Crystallisation Challenges in API Manufacture & Scale-up

Kevin J Roberts

Institute of Particle Science & Engineering, School of Process, Environment & Materials Engineering, University of Leeds, Leeds LS2 9JT, UK.

Heidelberg PAT Conference 2007, University of Heidelberg & European Compliance Agency (ECA) 24th -26th October 2007

© European Compliance Academy (ECA)

Session Overview

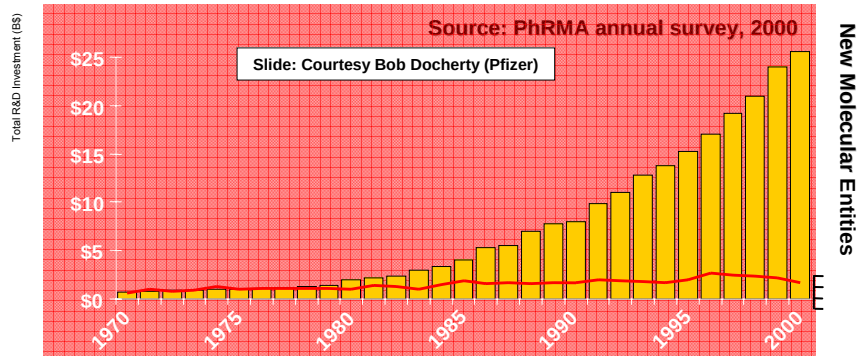
- **Reflect underpinning crystallisation science: nucleation, growth, morphology & polymorphism**
- **Review need for industrial innovation to improve competitiveness of process technology**
- **Consider holistic aspects of crystal science**
  - **Model, Measure, Manipulate & Manufacture**
- **Review process analytical techniques (PAT) for monitoring & controlling crystal formation**
  - **Turbidometric techniques for product solubility & meta-stable zone width**
  - **ATR-FTIR for solution concentration & supersaturation**
  - **Digital video microscopy for particle shape & polymorphic form**

© European Compliance Academy (ECA)

Productivity Paradox: Higher R&D Cost per Approved Product

Pharmaceutical industry getting more competitive but not any faster

Molecular complexity & hence solid form challenges increasing



Emerging importance of material properties on production efficiency

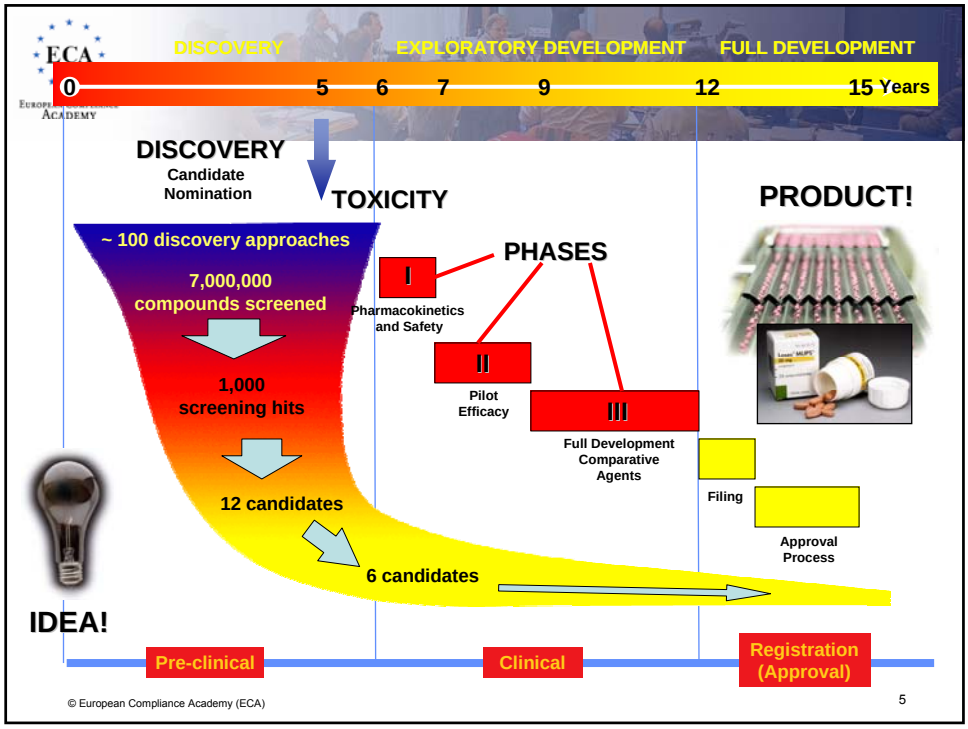
Increasing expectations from patient on product performance

Regulatory & Other Pressures: Need for Innovation

- Need for manufacturing innovation compounded by
  - Significant pressures to deliver product quickly to market post-approval to maximise patent revenue
    - ➢ hence discouraging innovation
  - Ever more complex drug products & processes which are hard to control during manufacturing
- Large number of drug candidates in R&D pipeline
  - With high attrition rate: R&D to market
  - Reduces feasibility of allocating significant engineering effort to candidates during R&D
  - Process effectively locked-in after approval via regulatory framework

Engineering currently cannot be on critical path: hence key driver against manufacturing innovation

