Modelling solution speciation to predict pH and supersaturation for design of batch and continuous organic salt crystallisation processes

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Abstract

Organic salt crystallisation is of great importance to the pharmaceutical industry as the majority of pharmaceutical products are marketed as salts. In this study a solution speciation model was developed and experimentally validated to predict pH and supersaturation during organic salt crystallisation processes when only the overall solution composition is known. By solving a particular system of equations simultaneously the full speciation and pH of the solution is calculated. Simply with knowledge of only the overall solution composition, dissociation constants and solubility products this model can be used to generate the design space for organic salt crystallisation and gain deeper understanding of the salt crystallisation process. In particular, the model can be used to calculate the maximum theoretical crystallisation yield and the corresponding mother liquor pH which would be impossible to determine otherwise without performing experiments. The case study used in this work is the polymorphic organic salt ethylenediammonium 3,5-dinitrobenzoate (EDNB) which is the 2:1 salt of 3,5-dinitrobenzoic acid (3,5-DNBA) with ethylenediamine. In this system three solid forms can be produced: EDNB monoclinic, EDNB triclinic and/or the 3,5-dinitrobenzoic acid (3,5-DNBA) starting material. The solution speciation model was used to investigate the crystallisation process for each solid form and test different feed molar ratios and different solution addition/mixing approaches for semi-batch and continuous processes.

Keywords

Organic Salt Crystallisation; Solution Speciation Modelling; pH Prediction; Crystallisation Design.

1. Introduction

Organic salt crystallisation is of great importance to the pharmaceutical industry as more than half of the world's pharmaceutical products are marketed as salts [1]. Salt formation is a popular technique as it modifies and optimises physiochemical properties. Important properties including solubility, dissolution rate and stability can be improved by using a range of pharmaceutically acceptable counter-ions [1]. In fact, it is possible to form a wide range of salts from an acidic or basic compound and therefore a salt screen is typically carried out in order to discover which salt has the best overall properties for the intended application [2, 3]. Despite the importance of organic salt crystallisation there is a lack of literature describing appropriate design principles which is in stark contrast with the crystallisation of single component molecules.

Developing design principles requires an understanding of ionic equilibria and the speciation of acids and bases which is well covered in textbooks [1, 4]. Strong acids and bases are assumed to be fully dissociated in whatever solvent they occupy but the speciation of weak acids and bases are more difficult to determine. Their speciation depends on solvent, pH and temperature and needs to be calculated from measured pK_a values. An active pharmaceutical ingredient (API) is almost always a weak acid or base so it is therefore necessary to determine relevant pK_a values associated with it and to know which of its species will combine with the counter-ion in solution to form the salt. With this knowledge the salt can be formed experimentally by reaching a target pH for a particular solvent and temperature.

In salt crystallisation experiments there will typically be a target pH value based on understanding of the solution speciation. Organic salt crystallisation literature covers semi-batch potentiometric titrations experiments where a strong acid is continually added to a basic solution until the desired pH level is reached [5, 6]. Some literature concerned with the semi-batch reactive crystallisation of L-glutamic acid goes further where models are utilised that have pH as an input to calculate the change in pH when a certain quantity of acid is added [7-11]. With this approach it is possible to create an acid addition profile based on the properties of the initial L-glutamic acid solution. Elsewhere, there have been modelling studies looking at applying control strategies to the semi-batch reactive crystallisation of L-glutamic acid in an effort to control the solution concentration and particle size distribution [12, 13]. Model based predictive approaches have been investigated in single phase systems [14, 15] and in a few inorganic crystallisation systems [16-18] but they have not been previously applied to organic salt crystallisation processes.

As already stated, previous crystallisation modelling approaches rely on *a priori* determination of target pH values which need to be provided as an input into speciation models. Therefore, attainable pH values and supersaturations cannot be ascertained and concentration trajectories during acid or base addition and subsequent crystallisation cannot be predicted. In this paper we present a model that can predict the pH and speciation of a solution containing any combination of acids and bases. The only information required are liquid phase concentrations and pK_a values of each component and the solvent dissociation constant at the temperature of interest. In the application of organic salt crystallisation, knowledge of the solubility products for potential salts will also allow for the supersaturation with respect to the relevant salt to be predicted [19]. In a semi-batch or continuous salt crystallisation process, the model would be used to calculate the pH of the initial solution, the volume (or flowrate) and concentration of strong acid or base required to reach the target pH and the change in solution pH and composition as crystallisation initialises and progresses to completion, as a function of the solid yield from zero to the theoretical equilibrium yield. Therefore, this model can be used to explore the entire salt crystallisation design space and guide the design of organic salt crystallisation processes.

2. Materials & Methods

2.1. Materials

3,5-dinitrobenzoic acid (99%), ethylenediamine (≥99.5%), sulphuric acid (95-98%), sodium sulphate (≥99%) and sodium chloride (≥99.5%) were supplied by Sigma Aldrich. Sodium hydroxide (98%) was supplied by Fisher Scientific. Deionised water was produced using an in-house Millipore Milli-Q system. Potassium hydroxide (KOH) 1 M and hydrochloric acid (HCl) 0.5 M were supplied by Fisher Scientific. The HPLC grade water used to dilute the KOH solution to 0.5 M was obtained using an Elga UHQ2 system.

2.2. Experimental methods: Determination of 3,5-DNBA aqueous pH-solubility measurements

The 3,5-DNBA aqueous pH-solubility profile was experimentally measured using the Sirius T3 titrator (Sirius Analytical Instruments Ltd., East Sussex, UK), in ionic strength adjusted (ISA) water containing 0.15 M potassium chloride. Experiments were conducted at a temperature of 25 ± 0.5 °C under an argon atmosphere. The apparatus was controlled using Sirius software. The T3 set up includes an Ag/AgCl double junction reference pH electrode, a Peltier temperature control device, with thermocouple temperature probe and an overhead stirrer (variable speed, computer controlled). The

spectrophotometer was a MMS UV–Vis Carl Zeiss Microimaging spectrophotometer with an ultra-mini immersion probe attached (Welwyn Garden City, Hertfordshire, UK.).

Solubility determination was carried out using the CheqSol assay. 5.3 mg 3,5-DNBA was weighed into a vial and 1.5 mL ISA water was added. The first step in the experiment was to adjust the pH to 10 as it was expected that 3,5-DNBA would be completely solubilised at this point. After dissolution of the solid was complete the sample was titrated from ionisation to non-ionisation through the addition of acid until precipitation was detected. After this point more acid was added to increase precipitation before alternating aliquots of acid (HCl, 0.5 M) and base (KOH, 0.5 M) were added until twenty crossing points had been titrated. A crossing point is where the pH change versus time $(\Delta pH/\Delta t)$ is zero [20]. The concentration at each crossing point is calculated using a series of equations [21] with the intrinsic solubility being the mean of the crossing point concentrations.

2.3. Experimental methods: Determination of EDNB aqueous pH-solubility measurements

The EDNB aqueous pH-solubility measurements were obtained via gravimetric analysis. This was performed by one of two methods; the crystallisation method or the dissolution method. The crystallisation method involved mimicking larger scale crystallisation experiments by adding the sulphuric acid solution to the basic solution containing 3,5-DNBA, ethylenediamine and NaOH in order to induce crystallisation of the EDNB polymorph of interest. 2 mL sulphuric acid solution was added to 18 mL basic solution in a 28 mL vial. This slurry was then stirred for either 24 hours or 48 hours to ensure equilibrium was reached. The dissolution method involved dissolving the EDNB salt polymorph of interest in the aqueous solution of interest. Either a water, NaOH, NaCl or Na_2SO_4 solution was used. These different solutions were used to investigate the effect of ionic strength on the EDNB salt solubility. 20 mL solution was added to a particular mass of EDNB in a 28 mL vial. This slurry was then stirred for either 3 hours, 6 hours or 24 hours to ensure equilibrium was reached. The dissolution method was used to confirm that the crystallisation method was allowing equilibrium to be reached.

