packard Model 8453) based on the characteristic UV absorbance peak at 243 nm. The calibration experiments were carried out from six known concentrations of 0, 0.3, 0.5, 0.7, 1.0, 1.3 g L^{-1}. A linear relationship of the absorbance, A, as a function of the concentration, C, was established as: $A = -0.0015 + 0.686 \, C$ (g L^{-1}), with a correlation coefficient of 0.9984.

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The crystal size distributions were analyzed by a Mastersizer 3000™ (HYDRO, Malvern); the polymorphism of crystals by PXRD (Chemistry Department, Heriot-Watt University with the scanning range from 5 ° to 85 °) and a Leica ATC 2000 Trinocular Microscope; the molecule structures of the products by the AV300 Proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR).

2.2 Experiments procedures

In the synthesis, paracetamol is produced with acetic acid as a side product, which is also the solvent for the following crystallization process. In order to maximize the solubility of paracetamol, a range of solubility were examined by mixing acetic acid with various water contents at different temperatures. 10 mg of paracetamol was firstly weighted in a 10 mL scintillation vial; the solutions of water and acetic acid with six different ratios (Acetic acid:Water = 0:10, 3:7, 5:5, 7:3, 8:2 and 10:0) were then carefully titrated into the vial by a micropipette with intermittent shaking until all solids had been dissolved. The solubility data at temperatures of 20, 35, 50, 65, and 75 °C were determined in a water bath, and each measurement was repeated three times. The solubilities of paracetamol in various solvents were calculated by dividing the weight of paracetamol solid by the total weight of solvents added to the vial, from which the amounts of reactants required to deliver such solubility in the said ratio of acetic acid to water can then be back-calculated.

Once the ratio and the amounts of reactants have been determined, the reaction was then proceeded by charging 4-aminophenol (10 g or 0.09 mol), acetic anhydride (35 g or 0.34 mol) and different amounts of water into a pre-heated 250 ml jacked reactor at 50 °C and at 200 rpm. The reactor was heated up to the desired constant temperature for the reaction to commence.

13 samples were taken at regular time intervals during the reaction process using a pipette with an accurate volume of 0.3 ml; quenched and diluted 10,000 times with the mobile phase solution (Methanol:Water = 1:3). The overall reaction time was about 60 min. The crystallization was thereafter immediately initiated by cooling the solution to 20 °C at a fixed cooling rate of 1.2 °C min^{-1}. A vacuum filtration was performed at the end of the crystallization at 20 °C and crystals were washed with distilled water and dried in an oven for 24 hours.

Some specific conditions are outlined below:

A) Water content effects – water contents of 0 g, 10 g (or 0.55 mol), and 20 g (or 1.11 mol) were used in reaction at a fixed operating condition of 70 °C and 200 rpm;

B) Temperature effects – this was investigated by performing the synthesis at four reaction temperatures (50 °C, 60 °C, 70 °C and 80 °C) at a fixed water content of 20 g (1.11 mol).

3 Results and discussion

3.1 Optimization of solubility and determination of reactants contents

Acetic acid is the main solvent for paracetamol according to the reaction scheme, the solubilities of paracetamol in the mixtures of acetic acid and water were measured and shown in Fig. 1. In terms of the solubility of paracetamol in water, these range from about 0.009 to 0.049 g g^{-1} water for temperatures from 20 °C to 75 °C in this work and are comparable with literature data, e.g. from 0.010 to 0.035 g g^{-1} water for temperatures from 20 °C to 55 °C[15, 16]; 0.021 g ml^{-1} water at 30 °C[17]; of 0.017 g g^{-1} water[18]. Granberg and Rasmuson[18] also reported the solubility of paracetamol in acetic acid as 0.083 g g^{-1} at 30 °C, which is slightly higher than our data of 0.053 g g^{-1} acetic acid. Operational errors from the gravimetric method might be the main reason for the difference.
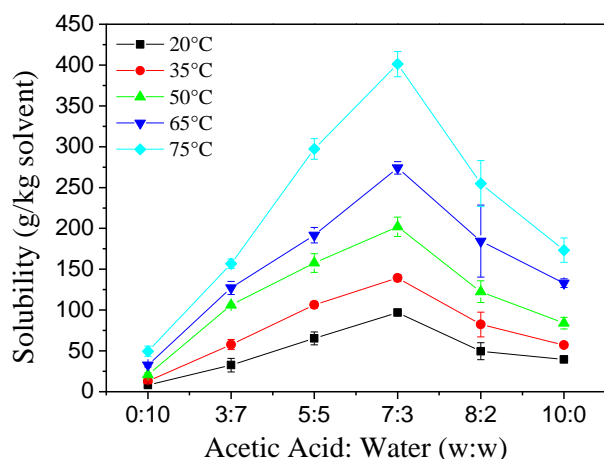
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Fig. 1. Solubility of paracetamol in different ratios of acetic acid to water