©
4


ECA
DISCOVERY
EXPLORATORY DEVELOPMENT
FULL DEVELOPMENT
0
5
6
7
9
12
15 Years
DISCOVERY
Candidate Nomination
TOXICITY
PRODUCT!
~ 100 discovery approaches
7,000,000 compounds screened
1,000 screening hits
12 candidates
6 candidates
PHASES
I
Pharmacokinetics and Safety
II
Pilot Efficacy
III
Full Development Comparative Agents
Filing
Approval Process
IDEA!
Pre-clinical
Clinical
Registration (Approval)
© European Compliance Academy (ECA)
5


ECA
European Compliance Academy
Pharmaceutical Manufacturing Supply Chain
• Manufacturing chain for drug compounds quite lengthy typically 12-18 months
▪ contrasting with 4-6 weeks for e.g. beverages
▪ this impedes flexibility - building in conservatism
• Pharmaceutical manufacturing involves many unit operations & even more processing steps
▪ API production involves ca. 8-12 synthetic stages
➢ each involving synthesis, isolation & separation
o i.e. between 20-40 steps in all
➢ each step has many processing parameters
o high potential for knock-on variability
• Many drug formulation steps also: milling, blending,
Key point: address downstream ProcessAbility of APIs via better upstream crystallisation control

Pharmaceutical Manufacturing Supply Chain

- Pharmaceutical manufacturing unit processes
  - unsophisticated processing equipment
  - processing ever more complex materials
- End product testing can often lead to batch failure
  - lengthening production cycles
  - encouraging stock build up between stages
    - increasing chemical inventory costs
  - keeping excess of production facilities
    - 25% capital assets utilisation common
- Variation in raw material & API properties impacts on performance of final drug product form
  - e.g. content uniformity, bioavailability, tablet properties (thickness, weight, hardness)

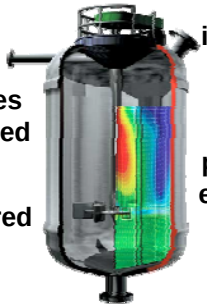
Overall, key need to intimately link supply & knowledge chains via more science-led approach

© Eu

Science-Based Manufacture: A Cultural Change

Where we are just now | **Where we need to be**

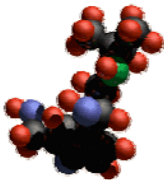
Process Down | **Molecule Up**



processes discovered → **engineered to work** → **products result from process**

improvements incremental → **poor product enhancement potential**

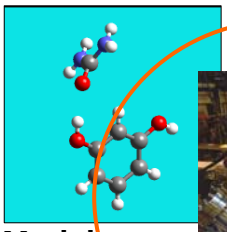
step change in capability → **dynamic control of properties**



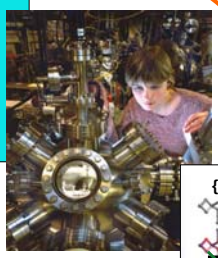
products built from molecules → **molecular design of product property**

Much of this approach is routine in areas such as drug discovery but not yet in processing

An Integrated Approach to Crystal Engineering Design & Control



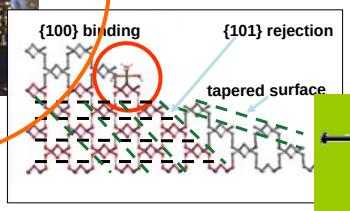
Model



Measure

Manufacturing chain: taking molecules through processes to make crystals into formulated products

Focus of this section



Manipulate

Manufacture

The 4Ms

Brian Scarlet, University of Delft

© European Compliance Academy (ECA)

Product vs Process - Need for Measurements

- **Process** engineering design relies on manipulation of thermodynamic state functions such as P, V, T, H
  - e.g. can improve process energy (H) efficiency via variation of state functions
- **Product** dependent parameters (polymorphic form, porosity, morphology, bio-availability, etc.) usually not directly driven by state functions

Paradigm shift: can't ONLY optimise the process flowsheet One MUST make measurements together with modelling to optimise processes to meet product requirements

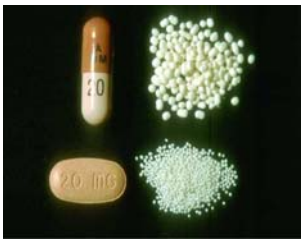
Defined Feedstock for Down-Stream Product Properties

- Solid-form materials properties of feedstocks impact on their overall processability
  - hence on properties of any formulated products made downstream
  - i.e. variability in feedstock results in variability of products
- Important solid-form properties
  - physical: particle size/shape, density, hardness/plasticity
  - chemical: purity, polymorphic form, crystallinity, hygroscopicity

- **Need for flexible PAT controlled processes**
  - **ensuring reproducible processes**
  - **producing highly consistent products**

Innovation in Manufacturing, Design Space & ICHQ8

- Major driver for ICHQ8 initiative
  - implement PAT in manufacturing
  - improve quality moving from
    - sigma 2.5 (0.5% variability) to
    - sigma 6 (few ppb variability) culture in longer term

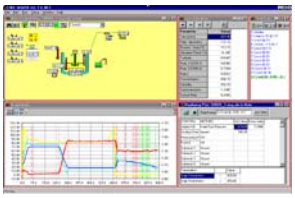


- Key need: improve science base
  - from products pragmatically engineered to work
    - process registered: - little scope for process improvement
  - to molecular design of particulate products manufactured via PAT controlled processes
    - design space registered: - flexible processes