Apart from whether the crystallisation or dissolution method was used the experimental apparatus and procedure was the same for all measurements. Once the slurry was created in the vial, a magnetic stirrer was placed inside and the vial was placed on a magnetic stirrer plate inside an incubator set at the temperature of interest. Once the target period of time had passed, the vial was removed from the incubator, a pH probe was immersed until a stable pH reading was obtained, and then the slurry was filtered. The EDNB solid was then dried to constant weight in a vacuum oven and weighed. Knowledge of the solid mass allowed for the solution concentration to be calculated at the measured pH.

2.4. Speciation, solubility and supersaturation in model system

The system being studied in this work is the crystallisation of the polymorphic organic salt ethylenediammonium 3,5-dinitrobenzoate (EDNB). EDNB is the 2:1 salt of 3,5-dinitrobenzoic acid (3,5-DNBA) with ethylenediamine where 3,5-DNBA is a weak acid and ethylenediamine is a weak base [22, 23]. Figure 1 shows the molecular structure of the 2:1 EDNB salt.

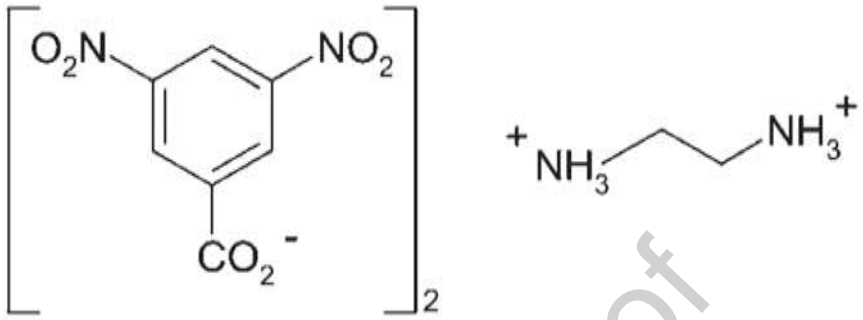

Figure 1. Molecular structure of ethylenediamine 3,5-dinitrobenzoate (EDNB).

The two polymorphs of EDNB are recorded in the Cambridge Crystallographic Database: a monoclinic form (VUJXIH01; $P2_1/c$) and a triclinic form (VUJXIH; $P\bar{1}$) [6]. The crystal structure diagrams of both polymorphs have been reported in literature [5].

3,5-DNBA is a monoprotic acid with a pKa value and ethylenediamine is a diprotic base with a pKa_1 and a pKa_2 value. A summary of the pKa values taken from literature and used in this work are shown in Table 1.

Table 1. Summary of literature pKa values for 3,5-DNBA and ethylenediamine [24-26].

Compound	Temperature (°C)	pKa	pKa_1	pKa_2
3,5-DNBA	25	2.82	–	–
	50	3.07	–	–
Ethylenediamine	25	–	6.86	9.92
	50	–	6.33	9.00

Knowledge of the pKa values allowed for the 3,5-DNBA and ethylenediamine speciation profiles to be plotted and shown in Figure 2.

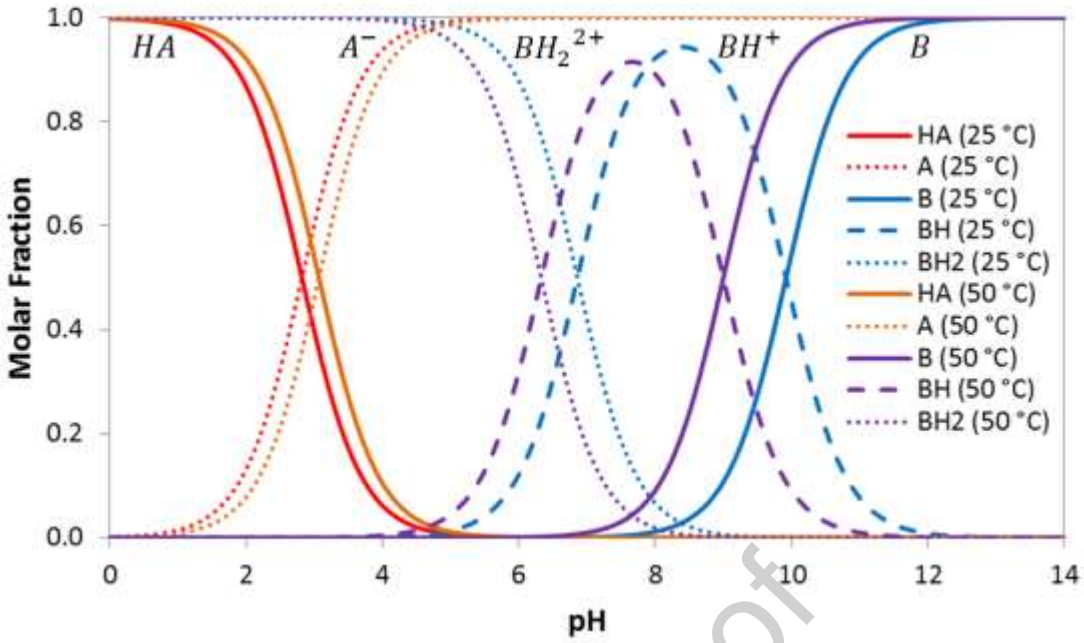

Figure 2. Speciation profiles for 3,5-dinitrobenzoic acid and ethylenediamine at 25 °C and 50 °C.

The speciation profiles illustrate the acid-base equilibria which are described by the dissociation constants in equations 1–3.

$$K_a = \frac{[A^-][H^+]}{[AH]} \quad (1)$$

$$K_{b1} = \frac{[BH^+][H^+]}{[BH_2^{2+}]} \quad (2)$$

$$K_{b2} = \frac{[B][H^+]}{[BH^+]} \quad (3)$$

When dealing with crystallisation processes it is vital to determine the solubility and supersaturation with respect to each material that has the potential to crystallise. In this system the materials of interest are EDNB monoclinic and EDNB triclinic and their solubilities (assuming congruous dissolution where the solutes have the same stoichiometry as the solid) are determined by equation 4 [5].

$$[EDNB]_S = \left\{\frac{1}{4}K_{sp}\left(1 + \frac{K_{a2}}{[H^+]} + \frac{K_{a1}K_{a2}}{[H^+]^2}\right)\left(\frac{[H^+]}{K_a} + 1\right)^2\right\}^{1/3} \quad (4)$$

Knowledge of the solubility product, K_{sp}, is required to calculate the solubility and is defined for the 2:1 EDNB salt in equation 5 where each polymorph will have a different value and this will be different for each temperature (25 °C and 50 °C).

$$K_{sp} = [A^-]^2_{Eq}[BH_2^{2+}]_{Eq} \quad (5)$$

The K_{sp} values were estimated in literature by fitting experimental EDNB salt solubility measurements using equation 4. These experimental solubility measurements were observed by adding the EDNB salt to water before adding sodium hydroxide solution to reach a desired pH and then allowing the slurry to equilibrate. A summary of the solubility products taken from literature and used in this work are shown in Table 2.

Table 2. Summary of literature values for the solubility products [5, 6].

EDNB Polymorph	Temperature (°C)	K_{sp} (mol^3/dm^9)
Monoclinic	25	5.20×10^{-5}
Monoclinic	50	3.73×10^{-4}
Triclinic	25	7.70×10^{-5}
Triclinic	50	5.20×10^{-4}

Inserting the estimated K_{sp} values into equation 4 gives the pH-solubility profiles for EDNB monoclinic and EDNB triclinic, at 25 °C and 50 °C, which are shown in Figure 3.

