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On-Line Analytical Techniques for Monitoring Crystallisation Processes of Organic Speciality Chemicals

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In order to examine on-line batch crystallisation processes a new integrated batch process engineering laboratory has been established providing facilities for the on-line measurement and control of:

- reactant supersaturation via ATR-FTIR spectroscopy;
- crystal size via acoustic attenuation spectroscopy;
- particle perfection and polymorphic form via X-ray diffraction;
- crystallisation on-set and meta-stable zone width via UVvis spectroscopic turbidometric measurements.

These facilities are complemented via assessment of reactant mixing as measured via laser doppler anemometry and simulated using multi-phase computational fluid dynamics. An overview of the planned research programme and material systems to be examined are presented:

Keywords: Crystallisation; on-line analytical techniques; batch processing; process mixing scale up

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INTRODUCTION

In recent years the developed world has seen much of the quality end of the chemical product market moving away from capital-intensive bulk chemicals towards the manufacture of high value-added speciality materials. In the speciality chemical sector much of the processing is by batch manufacture rather than continuous operation, and is often of high added value. Frequently the products are particulate solids with crystallisation used as the primary formation process in order to achieve purity of product as well as desired product form.

The non-linearity of process variables inherent in batch processing provides additional problems for controlling the product form and rarely have crystallography and surface chemistry been manipulated in any direct way to improve and optimise product properties. Often the complex organic molecular chemistry of the product together with non-equilibrium conditions leads to poorly defined process conditions, not readily amenable to empirical modelling. In this scenario, improved understanding of the interrelations between reaction mixing, supersaturation control and solid-state property control could have a direct impact on the ability of process engineers to improve and optimise the production process. Driven and tensioned by this agenda, a new on-line batch process engineering laboratory has been recently set up.

The new facility is aimed at bringing in mainstream chemical engineering to interface with this molecular science and tackle non-linear and non-steady-state batch processing problems. Specifically, the new facility provides batch processing facilities for particle production via crystallisation techniques which are equipped with a range of advanced on-line analytical tools optimised for the measurement and continuous

monitoring of reactant properties, such as solution supersaturation, meta-stable zone width (MSZW), particle size and crystal structure with the aim of correlating these parameters with process control variables.

The new facility is founded on previous work in which, for example, X-ray diffraction and optical scattering techniques have been used to measure **on-line** the structuro-kinetic parameters important in crystallisation and precipitation processes [1-5]. This work has been extended and enhanced via further development involving the integration of additional and complementary on-line techniques such as: ultra-sonic spectroscopy for particle sizing, which has been developed by DuPont de Nemours and Malvern Instruments; Fourier transform infra-red spectroscopy for measurement of solution supersaturation, developed by Berglund and co-workers [6-8] at Michigan State University; and laser doppler anemometry for the assessment of particle velocity.

In particular, the aim is to use all these on-line analytical techniques and others simultaneously to examine, in a self-consistent manner, the important physical properties of both mother phase and solid product within a batch crystallisation reactor during realistic processing conditions. In particular, the research aims are to inter-relate processing parameters with the molecular and solid-phase structure of the product and vice versa.

The project is also examining the issue of reactor scale-up and address the role of hydrodynamics and reactant mixing as highlighted by recent work by Villermaux's group [9] in France. Through a synergetic approach, involving experimental studies of particle velocity/size distributions across the reactor vessel and computational fluid dynamics (CFD) modelling [10], process/property relationships as a function of reactor size and internals are being assessed with batch scale size initially at the 2 litre scale, moving through to the 20 litre scale towards industrial pilot plant scale sizes in due course.

Overall the project aims to understand, for the first time, the key processing parameters that impact on the robustness of many badly behaved batch manufacturing processes, i.e:

- robust process - suitable for manufacture using facilities with a modest degree of process control;
- non-robust process - demands high technology production plants and good process control.

The development of system-specific process robustness criteria and resultant process development protocols is one of the key research objectives of this research which can be expected to have ramifications

in the minimisation of plant-scale difficulties associated with the manufacture of speciality chemical products.