Major challenge: developing & applying the science underpining future technical innovations

Innovation or Stagnation: FDA's 2004 White Paper

"… pharmaceutical industry generally hesitant to introduce state-of-art science & technology into its manufacturing processes, part due to regulatory impact concerns leading to



- high in process inventories
- low factory utilisation
- significant product wastage
- compliance problems

but driving up costs & decreasing productivity"

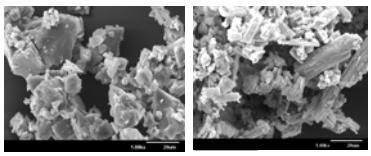
"FDA has stimulated use of PAT to improve efficiency & flexibility whilst maintaining high quality standards"

Design in Quality (QbD) rather than End Product Testing

Need for PAT for Advanced Control of Manufacturing Processes

Variable feedstocks → Fixed process → Variable product properties → Poor product quality

Existing



Variable feedstocks → PAT controlled process → Fixed product properties → Higher product quality

Future

More competitive product with lower variability & lower cost base

© European Compliance Academy (ECA)

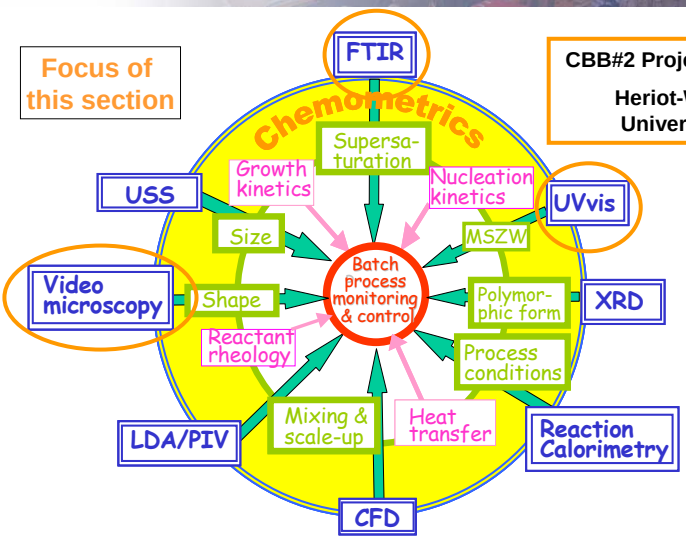
Batch Crystallisation Engineering Science

- Crystallisation (cooling, reactive, evaporative) key step in pharmaceutical manufacture
  - effects solid-liquid isolation & separation
  - enables product purification
- How does it do this?
  - molecular recognition on growth step controlled surfaces
  - via which growing crystal recognises host & rejects impurities
- Two main fundamental steps
  - Nucleation - assembly of molecular scale 3-D clusters (10-1000 molecules)
    - ➢ dominant step - many small crystals
  - Growth – simultaneous 2-D growth of nuclei on atomically

Controlling competing demands of nucleation & growth Is key issue for scale-up from laboratory to plant size

Chemicals Behaving Badly (CBB): Integrated In-Process Analytics

Focus of this section



CBB#2 Project: collaboration with

Heriot-Watt University & University of Newcastle

Sponsors

AEA Technology
AstraZeneca
Bede Scientific Instruments
BNFL
Clarient Scientific
DTI
EPSRC
GlaxoSmithKline
HEL
Malvern Instruments
Pfizer
Syngenta

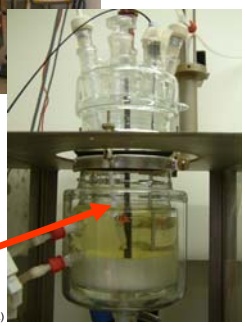
© European Compliance Academy (ECA)

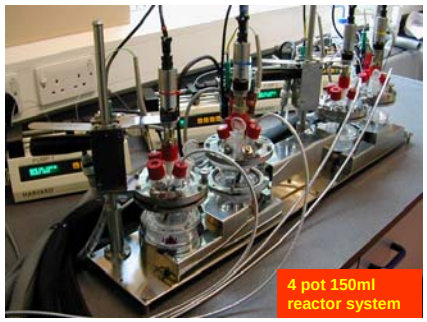
16

Automated Batch Reactors for Process (PAT) Monitoring

Batch reactor vessels (HEL Autolab & Simular) equipped with reaction calorimetry, turbidity, XRD, NIR, ATR FTIR, ultrasonic spectroscopy & digital video microscopy plus temperature & pH probes

150ml, 500ml, 2l, 20l & 200l scale sizes with solids & liquid dosing





20 litre reactor system

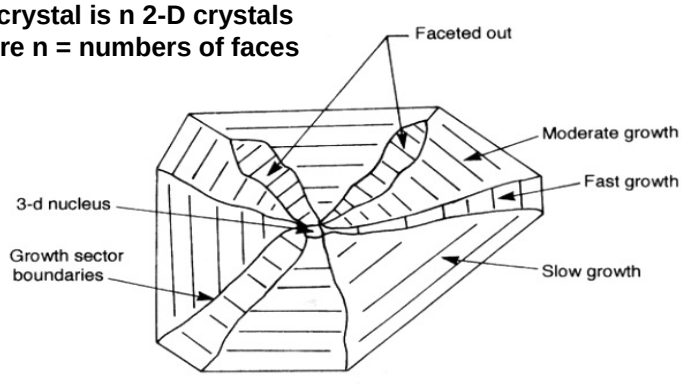
2 litre reactor system

4 pot 150ml reactor system

© European Compliance Academy (ECA)