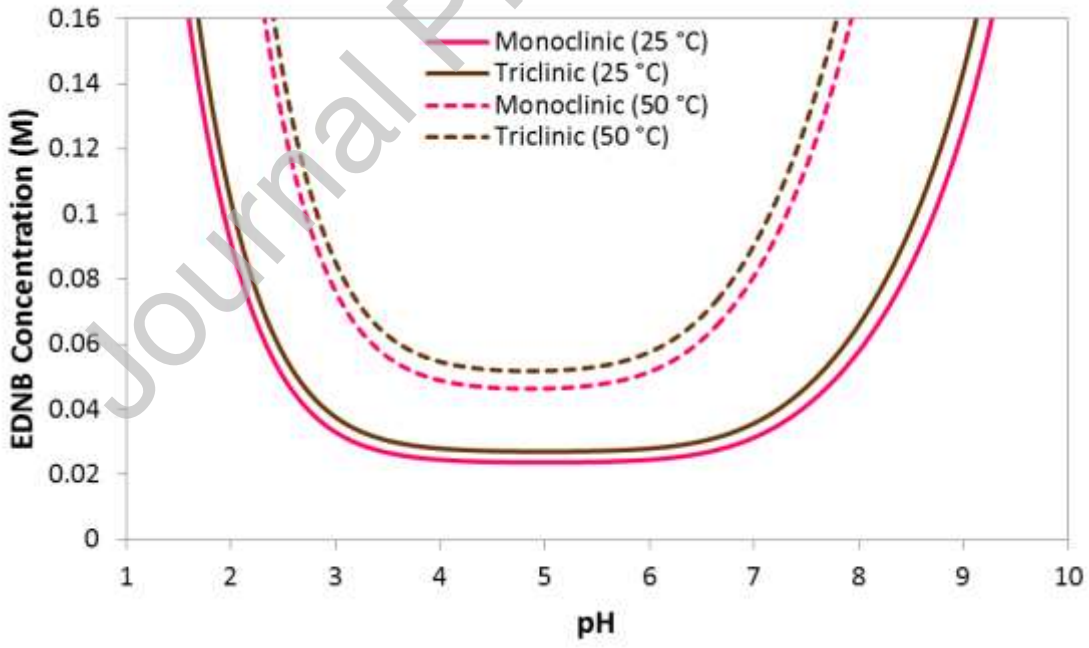

Figure 3. pH-solubility profiles for EDNB monoclinic and EDNB triclinic at 25 °C and 50 °C.

The driving force for crystallisation, the supersaturation, of the salt $[BH_2.A_2]$ can be calculated using the solubility product, K_{sp}, according to equation 6. Here the solubility product is independent of pH

whereas the concentration product is dependent on pH. It should also be noted that this definition of supersaturation implies that the solution is saturated when $S = 0$.

$$S = \ln\left(\frac{[A^-]^2[BH_2^{2+}]}{K_{sp}}\right) \quad (6)$$

Using the relationship in equation 6 the supersaturation with respect to both EDNB monoclinic and EDNB triclinic can be calculated when the speciation of each component and the solubility products are known.

2.5. Activity coefficient modelling

Equations 1–6 assume that the solutions are dilute and exhibit ideal behaviour. When the solutions have moderate or high ionic strengths this assumption of ideal behaviour may not be valid. Therefore, activity coefficients for each species in solution may need to be calculated from the known ionic strength. The activity coefficient of a species with the ionic charge *z* can be expressed using equation 7 [27] where *I* denotes the ionic strength of solution. Activity coefficients (γ) can be calculated according to equation 7 for the anion of the weak acid (γ_A), the diprotonated base (γ_B) and the hydrogen ions (γ_H) in solution in order to account for non-ideal behaviour and correct solubility and supersaturation values. For the purposes of this study, the activity coefficient for any monovalent ion is represented by γ_1 while for divalent ions it is represented by γ_2.

$$-\log\gamma_i = 0.5\, z_i^2\left(\frac{I^{1/2}}{1 + I^{1/2}} - 0.3I\right) \quad (7)$$

The molar ionic strength of a solution is a function of the concentration of all ions present in that solution and is calculated using equation 8 where c_i is the molar concentration of ion i and z_i is the charge number of that ion.

$$I = \frac{1}{2}\sum_{i=1}^{n} c_i {z_i}^2 \quad (8)$$

Considering activity coefficients, the solubility product in equation 5 should be written in terms of the activities of the acid (a_{A^-}) and the base ($a_{BH_2^{2+}}$) rather than in terms of the concentrations. This is shown in equation 9.

$$K_{sp} = {a_{A^-}}^2 a_{BH_2^{2+}} = [A^-]^2 {\gamma_1}^2 [BH_2^{2+}]\gamma_2 \quad (9)$$

As with the solubility product, the supersaturation must be corrected due to the activity of the ions according to equation 10.

$$S = \ln\left(\frac{[A^-]^2\gamma_1{}^2[BH_2^{2+}]\gamma_2}{K_{sp}}\right) \quad (10)$$

Whether or not activity coefficients are needed is determined for each set of experimental conditions as the ionic strengths of the solutions vary significantly depending on the crystallisation procedure.

3. Mathematical Modelling of Solution Speciation

3.1. Introduction

The equations used in the mathematical models developed here are commonly used in literature. However, in literature they are almost always applied to situations where pH is known (or assumed) and are solved based on that knowledge. These mathematical models use the equations in situations where only the overall system composition is known. By solving a particular system of equations simultaneously the pH and full speciation of components in solution is calculated. It should be noted that there is no analytical solution to these systems of equations and instead they must be solved numerically. In this work MATLAB software was used to implement the numerical solving. In the present study there are 3 mathematical models applied which are described in detail. Each model describes a different physical state with different assumptions, inputs and outputs. For this reason, each model has a different system of equations which needs to be solved.

The single-phase model (liquid phase pseudo equilibrium) is applied to a system where no solid is present. This typically corresponds to the metastable solution created in the initial step of the salt crystallisation process. The two-phase model (liquid phase pseudo-equilibrium in the presence of solids) is applied to a system where solid is present but the liquid and solid phases aren't in mutual equilibrium. This typically corresponds to the later stage where the salt crystallisation commenced but solution desupersaturation hasn't been reached yet. The two-phase model (solid-liquid equilibrium) is applied to a system where solid is present and the liquid and solid phases are in mutual equilibrium. This corresponds to the end of the crystallisation process where solution saturation has been reached and the theoretical yield can be calculated. Please note these models were experimentally validated in this work with full details available in the supplementary materials.

3.2. Single-phase model (liquid phase pseudo-equilibrium)

When all the components are dissolved in the aqueous solution there exists only a single-phase. In order to fully model the speciation in the solution several physical phenomena must be taken into account. These are the materials balances and acid-base equilibria associated with the weak acid and base, the dissociation of the water solvent and the overall charge balance which takes the presence

of the strong acid and base into account. For the EDNB salt $[BH_2.A_2]$ made from a monoprotic weak acid, (AH), and a dibasic weak base, (B), the appropriate material balances are described by equations 11–12.

$$[\text{3,5-DNBA}] = [AH] + [A^-] \quad (11)$$

$$[\text{Ethylenediamine}] = [B] + [BH^+] + [BH_2^{2+}] \quad (12)$$

As the solution is completely aqueous, the water dissociation constant is accounted for in equation 13, including the relevant activity coefficients.

$$K_w = [OH^-]\gamma_1[H^+]\gamma_1 \quad (13)$$

The acid-base equilibria dissociation constants from equations 1–3 can now be updated with the appropriate activity coefficients to produce equations 14–16.

$$K_a = \frac{[A^-]\gamma_1[H^+]\gamma_1}{[AH]} \quad (14)$$

$$K_{b1} = \frac{[BH^+]\gamma_1[H^+]\gamma_1}{[BH_2^{2+}]\gamma_2} \quad (15)$$

$$K_{b2} = \frac{[B][H^+]\gamma_1}{[BH^+]\gamma_1} \quad (16)$$

Finally, due to the presence of the strong base (NaOH) and strong acid (H_2SO_4) the overall charge balance is taken into account in equation 17.

$$[Na^+] + [H^+] + [BH^+] + 2[BH_2^{2+}] = [A^-] + [OH^-] + 2[SO_4^{2-}] \quad (17)$$

Equations 11–17 are treated as a system of 7 equations which can be solved when there are 7 unknowns. In practice this means that when the concentrations of all the components are known in addition to the dissociation constants then the proton concentration (indirectly gives pH) and speciation of each component can be determined.