ON-LINE ANALITICAL TECHNIQUE FOR BATCH CRYSTALLISATION CONTROL

On-line techniques need to be able to analyse a process as it takes place so that process actuators can be adjusted to produce the desired product form. To improve process efficiency a tight control loop between the actuator and its resultant outcome is needed. In addition, on-line data can be used to produce and stabilise product material in novel forms and structures. Overall, analytical techniques should be able to:

- examine structure on an atomic length scale;
- be non-destructive;
- enable process to be examined *in-situ* and dynamically.

Mapping out Reactant MSZW using UV_{vis} Turbidometric Measurements

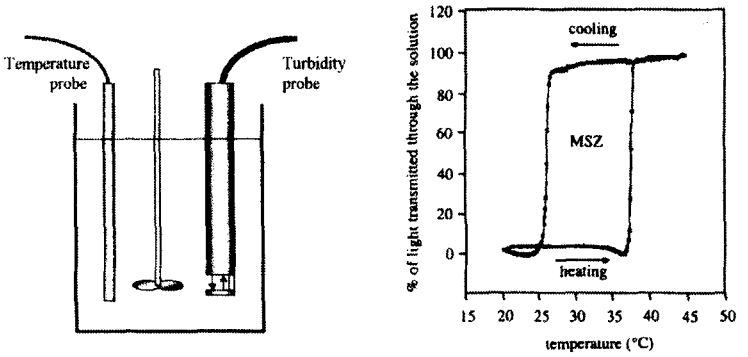


FIGURE 1. MSZW data via turbidometric measurements: (a, left) turbidometric reactor; (b, right) MSZW data on sodium laurate consistent with a MSZW of C at a temperature cooling rate of 0.75C°/min [4].

Turbidity techniques are routinely used to measure the on-set of crystallisation and, via cooling/heating cycles as a function of temperature rate, the equilibrium solubility and solution meta-stable zone width. UV_{vis} spectroscopy merely provides the capability to measure turbidity as a function of wavelength thus providing size-dependent (and hence to a degree growth-rate dependent) information.

Figure 1a shows a typical turbidometric test reactor comprising of fibre-optic turbidity probe, PT100 platinum resistance thermometer and stirrer. Temperature cycling data (Figure 1b) reveals the characteristic hysteresis turbidity vs temperature curve revealing the MSZ between the kinetically dominated crystallisation on-set point and the thermodynamic equilibrium dissolution limit [4].

Monitoring Solution Supersaturation within the MSZ using ATR FTIR Spectroscopy

FTIR together with an ATR probe has been successfully used to monitor on-line reaction rates within small scale reactor vessels. Recently, Berglund and co-workers at Michigan State University have demonstrated that ATR FTIR can also be used for the on-line determination of reactant supersaturation [7].

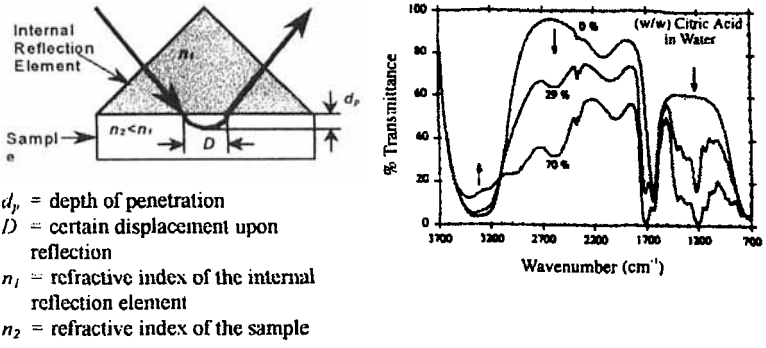


FIGURE 2. (a: left) Schematic representation of path of a ray of light for total internal reflection. The ray penetrates a fraction of a wavelength (d_p) beyond the reflecting surface into the rarer medium of refractive index n_2 and there is a certain displacement (D) upon reflection [11]. (b: right) IR spectra of citric acid in water compared to the IR spectrum of water. The arrows indicate the directions of change of the spectrum as the concentration of citric acid in water is increased. Spectra recorded here were taken at 35°C. Spectra both at 10 and 30° follow the same trend [7].