Crystal Shape: Outcome of 3-D Nucleation & 2-D Growth Processes

3-D crystal is n 2-D crystals where n = numbers of faces



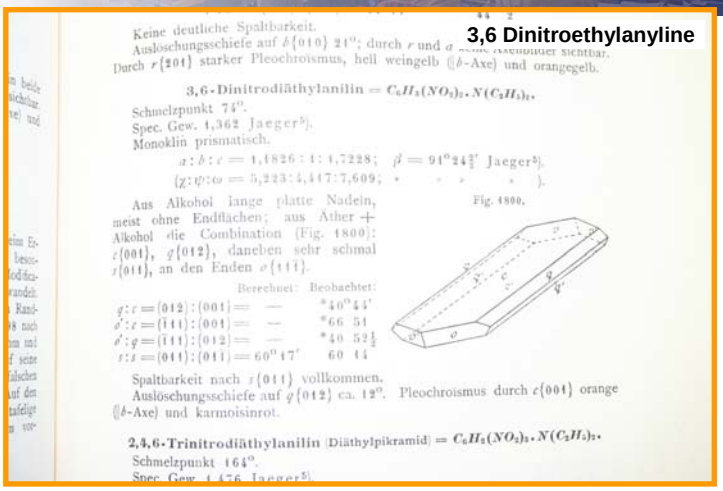
Each habit face has different surface chemistry & hence different processing properties

Crystals exhibit well-defined shape below roughening transition with surfaces defined by low-indexed planes

© European Compliance Academy (ECA)

18

Chemische Kristallographie, P Groth (1907)



3,6 Dinitroethylanyline

Keine deutliche Spaltbarkeit.
Auslöschungsschiefe auf $b\{010\}$ 21°; durch r und d [illegible] sichtbar.
Durch $r\{201\}$ starker Pleochroismus, hell weingelb ($\parallel b$-Axe) und orangegelb.

3,6-Dinitrodiäthylanilin = $C_6H_3(NO_2)_2.N(C_2H_5)_2$.
Schmelzpunkt 74°.
Spec. Gew. 1,362 Jaeger[5].
Monoklin prismatisch.
$a:b:c = 1,1826:1:1,7228$; $\beta = 91°24\frac{1}{2}'$ Jaeger[5].
$(\chi:\psi:\omega = 5,223:4,417:7,609$; " " " ").

Aus Alkohol lange platte Nadeln, meist ohne Endflächen; aus Äther + Alkohol die Combination (Fig. 1800): $c\{001\}$, $q\{012\}$, daneben sehr schmal $s\{011\}$, an den Enden $o\{111\}$.

Fig. 1800.

	Berechnet:	Beobachtet:
$q:c = (012):(001) =$	—	*40°44'
$o:c = (111):(001) =$	—	*66 51
$o:q = (111):(012) =$	—	*40 53½
$s:s = (011):(011) =$	60°17'	60 14

Spaltbarkeit nach $s\{011\}$ vollkommen.
Auslöschungsschiefe auf $q\{012\}$ ca. 12°. Pleochroismus durch $c\{001\}$ orange ($\parallel b$-Axe) und karmoisinrot.

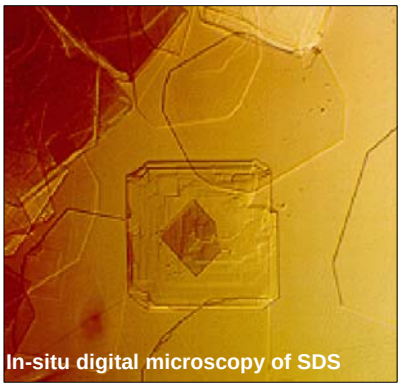
2,4,6-Trinitrodiäthylanilin (Diäthylpikramid) = $C_6H_2(NO_2)_3.N(C_2H_5)_2$.
Schmelzpunkt 164°.
Spec. Gew. 1,476 Jaeger[5].

Five Volume Reference Work Providing Details of all Morphologies for then Known Crystallographic Phases

© European

Digital Video Microscopy for Monitoring Crystal Shape

Identify pseudo-polymorphic form of Sodium Dodecyl Sulphate (SDS) via morphological simulation



In-situ digital microscopy of SDS

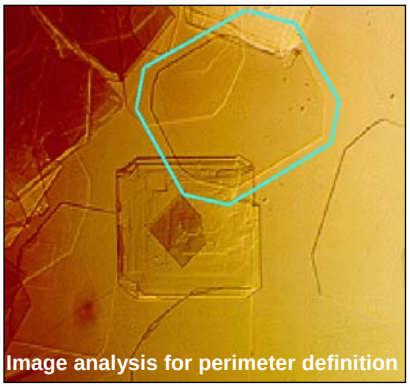
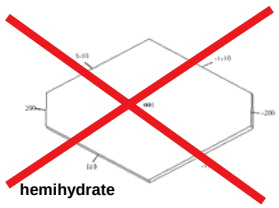
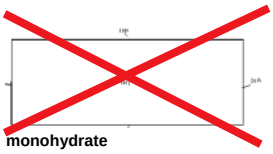