3.3. Two-phase model (liquid phase pseudo-equilibrium in the presence of solids)

When crystallisation commences the system becomes a two-phase system (liquid and solid). As EDNB is crystallising 2 moles of $[A^-]$ ions are being removed from solution for every mole of $[BH_2^{2+}]$ ions. For this reason, the acid-base equilibria in the solution changes as the crystallisation proceeds. This change in solution speciation can be captured in a two-phase model simply by changing equations 11 and 12 so that the concentration of solid EDNB salt $[EDNB_x]$ is incorporated into the material balance as shown in equations 18 and 19.

$$[\text{3,5-DNBA}] = [AH] + [A^-] + 2[EDNB_x] \quad (18)$$

$$[\text{Ethylenediamine}] = [B] + [BH^+] + [BH_2^{2+}] + [EDNB_x] \quad (19)$$

This model is applied when the liquid and solid phase are not in equilibrium so the critical input must either be supersaturation or the solid EDNB concentration. Simultaneously solving the 8 equations of 6 and 11–17 give the important outputs of proton concentration and the speciation of each component exactly as the single-phase model did with the additional output being either solid EDNB concentration or supersaturation. In practice, this model can be applied to an experiment where pH is known during the crystallisation process but concentration is not or vice versa. This allows more information to be obtained from an experiment without the use of additional probes.

3.4. Two-phase model (solid-liquid equilibrium)

The model can be modified again when there is equilibrium between the liquid and solid phase i.e. when crystallisation is complete and the solution is completely desupersaturated. As with the non-equilibrium two-phase model, one must simultaneously solve the 8 equations of 6 and 11–17. The difference here is that the supersaturation value is set to 0 according to equation 6 in order to denote saturation. When there is liquid-solid equilibrium the concentration of solid EDNB becomes an unknown which is to be solved rather than an input. In practice, this model can be used to determine the actual yield of a salt crystallisation experiment as the mass of crystals which should have been recovered is solved and the mass of crystals which are actually recovered is known.

4. Results & Discussion

4.1. Experimental aqueous pH-solubility profile of 3,5-DNBA

The measured aqueous pH-solubility profile of 3,5-DNBA is shown in Figure 4. The solubility is experimentally measured up to a pH of 3.04 and above this pH the solubility can be extrapolated based on the pKa and intrinsic solubility of 3,5-DNBA. The pKa value used for the solubility measurement was experimentally measured using the Sirius T3 automatic titrator rather than the value from literature. The experimentally determined pKa value was 2.58 rather than the 2.82 value from literature. The experimentally determined intrinsic solubility value from the solubility measurement was 7.72 mmol/L. Knowledge of the 3,5-DNBA pH-solubility profile allows for the determination of the point in a titration where 3,5-DNBA will crystallise.

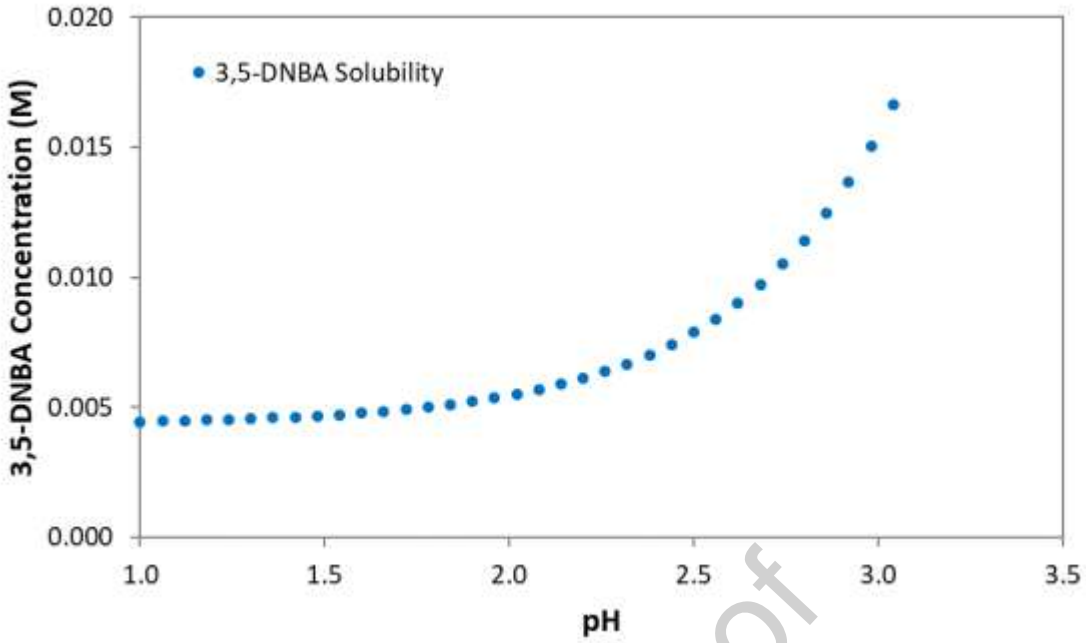

Figure 4. 3,5-Dintrobenzoic acid pH-solubility profile.

4.2. Experimental aqueous pH-solubility measurements of EDNB triclinic

The aqueous pH-solubility measurements of EDNB triclinic at 25 °C are shown in Figure 5. The uncorrected and activity-corrected solubility lines from the present study are also shown. The activity-corrected solubility line was determined from equation 20.

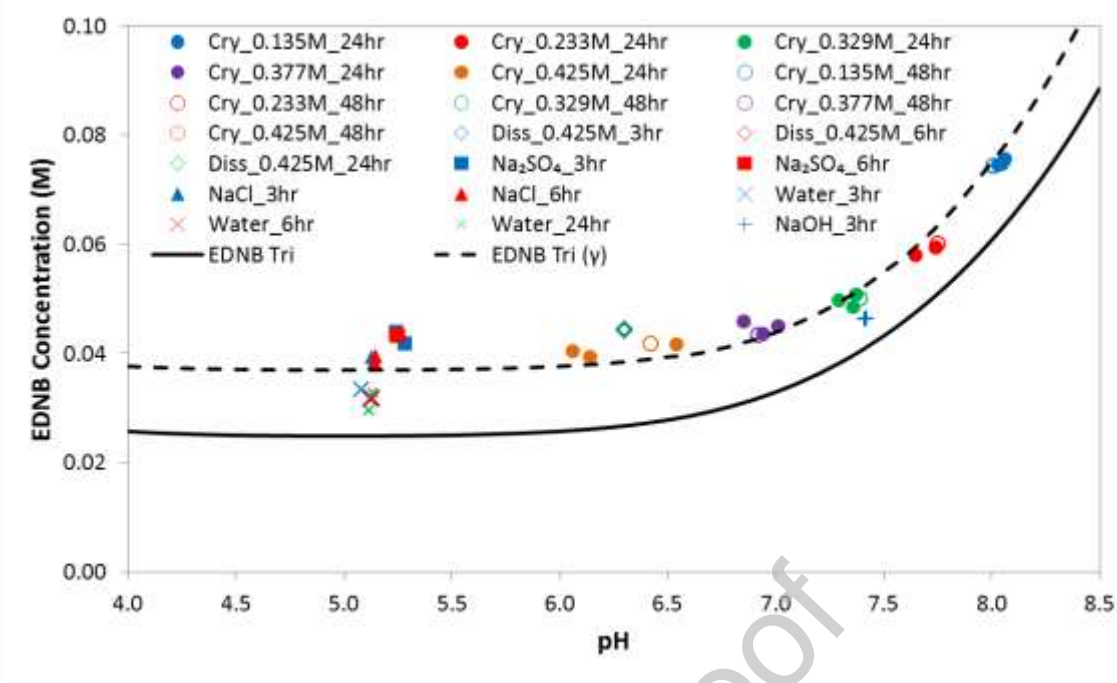

Figure 5. EDNB triclinic solubility measurements compared with solubility lines. Solid black line and dashed black line are uncorrected (ideal) and activity-corrected (γ) solubility lines respectively. Open and closed circle-shaped data points represent solubility measurements made using the described crystallisation method with the labels including the molar concentration of the sulphuric acid solution used, and the slurry equilibrium time. Remaining data points represent solubility measurements made using the described dissolution method with the labels including the solution type, and the slurry equilibrium time.