As shown in Fig. 1, the highest solubility occurred when the mass ratio of acetic acid to water was at 7:3; the solubility increased from 96.83 to 401.23 g kg^{-1}$_{solvent}$ with the increasing reaction temperature from 20 °C to 75 °C, the latter was the reaction temperature. From the maximized solubility, the amounts of reactants were reversely calculated based on the reaction stoichiometry. In order to make up the desired ratio of 7:3 acetic acid to water, about 14.48 g (0.13 mol) 4-aminophenol should theoretically be reacting with an excessive amount of acetic anhydride (36.55 g or 0.36 mol) in the 250 ml reactor at 75 °C, the extra acetic anhydride is then converted to acetic acid via a hydrolysis with water. In practice, however, the mass of crystals generated at the end of crystallization was so large that the mixing condition was adversely affected. On balance, the contents of 4-aminophenol and acetic anhydride were accordingly reduced by 30 % to 10 g (0.09 mol) and 35 g (0.34 mol) respectively; the temperature to 70 °C, this gives the best controls over both good supersaturation and better mixing.

3.2 Effect of water content on reaction mechanism

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Water in the paracetamol synthesis generally helps the hydrolysis of acetic anhydride, promoting the formation of paracetamol, however, there have been very few studies on the effects of water on reaction kinetics and crystal properties. In this work, the effects of water content on reaction kinetics and mechanism were fully examined; we added 0 g, 10 g (0.55 mol) and 20 g (1.11 mol) distilled water into the synthesis, Fig. 2 shows the profiles of concentrations of paracetamol with and without water. It is clear that the rising curve becomes steeper with water and the degree of steepness increases with the increasing amount of water. From the general reaction mechanism (nucleophilic addition-elimination) of paracetamol synthesis[14], on one hand, the lone pair of electrons on the amine of 4-aminophenol attacks the C=O bond of acetic anhydride to cause it polarized. Nitrogen has then a positive charge but regains electrons by losing a proton. The negative charge on the oxygen comes back in to reform the C=O bond. This leads to the other C-O bond to break and forms acetic acid as a by-product, while paracetamol is the product from the amide bond formation process. When water is added, the hydrolysis reaction between acetic anhydride and water generates H^+, these free hydrogen ions increase the reactivity in the solution, thus improve the reaction performance, as shown in Fig. 2 that the more the added water, the quicker the level off becomes.

On the other hand, however, the excessive acetic anhydride in this work also leads to a reduction of paracetamol, with 4'-acetoxyacetanilide being detected in the solution. This can be postulated from the fact that the amount of diacetamate formed in the presence of the excess of acetic anhydride is very small and unstable in solution; is quickly hydrolyzed until an equilibrium has been reached. The fluctuations of the concentration of paracetamol near 10 minutes during the reaction in Fig. 2 are the clear evidence.
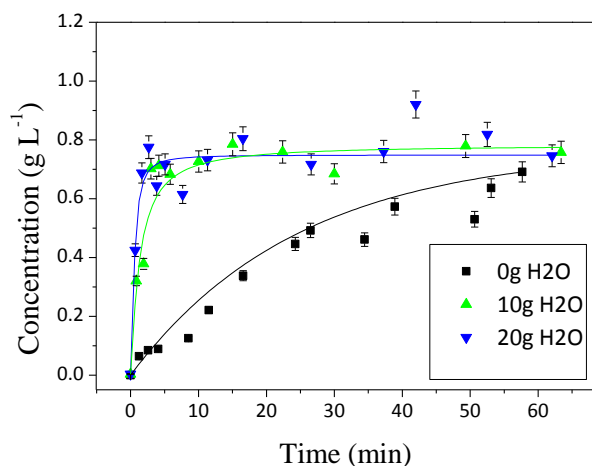
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Fig. 2. Concentration of paracetamol with different water contents (Temperature = 70 °C)