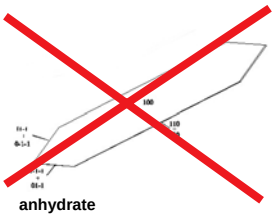
Image analysis for perimeter definition

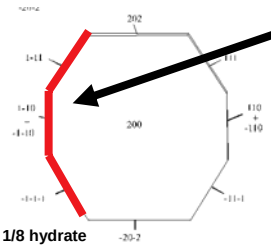
Note: prior to XRD (Bragg 1914) all crystallography was via morphological examination, e.g. Groth (1907)

Polymorph Identification from Crystal Shape via Video Microscopy









Extracted perimeter segment

… good match to observed morphology …

Shapes predicted from crystal structures via HABIT95 program

L A Smith, A Duncan, G B Thomson, K J Roberts, D Machin & G McLeod, J Crystal Growth 263 (2004) 480-490

© European Compliance Academy (ECA)

Monitoring of Crystal Shape via Digital Video Microscopy

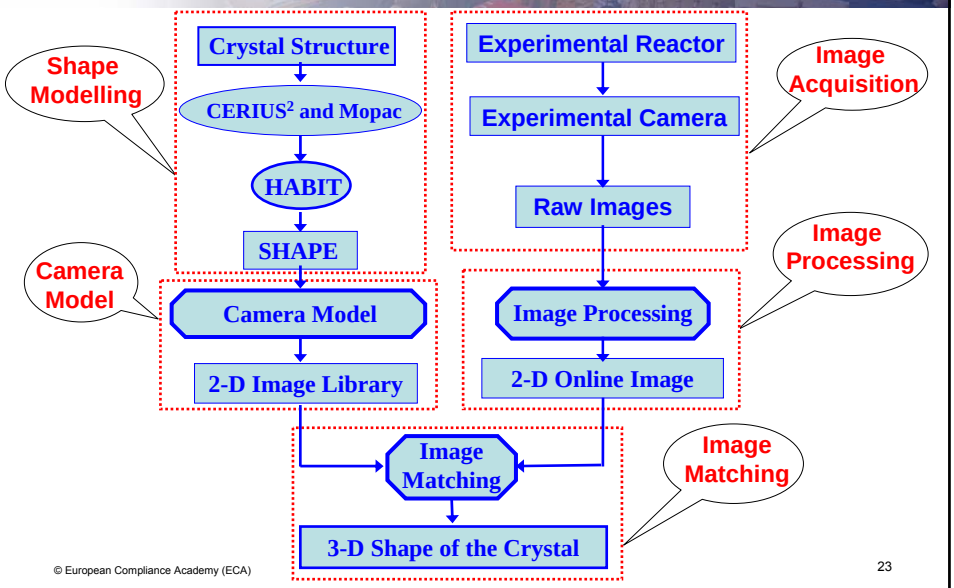
Stroboscopic digital video Microscopy for crystal shape monitoring developed by GlaxoSmithKline, Harlow, UK

Enables examination of crystal shape during batch processing at ca. 1 litre scale size

Advantage of in-process Measurements whilst being but non-invasive

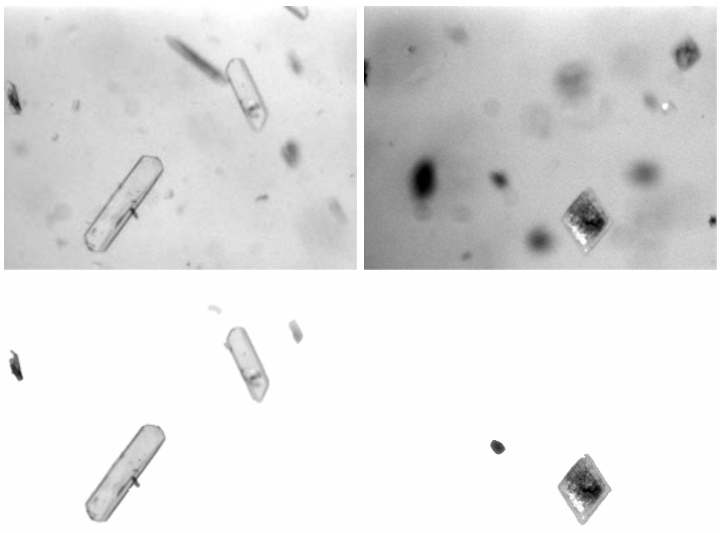
Enabling technology for Malvern Instruments PVS380 *Pharmavision* & *Morphologi* shape analysis systems

Integration: Shape Monitoring with Morphological Prediction



© European Compliance Academy (ECA)

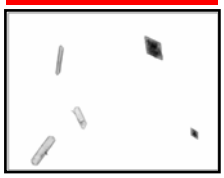
Real Time In-process Data using GSK system



© European Compliance Academy (ECA)