When dissolving EDNB triclinic in pure water or in NaOH solutions the solubility measurements don't differ greatly form the uncorrected solubility line due to the low ionic strength of those solutions. However, when there is a significant concentration of chloride or sulphate ions in solution the EDNB triclinic solubility becomes significantly greater than the uncorrected values. On the other hand, these solubility measurements closely match the new activity corrected solubility line. EDNB triclinic was dissolved in NaCl solutions in addition to Na_2SO_4 solutions in order to check if the increase in EDNB triclinic solubility was simply due to the increase in ionic strength or if the sulphate ions in particular played some additional role. It can be seen from the solubility measurements that NaCl solutions did lead to a greater EDNB triclinic solubility relative to pure water but it still isn't as great as the solubility obtained in the Na_2SO_4 solutions. Therefore, the sulphate ions are playing some additional role, beyond ionic strength, which is affecting the EDNB triclinic solubility.

To account for the effects of activity, the salt solubility equation shown in equation 4 was re-derived with activity coefficients as appropriate, resulting in the activity-corrected solubility equation shown in equation 20.

$$[EDNB]_S = \left\{\frac{1}{4}\, K_{sp} \left(\frac{1}{\gamma_2} + \frac{K_{a1}}{[H^+]\,\gamma_1^2} + \frac{K_{a1}\,K_{a2}}{[H^+]^2\,\gamma_1^2}\right)\left(1 + \frac{[H^+]\,\gamma_1^2}{K_a}\right)^2\right\}^{1/3} \quad (20)$$

Knowledge of all the activity coefficients allows for the activity-corrected solubility to be calculated. A new K_{sp} value was fitted to this activity-corrected equation in order to determine the actual solubility of EDNB triclinic. This new K_{sp} value is 6.0 x 10^{-5} mol^3/dm^9. It is interesting to note that this value is similar to the corresponding literature value of 7.7 x 10^{-5} mol^3/dm^9.

4.3. Modelling titration curves

The solution speciation model was firstly applied to semi-batch titration type experiments without considering crystallisation. Utilising the standard addition approach from literature [5, 6], these are experiments where there exists an initial aqueous solution containing 3,5-DNBA, ethylenediamine and NaOH into which sulphuric acid is added. The model assumes perfect mixing so the vessel type, agitation method and acid addition method won't be accounted for but would of course affect the mixing efficiency of the process. The 3,5-DNBA, ethylenediamine and NaOH concentrations were 0.2 M, 0.1 M and 0.105 M respectively. The initial solution had a volume of 90 mL with 10 mL of the titrant being added. Using this set of 3,5-DNBA, ethylenediamine and NaOH concentrations, in addition to this volume ratio, a semi-batch titration was modelled using a 2 M sulphuric acid solution as the titrant. Such a high concentration of sulphuric acid was used in order to show the full range of possible outcomes from the titration process. The results of this modelled titration are shown in Figure 6.

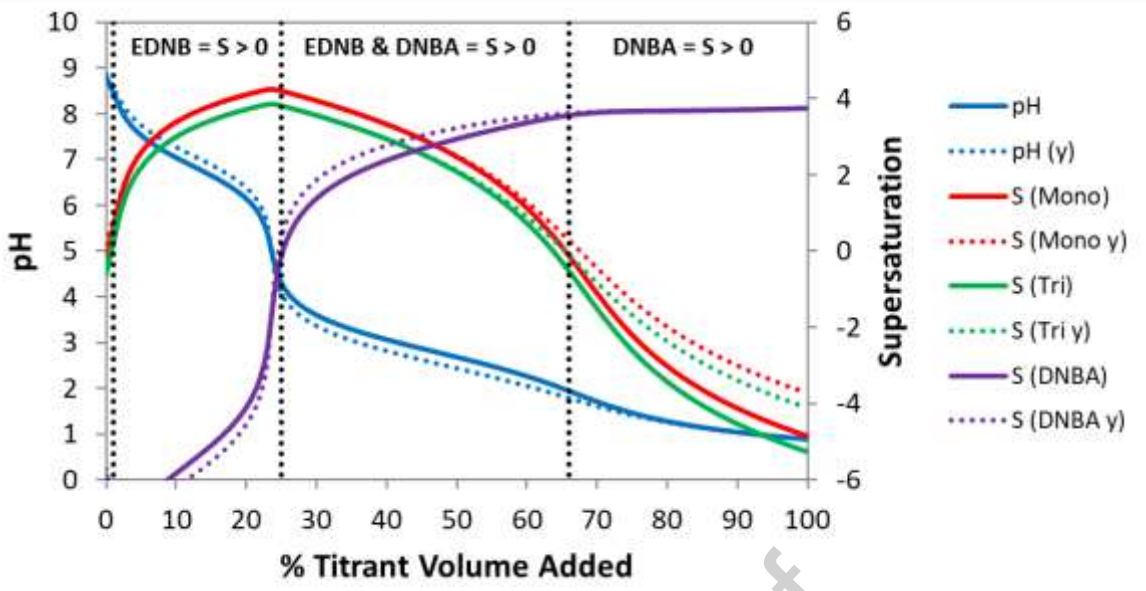

Figure 6. Modelled titration process. Both activity corrected (γ) and uncorrected model data are shown for comparison. Different regions are highlighted denoting where each of the potential solid forms are supersaturated.

The shape of the modelled titration curve demonstrates how sensitive the pH and supersaturation are to the titrant volume and concentration. Furthermore, the titration curve shows the full range of possible regions of interest and allows for the correct titrant volume and concentration to be selected in order to crystallise the desired solid form (EDNB monoclinic, EDNB triclinic or 3,5-DNBA) at the desired pH and supersaturation.

4.4. Semi-batch crystallisation processes

4.4.1. Addition approaches for 2:1 EDNB salt crystallisation

As previously stated, the solution addition approach from literature [5, 6] involves adding a strong acid (HCl or H_2SO_4) to an initial aqueous solution containing 3,5-DNBA, ethylenediamine and NaOH. The initial solution composition was designed in order to have the maximum concentrations of 3,5-DNBA and ethylenediamine while keeping a stoichiometric 2:1 molar ratio of 3,5-DNBA:ethylenediamine and keeping the solution pH below 9. The solution pH should be kept below 9 because above this value 3,5-DNBA is reported [28] to react with hydroxide ions to yield a red coloured solution containing 2,3-dihydroxy-5-nitrobenzoic acid and 3,3'-dinitro-5,5'-dicarboxyazoxybenzene. This standard solution addition approach was utilised for modelling all of the batch EDNB crystallisation processes in this study. However, alternative solution addition approaches were considered.

When considering alternative solution addition approaches several issues had to be kept in mind. Firstly, the initial solution containing 3,5-DNBA had to maintain a pH high enough to achieve reasonable solubility but not so high as to lead to decomposition. This typically meant the solution was required to have a pH value between 4.5 and 9. In addition, if 3,5-DNBA and ethylenediamine were in the same initial solution then the EDNB salt had to be undersaturated. Similarly, the final mixed solution had to be supersaturated with respect to the EDNB salt but undersaturated with respect to 3,5-DNBA. This usually meant that the initial solution containing 3,5-DNBA had a pH greater than the mixed solution pH, the other initial solution had a pH less than the mixed solution pH and the mixed solution had a pH where the EDNB salt was supersaturated.

The most likely alternative solution addition approach was to add a solution containing ethylenediamine and sulphuric acid to an initial solution containing 3,5-DNBA and NaOH. This allowed for a high concentration of 3,5-DNBA to be dissolved in the initial solution as a reasonable pH could be maintained by using the required NaOH concentration. The stoichiometrically required concentration of ethylenediamine was then used in the other solution and the sulphuric acid concentration to be used was determined by the target pH of the mixed solution.