To understand better the reaction mechanism with the presence of water, we analyzed the samples taken from the reacting solution using the LC-MS, Fig. 3 shows the chemical structures of paracetamol and diacetamate: the first peak at 3 min is the paracetamol molecular with a total density of 152.0647 g mol^{-1}, and the second peak at 4.7 min is an diacetamate of 194.0706 g mol^{-1}, the latter is also the molecular weight of 4'-acetoxyacetanilide. With this knowledge, the reaction scheme for paracetamol synthesis with and without water can now be illustrated in Fig. 4. We see that the synthesis of paracetamol (Reaction (1) in Fig. 4) and the reaction between excess acetic anhydride and water (Reaction (2) in Fig. 4) are the two main reactions. When water is absent in the system, diacetamate is formed as a side product (Side reaction in Fig. 4). When water is added, the excess acetic anhydride is more likely to react with water, rather than to consume the –OH bonds of paracetamol molecules. As a result, the acetic acid generated from reactions (1) and (2) together with water left in the system are the solvent for the follow-on cooling crystallization of paracetamol.
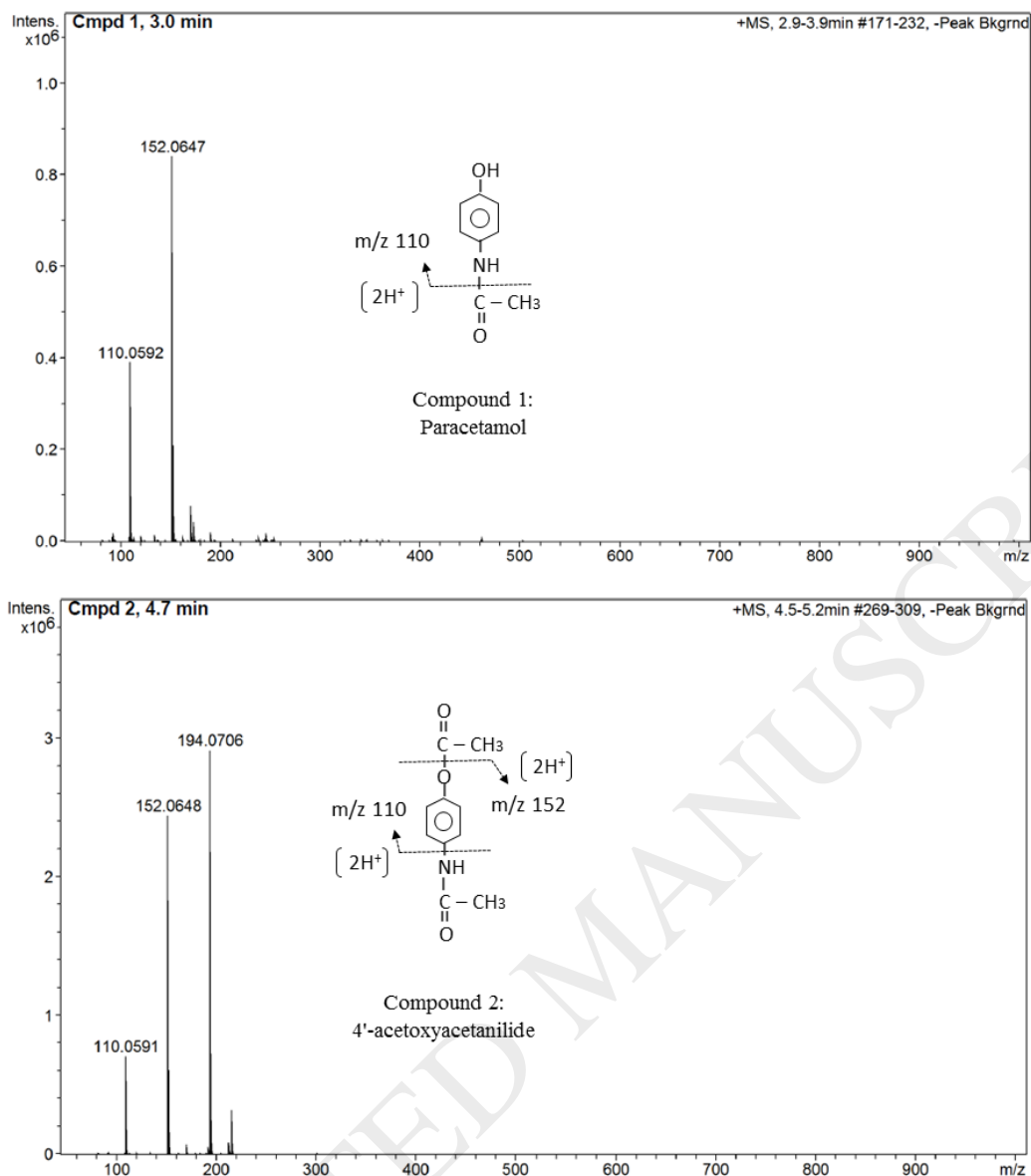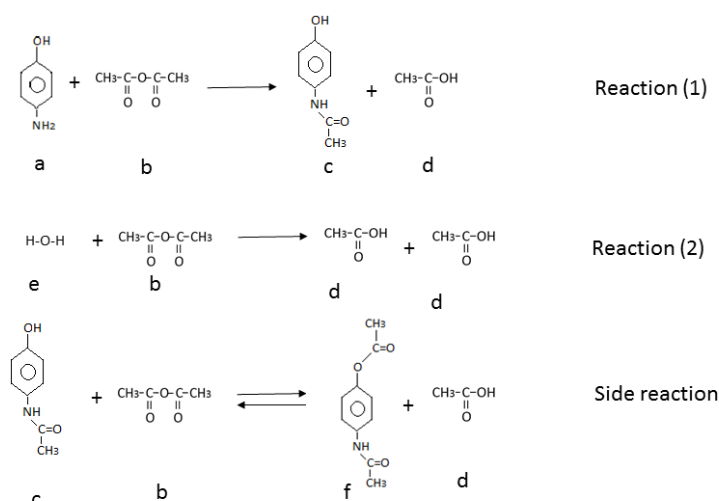
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Fig. 3. Sample analysis by LC-MS