Integrating Simulation with On-line Digital Video Microscopy

On-line image shapes

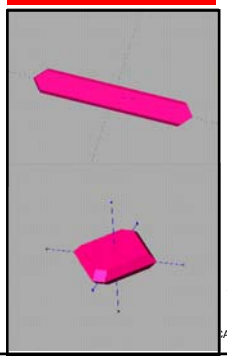


FEATURE EXTRACTION

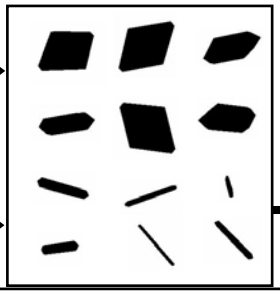
Database Retrieval

Online Images	Retrieved Image Reference	Similarity Distance	Polymorph
	BetaM042182	0.0140	β
	BetaM112182	0.0144	β
	BetaM112358	0.0148	β
	BetaM280330	0.0088	β
	BetaM104030	0.0089	β
	BetaM284330	0.0096	β
	AlphaM176054	0.0087	α
	AlphaM356126	0.0088	α
	AlphaM176234	0.0088	α
	BetaM022228	0.0046	β
	BetaM022048	0.0051	β
	BetaM320134	0.0052	β
	AlphaM356018	0.0065	α
	AlphaM354198	0.0068	α
	AlphaM004016	0.0068	α

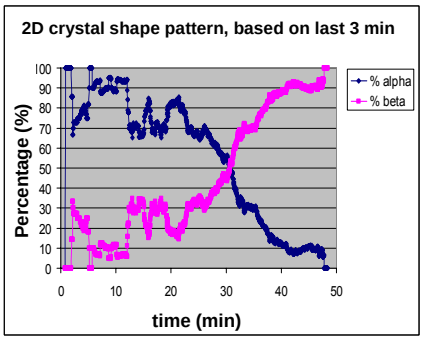
3D shapes predicted

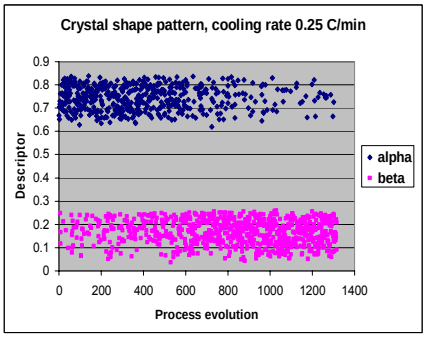


Modelled shape Image Library



Shape for Descriptors for following Polymorphic Transformations



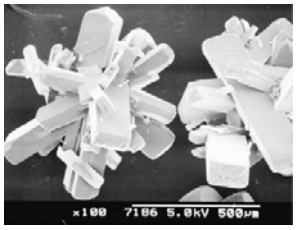


Studies of Phase Transformation between the Stable β-Form Meta-stable α-Form of L-glutamic Acid

© European Compliance Academy (ECA)

Impurity Incorporation Strongly Affect Crystal Properties

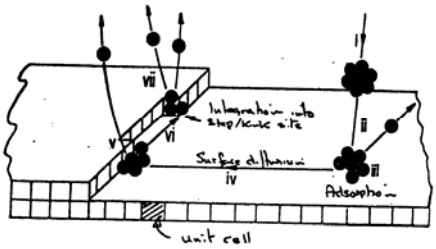
- Note: low levels of impurities have big effect on crystals growth, i.e.
  - ppm of sodium ferrocyanate changes salt crystal morphology to dentritic
- Hence, consider typical 100 $(\mu m)^3$ crystal of Aspirin having a ca. 0.1% impurity content
- Such a particle would have ca. 10nMol (10^{16} molecules) of material & hence 10^{13} molecules of impurity
- Moving towards a sigma 6 culture demands a drastic reduction in impurity content in crystals to reduce product variability
- Demanding much better selectivity in synthesis to reduce formation of hetero-impurity side-products



Need for better linkage between synthetic chemistry & downstream isolation & separation processes

© European Compliance Academy (ECA)

Mass Transfer Stages in Crystal Growth from Solution

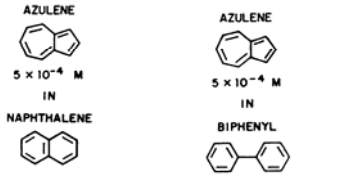


- bulk transport (i): here under the driving force of supersaturation solvated monomers in the bulk mother phase solution are transported towards the growth interface;
- boundary layer diffusion (ii): close to the crystal/solution interface the solution is depleted of solute and a concentration boundary layer, through which the solvated monomers must diffuse, is set up;
- surface nucleation/adsorption of monomers on the surface (iii);
- interfacial diffusional processes (iv-vii): here the adsorbed monomers find their optimum incorporation sites (flat surface, step or kink site) and undergo varying degrees of desolvation.

The Crystal Growth Interface Can be Highly Selective on Molecular Scale

Purification via crystallisation reflects molecular selectivity at the crystal growth interface

Molecular size and shape can be important factors as to whether a given material can be easily purified.



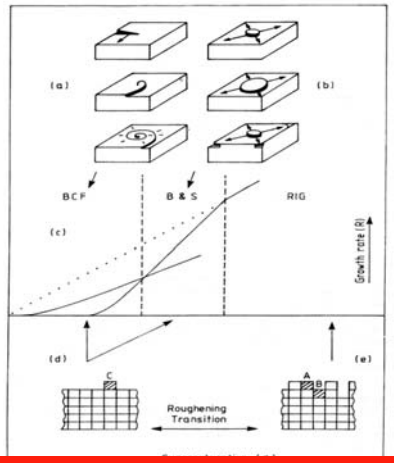
poor segregation

complete segregation.