In order to model either the standard addition approach or the alternative addition approach a set of solution concentrations, solution volumes and a target pH of the mixed solution had to be selected. In order to compare the approaches, the initial solution (containing 3,5-DNBA and NaOH with or without ethylenediamine) had a volume of 90 mL while the titrant (containing sulphuric acid with or without ethylenediamine) had a volume of 10 mL in both approaches. Also for both approaches the mixed solution had a target pH of 6. For the standard addition approach the 3,5-DNBA, ethylenediamine, NaOH and H_2SO_4 concentrations were 0.2 M, 0.1 M, 0.105 M and 0.419 M respectively. For the alternative addition approach the 3,5-DNBA, ethylenediamine, NaOH and H_2SO_4 concentrations were 0.2 M, 0.9 M, 0.2 M and 0.846 M respectively. The modelled EDNB crystallisation processes for both the standard and alternative solution addition approaches, with a titration endpoint of pH 6, are shown in Figure 7.

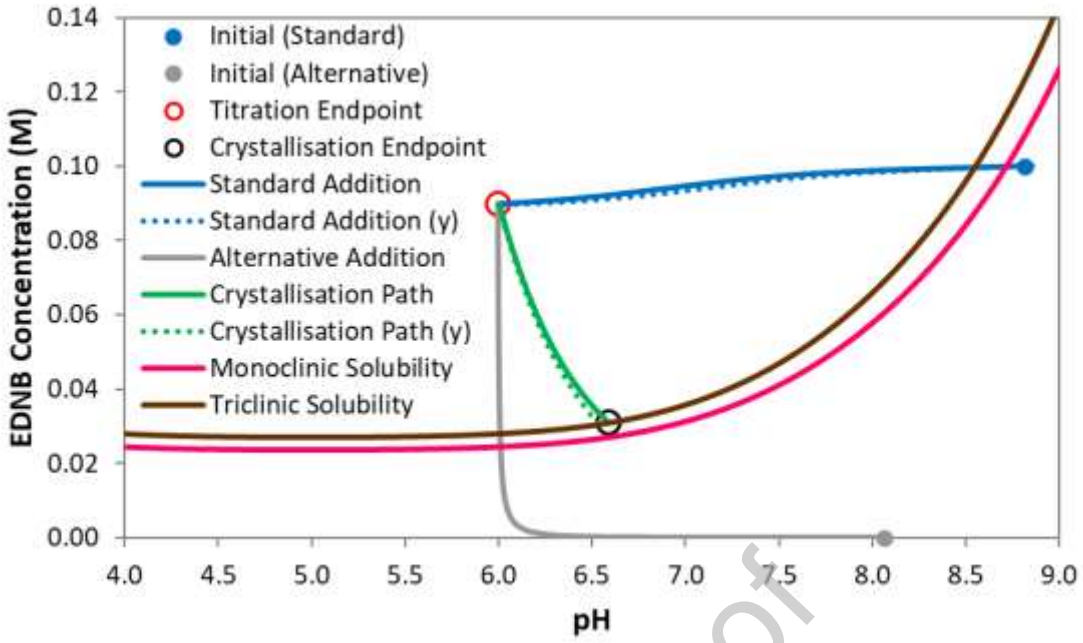

Figure 7. Modelled 2:1 EDNB crystallisation processes for both the standard and alternative solution addition approaches with titration endpoint of pH 6. Both activity corrected (γ) and uncorrected model data are shown for comparison.

It can be seen for the standard addition approach that as the sulphuric acid is added to the initial solution containing 3,5-DNBA, ethylenediamine and NaOH, the concentration of the EDNB salt decreases to the target value (due to dilution) and the pH of the initial solution decreases to the target value. It can be seen for the alternative addition process that as the solution containing ethylenediamine and sulphuric acid is added to the initial solution containing 3,5-DNBA and NaOH, the concentration of the EDNB salt increases to the target value (due to creation of EDNB salt in solution) and the pH of the initial solution decreases to the target value. Despite these differences between the approaches the crystallisation process which occurs after the end of the titration process is the same. The alternative addition approach may be advantageous to the standard approach used in this work as the concentrations of 3,5-DNBA and ethylenediamine can be increased without the pH values of the initial solutions changing greatly. This is because the concentrations of NaOH and sulphuric acid can be increased in each solution to counteract the pH change resulting from the increase in 3,5-DNBA and ethylenediamine concentrations. By having increased concentrations, the yield of the EDNB salt can be increased. Therefore, this alternative addition approach could be investigated experimentally in the future.

4.4.2. Modelling 2:1 EDNB salt crystallisation

As previously mentioned the model can be applied to the two-phase system which exists during the crystallisation process. Initially the model tracks solution speciation without the presence of solids as the titration progresses. Once crystallisation occurs the model starts re-calculating the solution speciation due to material being removed from solution and this continues until the solution reaches saturation because the liquid and solid phases are at equilibrium. Figure 8 shows modelled EDNB crystallisation processes with different titration endpoints. The process essentially consists of two parts. The first part is the single-phase titration where the titrant is added to the basic solution until completion, the second part is the crystallisation pathway showing the decrease in EDNB solution concentration until the EDNB triclinic solubility line is reached. Eventually the process would reach the EDNB monoclinic solubility line when transformation takes place but this isn't shown explicitly. Using this solubility line as the endpoint is correct as the molar feed ratio and salt stoichiometry is maintained at all times. As with modelling the batch titration curves, the initial solution consisted of 3,5-DNBA, ethylenediamine and NaOH with concentrations of 0.2 M, 0.1 M and 0.105 M respectively. Using this initial solution composition, the sulphuric acid concentration was determined by the target titration endpoint and was therefore different for each titration endpoint. The sulphuric acid concentrations used for the titration endpoints of pH 7, 6, 5 and 4 were 0.211 M, 0.419 M, 0.472 M and 0.528 M respectively. The initial solution had a volume of 90 mL with 10 mL of the sulphuric acid being added. It should be noted that some of these titration endpoints may not be possible to achieve in practice if the metastable zone width (MSZW) would be crossed prior to reaching the desired pH. In addition, EDNB crystallisation at a pH less than 4.5 in reality would be complicated by the simultaneous crystallisation of the 3,5-DNBA starting material. However, this wasn't considered in this application of the model.

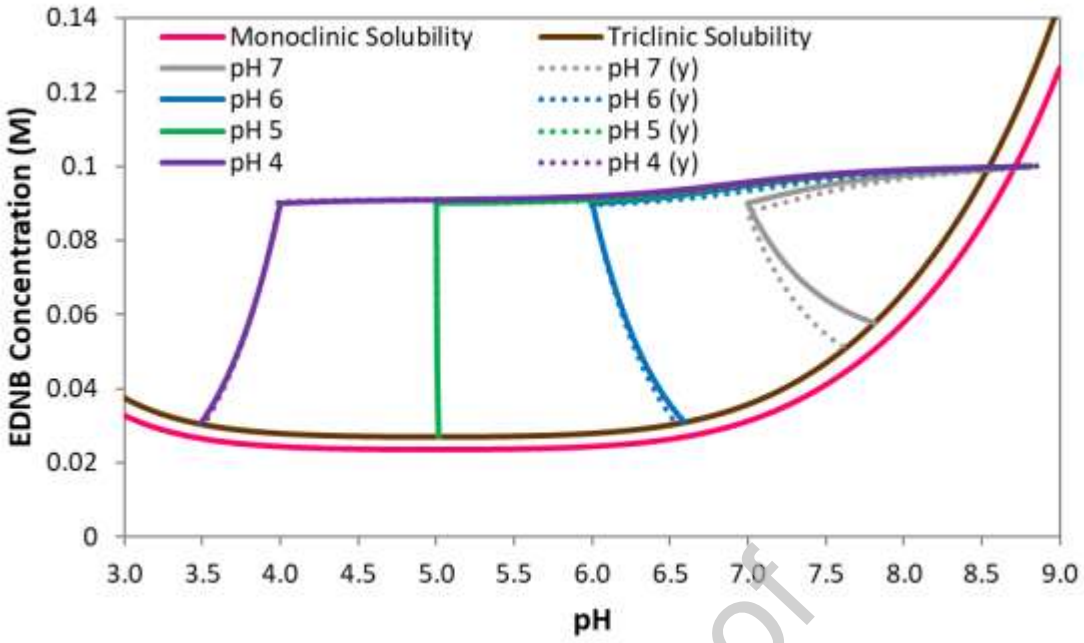

Figure 8. Modelled 2:1 EDNB crystallisation processes, using a 2:1 molar feed ratio, with different titration endpoints. Both activity corrected (γ) and uncorrected model data are shown for comparison.