Fig. 4. The reaction scheme for paracetamol synthesis with and without water (a, 4-aminophenol; b, acetic anhydride; c, paracetamol; d, acetic acid; e, water; f, 4'-acetoxyacetanilide)

3.3 Effect of temperature on reaction rate constant

From the reaction viewpoint, higher temperature leads to higher reaction rate. In the following experiments, reaction temperatures of 50 °C, 60 °C, 70 °C and 80 °C were studied at a fixed water content of 20 g (1.11 mol), Fig. 5 shows the profiles of the concentrations of paracetamol as a function of time. We see a common trend with an immediate increase in the concentration in the first five minutes of synthesis, then quick leveling off. As expected, higher concentrations of paracetamol were obtained for higher temperatures.
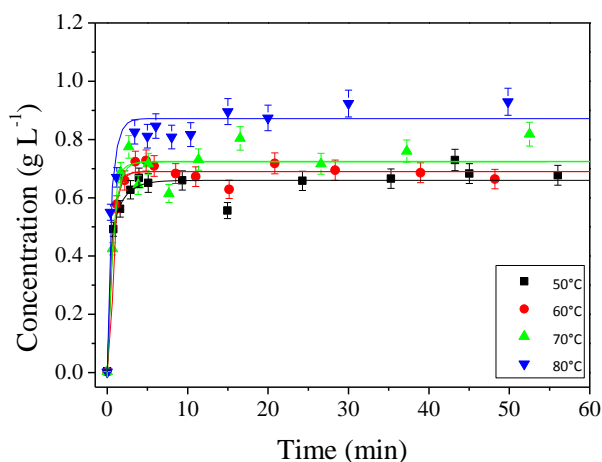
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Fig. 5. Concentration of paracetamol at different temperatures (water content = 20 g)

The data points in the first 5 minutes were then employed to extract the kinetics of the paracetamol synthesis. Because acetic anhydride was added in excess, this 2nd order reaction becomes a pseudo first-order reaction. Based on the limiting reagent of 4-aminophenol, we have:

$$r_R = -\frac{dC_A}{dt} = kC_A \tag{1}$$

where r_R is the generation rate of paracetamol (g L^{-1} min^{-1}); C_A and C_{A0} are the concentrations of 4-aminophenol at any time and at $t = 0$ (g L^{-1}) and k is the reaction rate constant. By plotting $\ln\left(\frac{C_{A0}}{C_A}\right)$ vs time, we obtained a straight line fit that confirms the order of the reaction; the slope of the trend line is the rate constants, k; Table 1 summarizes the rate constants at various temperatures. Following the Arrhenius equation, the activation energy for this reaction was determined as 37.31 KJ mol^{-1}.