Note: impurities can play an enormously powerful role in mediating & controlling both nucleation & growth stages in overall crystallisation process

© European Compliance Academy (ECA)

Crystal Surface Growth: Different Mechanisms

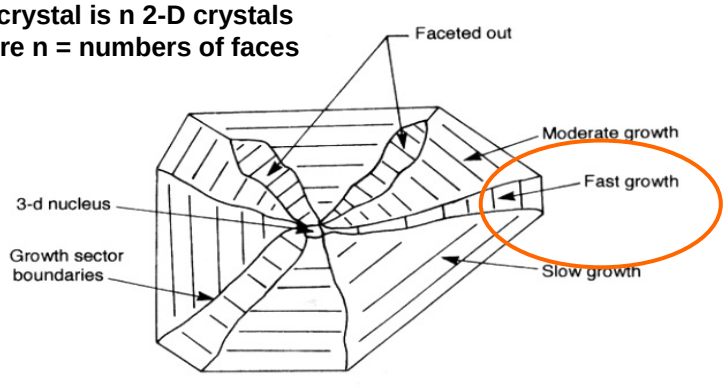


- Crystal growth interface relies on molecular recognition to effect high species selectivity
- 3 main mechanisms
  - screw dislocation (BCF)
  - birth & spread (B&S)
  - rough interface (RIG)
- At high supersaturation &/or temperatures growth interface roughens

For pure crystals growth interface needs to be singular as rough interfaces cannot easily reject impurities

Crystal Shape: Outcome of 3-D Nucleation & 2-D Growth Processes

3-D crystal is n 2-D crystals where n = numbers of faces

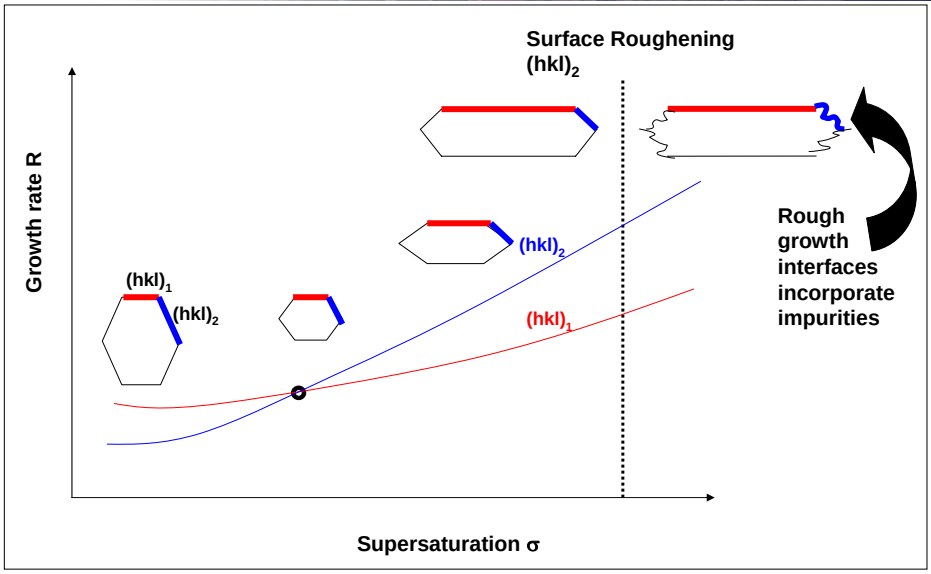


Each habit face has different surface chemistry & hence different processing properties

Crystals exhibit well-defined shape below roughening transition with surfaces defined by low-indexed planes

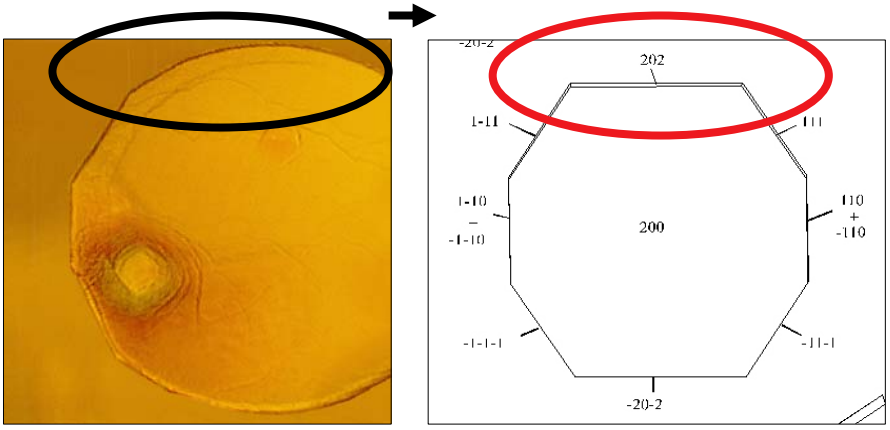
© European Compliance Academy (ECA)

High Purity Pharmaceutical APIs: Need to Eliminate Roughening



SDS Crystal Shape via Video Microscopy

Kinetic roughening at high supersaturation



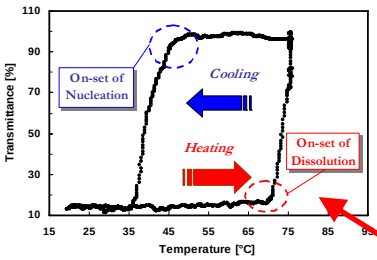
Morphological analysis identifies kinetically-roughened crystal surface as (202) form