ATR FTIR spectroscopy to measure solubility and supersaturation provides a unique sampling configuration, in which the infrared spectrum of the liquid phase of a slurry can be obtained without phase separation. Figure 2a demonstrates the principle of the ATR technique. The infrared light emitting radiation is totally reflected at the media

interface and is propagated as a transverse wave. The evanescent field generated by infrared radiation, penetrates into the rarer medium as a non-transverse, exponentially decaying wave, composed of electric vector components in all spatial directions.

The penetration of the exponentially decaying energy field is assessed by the so-called depth of penetration, which is related to important parameters as follows:

- d_p decreases as the angle of incidence increases;
- d_p decreases as the wavelength decreases;
- d_p decreases as the relative refractive index of the analyte medium to the denser propagating medium decreases.

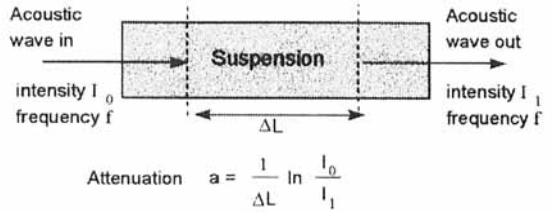
Due to this relationship it is possible to extend this technique for the measurement of solubility and supersaturation of a substance in the liquid phase of a slurry. The basis for this attempt is that the thickness of this solution phase barrier should be large relative to d_p, so that there is no interference from the undissolved solute particles.

Previous work [II] carried out with aqueous citric acid have shown that ATR FTIR spectroscopy can be successfully employed to determine solubility and supersaturation. The IR Spectra of aqueous citric acid solutions are given in Figure 2b. The decrease in intensity of infrared transmission bands of citric acid relative to that of water (in the vicinity of 3300 cm^{-1}: OH stretching; 1600 cm^{-1}: HOH scissoring) as the citric acid concentration is increased from 0 to 70 % is clearly evident.

Measuring Crystal Particle Size Distribution using Ultrasonic Spectroscopy

Difficulties in measuring on-line particle size distribution have resulted from the use of techniques such as light scattering which demand low concentration of solids for analysis. This, in turn, has demanded reactant dilution resulting in an unrealistic experimental set-up for industrial scale measurements. Early work by DuPont de Nemours and latterly Malvern Instruments on TiO_2 has demonstrated the advantage of ultrasonic spectroscopy (USS) to analyse on-line solids concentrations as high as 70% by volume thus making the technique optimal for crystallisation applications.

The USS system measures the attenuation of a sound beam passing through a suspension:



The relation of Sound Attenuation to Crystal Size Distribution (CSD) is described by Allegra & Hawley's mathematical model. Allegra & Hawley's theory is based on the laws of conservation of mass, energy, and momentum, the thermodynamic equations of state and stress-strain relations for the isotropic elastic solids or viscous fluids. The model requires the knowledge of the following physical parameters for both phases, particle and suspending medium:

- density
- sound attenuation
- speed of sound
- coefficient of thermal expansion
- thermal conductivity
- heat capacity
- viscosity (liquids), shear rigidity (solids)

An example of attenuation spectrum along with the related size distribution of the system is given in Figures 3a and 3b respectively:

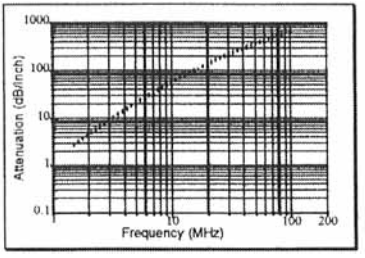


FIGURE 3a. Attenuation spectrum of for a sample of silica in water, D50=250nm

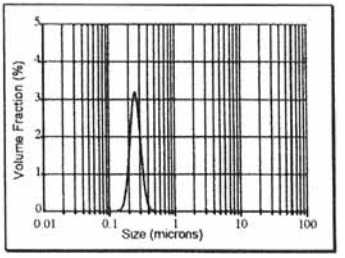


FIGURE 3b. Particle Size Distribution for a sample of silica in water, D50=250nm

As part of this research work physical properties (density, elastic moduli, etc.), needed for data analysis, are being calculated using molecular modelling and appropriate modelling software being developed. Malvern Instruments are providing detailed support of this

work and a prototype on-line USS system, incorporating a flow through cell, is currently being developed.