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Table 1. Influence of temperature on the rate constant of paracetamol synthesis

Temperature T (K)	Correlation coefficient	Rate constant, k (min^{-1})
323	0.7903	0.61
333	0.9733	0.94
343	0.9947	1.41
353	0.8645	1.99

Few literature has been found on the kinetics involving 4-aminophenol and excess acetic anhydride; one work close to our study involved almost equalmolar reactants and a 2nd order reaction kinetics was evaluated with a rate constant of 0.66 ml mg^{-1} min^{-1}[8]. It should be noticed that although the reaction between paracetamol and 4'-acetoxyacetanilide is affected by complex conditions (concentration, mixing, temperature, water content, PH and etc.), the reaction kinetics evaluated above is still applicable as the hydrolysis step has much faster kinetics and the overall kinetics is dominated by that of the slowest step. This is supported by the work of Lee et al[3] and Srabovic et al[14]. The reaction time in our work is approximately 10 minutes, which agrees with the literature results of from 3 to 15 minutes[5, 6, 8].

3.3 Effect of water content on supersaturation

The mixture of acetic acid and water is the solvent for crystallization after the reaction, different amounts of water used in the reaction step affect the solvent compositions as shown in Table 2, in turn the saturation and solubility. The degree of supersaturation is calculated for different water concentrations (see Fig. 6), according to the solubility of paracetamol in these aqueous acetic acid solutions. We see in Fig. 6 that less water leads to higher supersaturation, in turn smaller particle sizes. This is expected as higher supersaturation favours nucleation. The

morphology of paracetamol crystals went through from needles to rod-like shape with the increase of water in the synthesis, the degree of the agglomerations seems to decrease with the increase of water content (Fig. 7). The morphologies in our work are similar to these of previous studies by Sudha and Srinivasan [17]and Prasad et al[19]. The exception is for the crystals on the top left of Fig. 7, these were confirmed as 4'-acetoxyacetanilide particles of high purity by NMR. With excess acetic anhydride and in the absence of water in the reaction system, the nucleophilic addition-elimination takes place on both –NH and –OH functional groups, 4'-acetoxyacetanilide cannot be hydrolyzed to form paracetamol, as shown in the reaction scheme above. In addition, the solubility of paracetamol is much higher than that of the side product [18, 19]. In summary, 4'-acetoxyacetanilide is the product from this reactive crystallization without water, while paracetamol with the presence of water. Both products are of high purities as there is no visible impurity peak shown in the NMR data. In addition, 20 g of water content is the best condition for the desired crystal polymorph.

Table 2. Solvent compositions with different amount of water after reaction

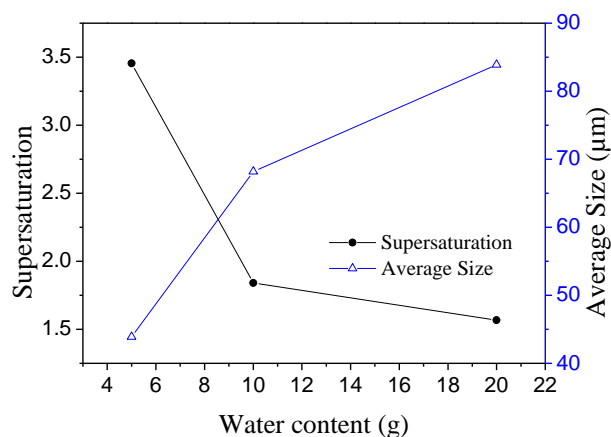| Samples	Water content	Solvent composition (mass ratio) (Acetic acid w%)
S1	0 g (0 mol)	Acetic acid : Acetic anhydride = 2 : 9 (no water)
S2	5 g (0.28 mol)	Acetic acid : Water = 226 : 3 (98.69 w%)
S3	10 g (0.55 mol)	Acetic acid : Water = 13 : 2 (86.67 w%)
S4	20 g (1.11 mol)	Acetic acid: Water=7:3 (70 w %)

