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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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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 °C; 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 °C; 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 °C; 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

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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.

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 h.

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.

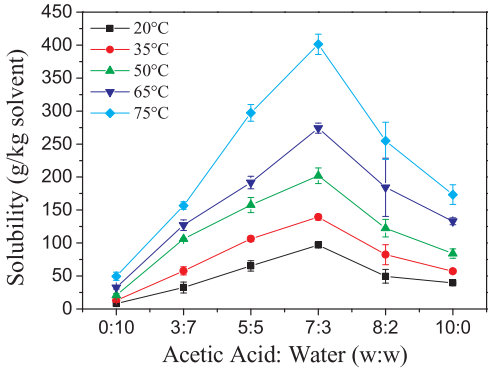

Fig. 1. Solubility of paracetamol in different ratios of acetic acid to water.

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 $kg_{solvent}^{-1}$ 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

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

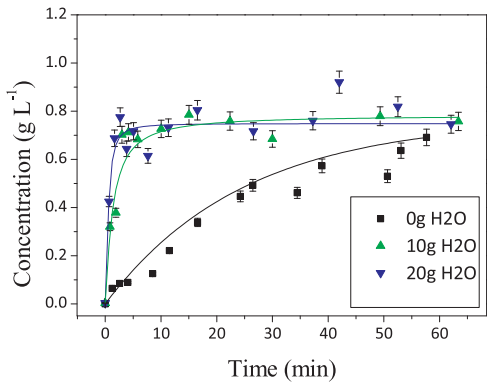

Fig. 2. Concentration of paracetamol with different water contents (Temperature = 70 °C).

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