Probing Particle Structure using X-ray Diffraction

Characterisation of polymorphic form is routinely carried out in the laboratory using powder X-ray diffraction techniques. As different polymorphs have different (3-D) crystal structures they provide distinctive XRD patterns. XRD carried out on-line using a flow through cell enables the phase to be determined whilst the crystals are being formed thus enabling process conditions to be optimised to obtain one form instead of another (see Figure 4). XRD can also be used to determine the particle strain and degree of crystallinity of the crystallised particles thus enabling the process to be optimised to maximise the product quality.

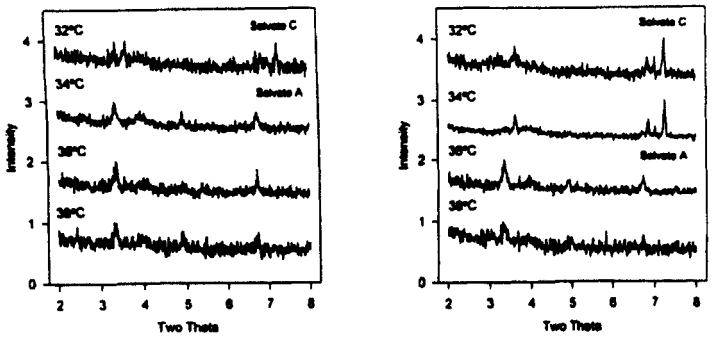


FIGURE 4. In-situ XRD data of antibiotic slow base addition, T_{trans} = 34°C (a: left), and fastbase addition, T_{trans} = 36°C (b: right) [3].

Optimising Reactant/Product Mixing using Laser Doppler Anemometry

Particle size, growth and nucleation will be influenced by the mixing regime within the batch crystalliser. In order to quantify the hydrodynamics in the laboratory scale reactor, LDA is used to measure fluid velocity profiles, turbulence levels and particle velocities in a full scale model of the 2 litre batch crystalliser. The model is constructed of thin-walled Acrylic sheet. It is contained in a plane glass walled tank containing process liquid to match refractive index of that used on the test reactor. (Figure 5). The LDA system being mounted on a 3-D scanning system enables radial, tangential and axial flow velocity profiles to be assessed.

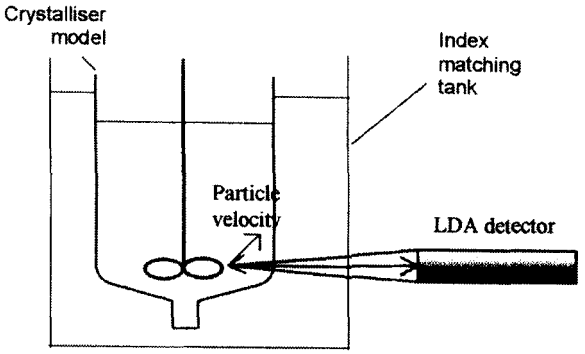


FIGURE 5. Experimental setup of the LDA measurement.

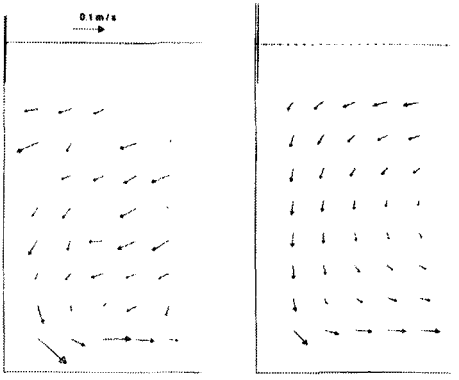


FIGURE 6. Velocity vectors in a 2 dimensional oil/water separator model; measured by LDA (a:left), and predicted by CFD (b:right) [12].

By correlating particle size distributions achieved in the crystalliser with fluid and particle velocity measurements in the model (e.g. Figure 6), the effects of process conditions on product particle qualities will be assessed. Via a comparison of the 3-D LDA velocity measurements with associated CFD predictions, parameters associated with scaling-up batch reactor size towards those more typical of an industrial pilot plant scale.