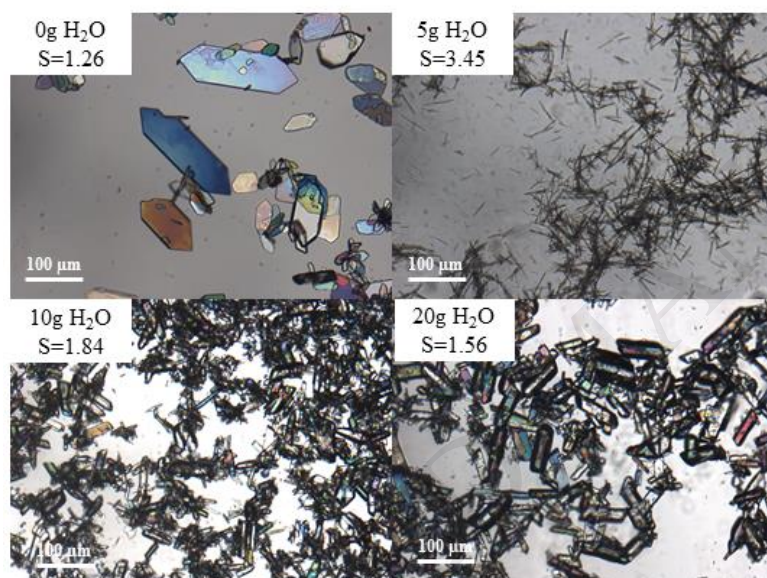**Fig. 6. The supersaturation and crystal size as a function of water contents**

Fig. 7. The effect of water content on crystals morphology

3.5 Effect of temperature on supersaturation

In continuous reactive crystallization, the temperature at the end of reaction will be the starting temperature of crystallization. For a constant temperature of 20 °C at the end of crystallization, the higher the reaction temperature, the larger the supercooling, in turn the supersaturation (see Fig.8), the smaller the crystal size. The morphology of crystal products at

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different temperatures is shown in Fig. 9; no visible change in crystal shapes are seen, whereas the mean crystals sizes decreased when the temperature increased from 50 to 80 °C. To perform the reaction at lower temperatures while having little effect on product quality has both operational and environmental benefits. Generally, the crystals from the reaction temperature of 70 °C had uniform morphology and better size distribution.
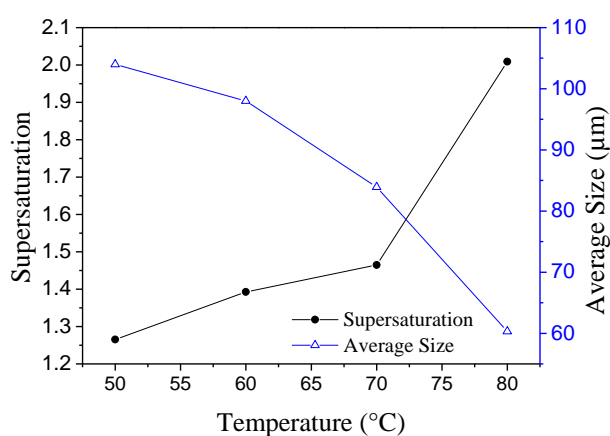

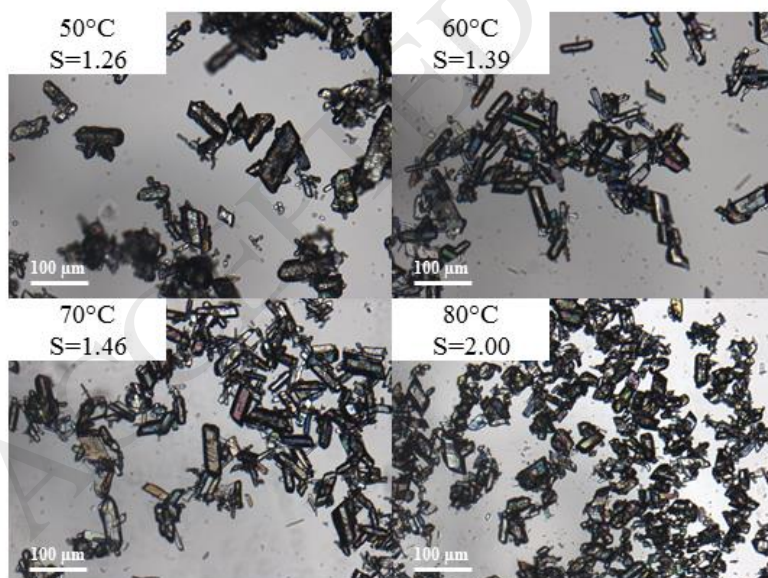**Fig. 8. The supersaturation and crystal size as a function of reaction temperature**

Fig. 9. The effect of temperature on crystals morphology

3.6 Crystal properties

From a large number of experiments carried out, paracetamol alone was produced from reactions with 10 g and 20g of water at temperatures from 50 °C to 80 °C, whereas 4'-acetoxyacetanilide was identified with 0 g and 5 g of water. Paracetamol particles with a high purity (~99 %) were made when enough water ($\geq$ 10 g, or 0.55 mol) were present, while temperature had little effect on the product purity.