What is most noticeable from the crystallisation pathways is how the pH changes as the crystallisation progresses. When the pH at the titration endpoint is greater than 5 then the pH will increase because while $[BH_2^{2+}]$ ions are being removed from solution, a low $[SO_4^{2-}]$ ion concentration is present and there are still $[BH^+]$ and $[Na^+]$ ions remaining in the solution. This can be seen clearly in Figure 8, when the crystallisation process commences at pH 7 the final pH at the end of crystallisation can be as high as pH 7.8. This increase in pH corresponds to an increase in final solubility from 0.036 M to 0.058 M which corresponds to a decrease in the maximum possible crystallisation yield from 60 % to 36 %. This large effect on the crystallisation yield would clearly be a major problem for an industrial organic salt crystallisation process and it is only with use of the model described in this work that this problem could be predicted and quantified prior to experimentation. An additional consideration for the model compound used in this work is that the stable EDNB monoclinic polymorph can only be reliably crystallised at a pH value greater than 6 [5, 6, 19] which means that the issue of decreased yield could not be simply avoided by using a target pH value of 5. Instead, a more complex control strategy (designed using the model in this work) would have to be implemented where additional strong acid was added to the system during crystallisation to counter the potential pH increase and thus maximise the crystallisation yield.

When the pH at the titration endpoint is around 5 then the pH will remain essentially constant because the $[SO_4^{2-}]$ and $[Na^+]$ ions have effectively neutralised each other and there are no $[BH^+]$ ions

remaining in the solution as the $[BH_2^{2+}]$ ions are being removed from solution. When the pH at the titration endpoint is less than 5 then the pH will decrease because there is an excess of $[SO_4^{2-}]$ ions after completely neutralising the $[Na^+]$ ions and there are no $[BH^+]$ ions remaining in the solution as the $[BH_2^{2+}]$ ions are being removed from solution.

Utilising a 2:1 molar ratio of 3,5-DNBA:ethylenediamine in the feed solutions should be the most suitable method for crystallising the 2:1 EDNB salt as potentially all of the starting material can be consumed. However, other molar ratios were tested with the model in order to study the effect that it had on the crystallisation process. This exploration of the design space is useful as there may be practical benefits in using more or less of either material in the crystallisation process. When considering industrial crystallisation processes, the most notable benefit of changing the molar ratio would be to minimise the concentration of the more expensive starting material and thus make the process less costly to run. This activity is commonly performed in industry where a molar excess of the cheaper starting material will be used to ensure that the maximum amount of the more expensive material is consumed. Full results of testing different molar feed ratios can be found in the supplementary materials.

4.4.3. Modelling 3,5-DNBA crystallisation

In addition to crystallising either polymorphic form of the EDNB salt, the 3,5-DNBA starting material may be crystallised instead. This typically happens when the pH drops below 4 but depends on the 3,5-DNBA concentration. Figure 9 shows modelled 3,5-DNBA crystallisation processes with different titration endpoints. As with modelling the batch EDNB crystallisation processes, the initial solution consisted of 3,5-DNBA, ethylenediamine and NaOH with concentrations of 0.2 M, 0.1 M and 0.105 M respectively. Using this set of 3,5-DNBA, ethylenediamine and NaOH concentrations, the sulphuric acid concentration was determined by the target titration endpoint and was therefore different for each titration endpoint. The sulphuric acid concentrations used for the titration endpoints of pH 4, 3 and 2 were 0.528 M, 0.836 M and 1.304 M respectively. The EDNB salt could also crystallise at these pH values but this was ignored in this application of the model.

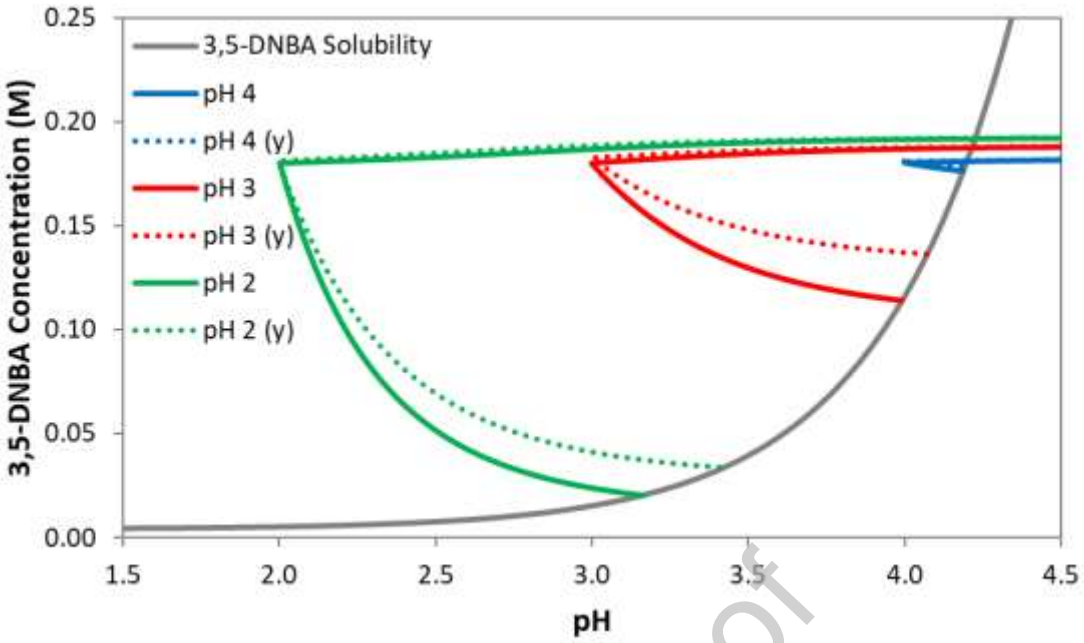

Figure 9. Modelled 3,5-DNBA crystallisation processes with different titration endpoints. Both activity corrected (γ) and uncorrected model data are shown for comparison.

When 3,5-DNBA crystallises the pH always increases as a pure acid is being removed from the solution. It is therefore crucial to consider that solution titration endpoints may need to be significantly lower in pH than the crystallisation endpoints, with significant effects on resulting crystallisation yields.

4.5. Continuous crystallisation processes

4.5.1. Continuous mixing approaches for EDNB salt crystallisation

The solution addition approach from literature, which was utilised for modelling all of the batch EDNB crystallisation processes, was directly translated to a continuous mixing approach to be used for modelling all of the continuous EDNB crystallisation processes in this work. This standard mixing approach involved continuously mixing the sulphuric acid solution with the solution containing 3,5-DNBA, ethylenediamine and NaOH. To achieve a target mixing endpoint of pH 6, the solution concentrations and volume ratio was the same as in the batch experiments. The change from the batch experiments being that instead of a gradual titration of the 10 mL sulphuric acid with the 90 mL initial solution, the two solutions are rapidly mixed together at a volumetric ratio of 9:1 in order to reach the mixing endpoint immediately. Similarly to the batch experiments, the model assumes perfect mixing so the mixing efficiency of the process isn't accounted for.

As with the batch EDNB crystallisation processes, an alternative mixing approach was modelled with this being a direct translation of the batch alternative addition approach. A 2:1 molar ratio of 3,5-DNBA:ethylenediamine was used as with the 2:1 EDNB salt crystallisation processes. The modelled continuous EDNB crystallisation processes for the standard and alternative mixing approaches, both with a mixing endpoint of pH 6, are shown in Figure 10.