PLANNED RESEARCH PROGRAMME FOR THE ON-LINE BATCH PROCESS ENGINEERING LABORATORY

Basic Strategy

The project is centred around:

- construction of batch crystallisation systems at the 2 litre and 20 litre scale sizes;
- development and implementation of analytical tools for on-line studies of crystallisation reactions;
- integration of on-line facilities within a typical batch reactor environment.

The on-line batch process engineering laboratory involves the integration of a number of state of the art on-line analytical systems such as X-ray diffraction (XRD), ultrasonic spectroscopy (USS), UV visible (UV_{vis}) spectroscopy, Fourier transform infra-red (FTIR) spectroscopy and laser doppler anemometry (LDA) into computer controlled batch crystallisation reactors at the 2 and 20 litre scales in an overall system, which includes the careful control of temperature, pH and mixing. The planned research programme detailed below can be summarised as:

- developing and enhancing the science underpinning the crystallisation and precipitation of organic materials which are inherently difficult to process via an integrated approach involving the use of molecular scale processing tools in the systematic design and control of batch manufactured advanced speciality chemical products. Associated with this, the programme has two main technical development areas:
  - ➢ building a 2 litre batch reactor system, which will incorporate all the on-line instrumentation and using this seeking to explore, measure, analyse and control fully the crystallisation of up to three types of organic materials. From this a working on-line system will be delivered;
  - ➢ CFD modelling will be developed based on existing basic programme codes and validated against experiment. Theoretical results from the CFD simulations together with experimental data from the 2 litre scale will be a critical component into the overall strategy to design the 20 litre scale batch reactor.

Inter-relating Molecular-Scale Factors with Process Variables

Particle formation will be effected via control of processing variables such as:

- temperature and rate of change of temperature;
- pH and rate of change of pH;

- mother phase mixing, control of stirring parameters;
- measured addition of other phases (reactive phases, solvent for drowning out, etc.);
- addition of seed material and/or nucleation additives.

Using the proposed 2 litre fully instrumented reactor we plan to cross-correlate process parameters with particle growth rate and structure and through this to evolve a deeper understanding of the particle formation process and its control. Through this work, using the unique combination of on-line facilities available in the proposed facility, we plan to define the key parameters important in the batch production process and to correlate these with the molecular chemistry of product material and the resultant particle properties. The overall batch crystallisation process can be usefully sub-divided into its nucleation and growth stages.

Particle nucleation and nucleation control

The nucleation stage involves the formation of nano-size 3-D clusters driven by supersaturation within the MSZ. For crystallisation from e.g. solutions the MSZ (typical values from 0.1 to 50°C) is the difference between saturation and crystallisation temperatures. Within the MSZ nucleation does not take place spontaneously with the supersaturation, but follows after an induction time (typical values are a few seconds to several hours). Anecdotal evidence supports the influence of process variables on nucleation properties, but very few definitive studies exist on industrially relevant materials prepared under representative batch reaction conditions. In this programme we plan to:

- determine, via MSZW measurements (XRD and UV_{vis}) as a function of starting temperature, whether solution pre-ordering is important in optimising the desired final physical form;
- establish control of the nucleation conditions (XRD, FTIR and UV_{vis}) to provide optimum crystal growth conditions (USS and XRD);
- examine the effect of seeding parameters (size, size range, quality, addition rate) on the nucleation process via cross correlation of seed dissolution and growth (USS and UV_{vis}) behaviour within the MSZ (FTIR);
- use additives for poorly nucleating systems in order to improve crystallisation efficiency and assess their performance on-line (XRD and UV_{vis}).