In general, the variations in shapes among each solvent system are quite similar. Non-centrosymmetric growth and crystal shapes in Figs. 7 and 9 agree with previous results predicted by steady–state morphologies [20, 21]. Sharp needle shaped crystals were observed for the reaction with less water concentration (5 g H_2O). Apart from the effect of high supersaturation, the presence of by-product is probably another reason for the development of needle-shaped crystals. Similar polymorphic forms were reported[22], involving aqueous solution containing 4'-acetoxyacetanilide.

All crystals with water are of Form I, see the PXRD patterns in Fig. 10 which are the same with these from Nichols and Frampton[23], while a different X-ray diffraction pattern is displayed for the crystals in absence of water; these hexagonal crystals are 4'-acetoxyacetanilide. This supports the NMR results. The size distribution of paracetamol is shown in Fig. 11 with $D_{50} = 84.3$ μm and is slightly broader when compared with the work of Fujiwara and Chow[16] in a supersaturation- controlled seeded batch crystallization. Agglomerations occurring during the crystallization step could be the potential reason for this. We found that there was less agglomerations for reactions with higher water contents, as the polarity of the solvent increases with the concentration of water. This agrees with previous study[24, 25] in that agglomerates became weaker in more polar solvents.
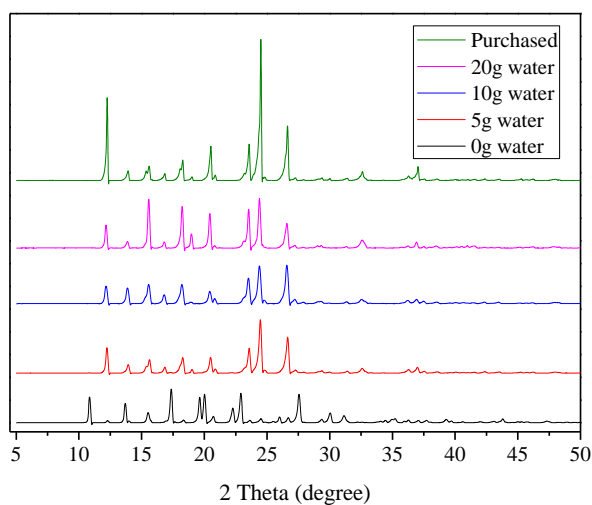
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Fig. 10. Powder X-ray diffractions for purchased and produced paracetamol with different water contents
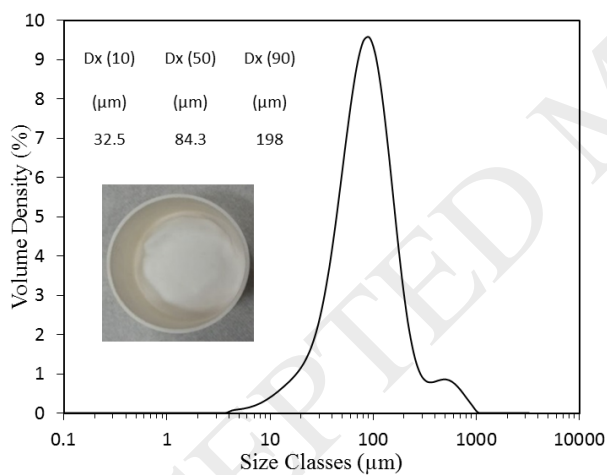

Fig. 11. Crystal size distribution for paracetamol particles

4 Conclusions

In this work, the reactive crystallization of paracetamol is considered as a single process for the purpose of continuous operation. The solubility for crystallization was optimized first,

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from which suitable reagent concentrations were determined. We investigated the effects of reaction temperature and water content on reaction kinetics and mechanism as well as product quality jointly for the first time; Form I crystals with high purity were obtained with the presence of water, and 4'-acetoxyacetanilide without water. The understanding gained and the process conditions identified from this work are the basis for continuous operation, which will be our next communication.

Acknowledgments

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