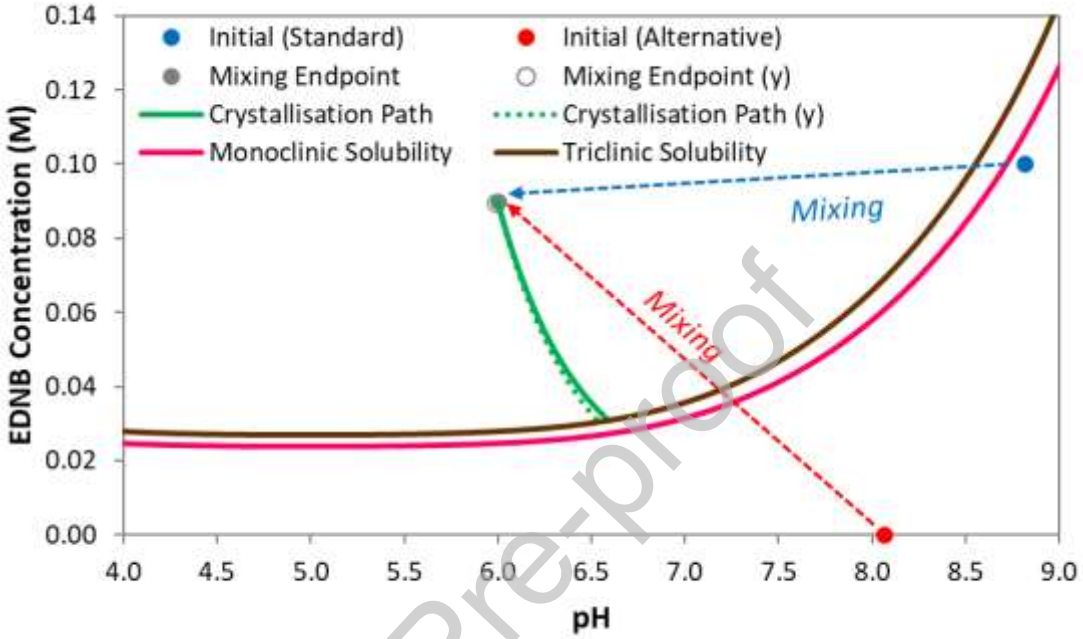

Figure 10. Modelled continuous EDNB crystallisation processes utilising either the standard or alternative mixing approach, both with a mixing endpoint of pH 6. Both activity corrected (γ) and uncorrected model data are shown for comparison.

The modelled continuous EDNB crystallisation process shows how continuous mixing can be used to reach the desired point on the phase diagram instantly if mixing is perfect. This means that in practice reaching any point on the phase diagram is only limited by the mixing efficiency. As with the batch alternative addition, the alternative mixing approach may be advantageous to the standard mixing approach as the concentrations of 3,5-DNBA and ethylenediamine can be increased without the pH values of the initial solutions changing greatly which allows for the yield of the EDNB salt to be increased.

4.5.2. Modelling 2:1 EDNB salt crystallisation

The solution speciation model was applied to continuous experiments where an aqueous solution containing 3,5-DNBA, ethylenediamine and NaOH was continuously mixed with sulphuric acid. Similarly to the batch experiments the model assumes perfect mixing so the mixing efficiency of the

process isn't accounted for. Using the same initial solution composition as the batch experiments, the model can be used to generate surface plots showing the pH and supersaturation outcomes for a range of sulphuric acid concentrations and flow ratios. Example surface plots are shown in Figure 11. These surface plots illustrate the range of pH and supersaturation outcomes that can be obtained in continuous EDNB experiments which makes them very useful for model guided design of experiments.

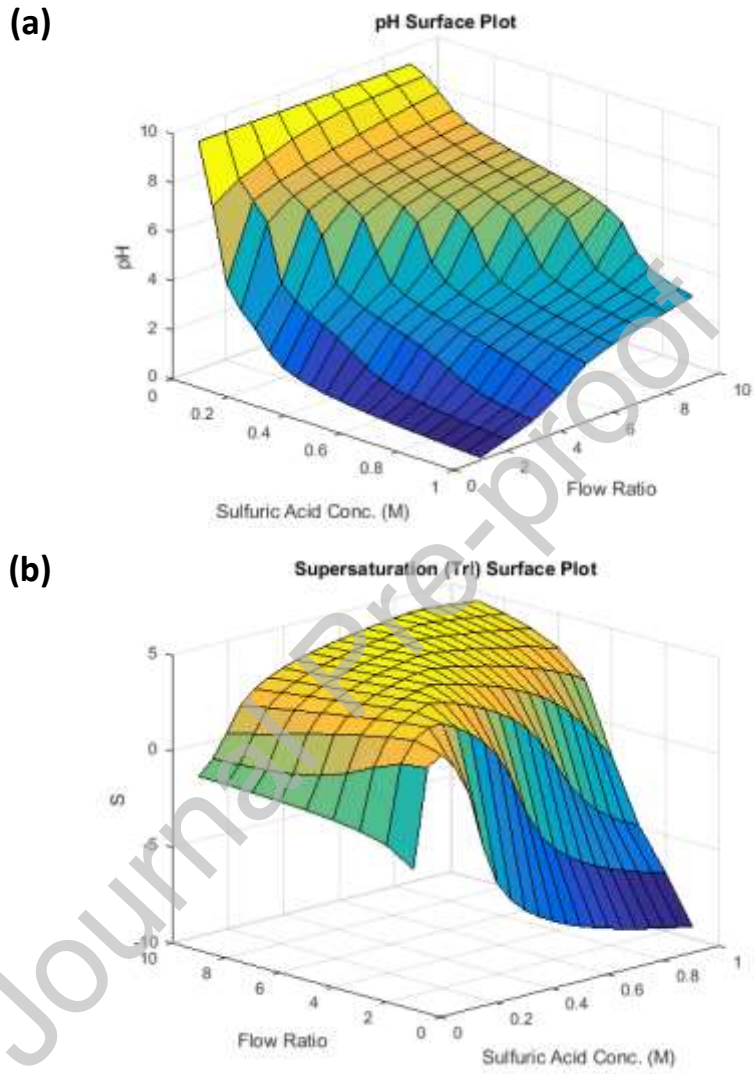

Figure 11. (a) Surface plot demonstrating how sulphuric acid concentration and flow ratio affect pH in continuous organic salt crystallisation design for a particular solution composition. (b) Surface plot demonstrating how sulphuric acid concentration and flow ratio affect EDNB triclinic supersaturation in continuous organic salt crystallisation design for a particular solution composition.

5. Conclusions

A mathematical model of organic salt crystallisation by the addition of a strong acid in either a semi-batch or continuous mode has been developed. The model utilises dissociation constants in addition to material and charge balances to predict pH and solution composition throughout a salt crystallisation process. It shows the change in pH and supersaturation which occurs when either one of the three possible solid phases crystallises. The pH-solubility profiles of each polymorph of the EDNB salt from literature were validated experimentally and the pH-solubility profile of the 3,5-dinitrobenzoic acid starting material was experimentally measured as part of the present study. When crystallisation commences in a pH region where 3,5-DNBA is undersaturated either one of the EDNB salt polymorphs will crystallise until the solution is saturated with respect to the polymorph present. During salt crystallisation the pH will change depending on the pH at which crystallisation commenced with the final pH and solubility values potentially much higher from those prior to the onset of crystallisation. This change in pH and solubility during crystallisation will significantly affect the crystallisation yield which would clearly be a major problem for an industrial organic salt crystallisation process. It is only with use of the modelling approach described in this work that this problem could be predicted and quantified prior to performing detailed crystallisation experiments. The speciation model introduced here can be combined with appropriate crystallisation models (e.g., population balance models) to provide pH and supersaturation for nucleation and growth kinetics in the course of crystallisation. In absence of physically correct speciation information, predictive modelling of organic salt crystallisation would not be possible.

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Credit Author Statement

JM and JS contributed to conception and design of the study. JM performed the modelling and experimental work. JM wrote the first draft of the manuscript. HW, CJP and JS wrote

sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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