Particle growth and processing

Following nucleation, particle formation to practical dimensions takes place via 2-D crystal growth on the individual habit faces of the particle. Very little is currently defined relating particle properties to process variables in batch reactors. In the proposed programme we plan to:

- measure on-line particle size distribution (USS) as a function of reactor residence time to:
  - ➢ correlate this with solution supersaturation (FTIR) in order to determine kinetic laws relating to particle growth rate in order to optimise product quality (XRD) and purity;
  - ➢ examine the inter-relationship between particle growth kinetics and particle ripening and clarify the potential use of surfactants in controlling inter-particle agglomeration;
- examine factors important in particle design via crystallisation processes such as the inter-relationships between:
  - ➢ supersaturation (FTIR) and final particle size (USS);
  - ➢ particle growth rate (USS) and reactor residence time (UV_{vis});
  - ➢ chiral properties, i.e. addition of stereo-chemically resolved additives, with growth rate;
- produce particulate products with defined defect structure/solubility and/or desired crystallographic structure (XRD), i.e. produce material in the correct:
  - ➢ polymorphic and/or solvate/hydrate form;
  - ➢ chirality, i.e. resolved versus racemic form;
- attempt to cross correlate particle size and size range (USS) with reactor agitation and particle/fluid mixing (LDA) to reduce:
  - ➢ generation of unwanted fines;
  - ➢ poor particle perfection (XRD) due to particle/particle attrition;
  - ➢ overall process inhomogeneity throughout the reactor.

Systems for Study

In the research programme three representative materials systems, aimed at the generation of generic output, are planned for study.

Urea

Urea represents a typical hydrogen-bonded material representative of many speciality products. It crystallises with a needle-like morphology, tends to easily agglomerate and ingest solvent. Due to its high solubility, urea solutions are highly viscous and exhibit large MSZWs from aqueous and ethanolic solutions. As its ethanolic solubility is quite low it

provides a useful representative system for assessing crystallisation via drowning out reactions.

Stearic acid and sodium stearate

Stearic acid, representative of materials such as oils, fats, soaps and waxes, has a plate-like morphology and crystallises in one of two different polymorphic forms dependent on the growth environment. Additionally, its neutralisation by sodium hydroxide to produce the simple soap, sodium stearate, provides a representative precipitation reaction for study as not only is the product difficult to process, but non-stoichiometry and variable hydration are significant issues in terms of product performance.

α-Amino acids

Understanding the molecular recognition processes between different α-amino acids is important in many bio-chemical processes. In addition, these materials provide useful representative systems for understanding hydrogen-bonding in small molecule chiral systems. For example, L- and DL-alanine have different polymorphic structures with the enantiomer crystallising in an easier manner than the racemate. In addition stereo-specific tailor-made additives, such as chirally resolved phenylalanine, can be used to define some of the structural factors important in the chiral resolution of optical isomers via crystallisation techniques.

CLOSURE

The new facility and its associated research programme will offer significant benefits to the chemical and pharmaceutical manufacturing sector in that it would offer the exciting prospect of a full system design capability, based on molecular-scale factors, for the preparation of speciality chemical products involving: theoretical molecular modelling; synthesis and purification; particle surface engineering; structuro-kinetic studies; reactor design, product mixing and process scale-up; robust control methodology and equipment; in an overall schematic resulting in the optimal design of the resultant manufacturing process.

The economic and industrial impact resulting from the successful conclusion of this work could be significant, e.g. the production of particulate materials with reliable and reproducible properties would impact in manufacturing via:

- manipulation of product structure and/or morphology in a defined way;
- elimination of batch to batch variability in solid-phase processing;
- removal of unnecessary processing steps due to definition of process robustness;
- derivation of optimal process scale-up parameters by detailed CFD modelling.

As the chemical industry develops towards the new millennium, the trend towards the manufacture of high value-added speciality chemicals, away from capital-intensive commodity materials can be expected to continue. Full exploitation of these markets, against competition world-wide, demands an improved understanding and control of processing factors on the molecular scale size. It is in this area that chemical companies, who have a strong intellectual research base, will be uniquely equipped to compete. For example, with many pharmaceutical products the definition of solid-state factors such as polymorphic form is now a pre-requisite for product profitability and hence the development of optimal on-line characterisation techniques in advanced product chemical process technology is also become increasingly more important. The new on-line batch process engineering laboratory recognises the potential importance of process analytical techniques in chemical product manufacture within this overall scenario and represents just one step towards an overall goal, which is to use molecular scale information in order to understand, predict, manipulate, control and refine particle formation processes.

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