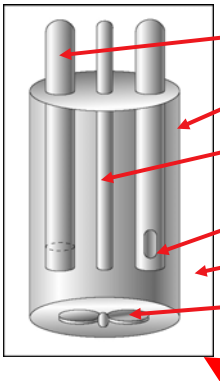
Meta-Stable Zone Width via Optical Turbidimetry

MSZW represents nucleation barrier to crystallisation process being temperature zone between:

- **Dissolution (thermodynamic)**
- **Crystallisation (kinetic)**

MSZW: - scale, system, reactor & operating condition dependant





Fibre-optic turbidometric probe

Glass cell (10 - 25ml)

Platinum resistance thermometer

pH/conductivity sensor

Thermostatic bath

Magnetic stirrer

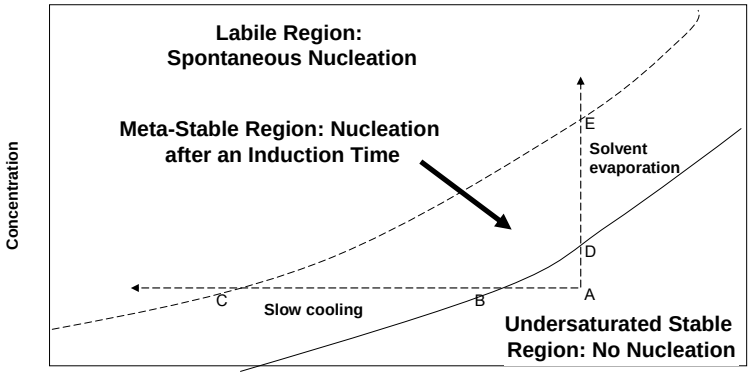
Measure MSZW using micro-reactor with in-process turbidometric probe

Use to detect on-set of crystallisation & dissolution processes

© European Compliance Academy (ECA)

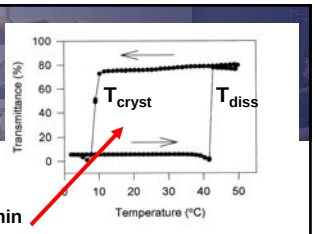
Meta-Stable Zone Width (MSZW)

Meta-stable zone – boundary between kinetic crystallisation Points (CE) & thermodynamic dissolution points (BD) wrt initially undersaturated solution state (A)



© Eu

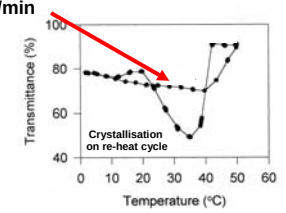
MSZW for Typical Pharmaceutical



MSZWs vary with process conditions e.g. cooling rates – kinetic process

0.50°C/min

0.75°C/min



Important that crystallising solutions are not cooled too fast

Need to match nucleation rate to excess solubility generation via (say) solution cooling

Too fast cooling creates excess supersaturation as solutions can't nucleate fast enough

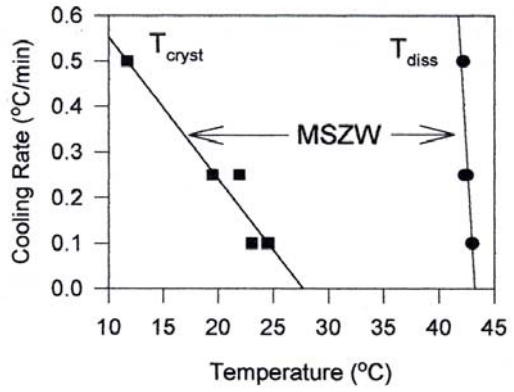
Effect changes with scale size, equipment & operational conditions

Cooling Rate /°C min^{-1}	MSZW /°C
0.50	30.5
0.25	22.1
0.10	19.0

pH	MSZW /°C
2	15.6
4	17.2
6	21.9

© European Compliance Academy (ECA)

MSZW for Typical Pharmaceutical Compound



Use turbidity to measure T_{cryst} & T_{diss} as function of heating & cooling rates (b)

Plotted slope indicates ease of nucleation & enables assessment of balance between

- **rate of solubility decrease with cooling**
- **rate of nucleation**

Fit plot of MSZW to b via Nyvlt equation

$$\log(b) = m \log(MSZW) + A$$

where m is reaction order &

$$A = (m-1) \log \frac{dC}{dt} + \log k$$

where c - concentration, k - rate constant & t - temperature

Calculate nucleation order (m): low order - T sensitive & high order – T insensitive

© European Compliance Academy (ECA)

MSZWs of Sodium Laurate (NaL-C12) & Myristate (NaM – C14)

Concentration (wt%)	MSZW (C) NaL	NaM
5	6.81	4.56
10	7.25	4.12
15	5.10	3.01
20	4.33	2.75

increase ↓ (NaL) ↑ decrease (NaM)

NaL/NaM ratio	MSZW (C)
1:0	4.33
3:1	5.73
1:1	3.99
1:3	7.45
0:1	2.75

MSZW smaller for longer chain length and for higher concentration

Solid solution behaviour for 1:1 mixtures but not 1:1

© European Compliance Academy (ECA)

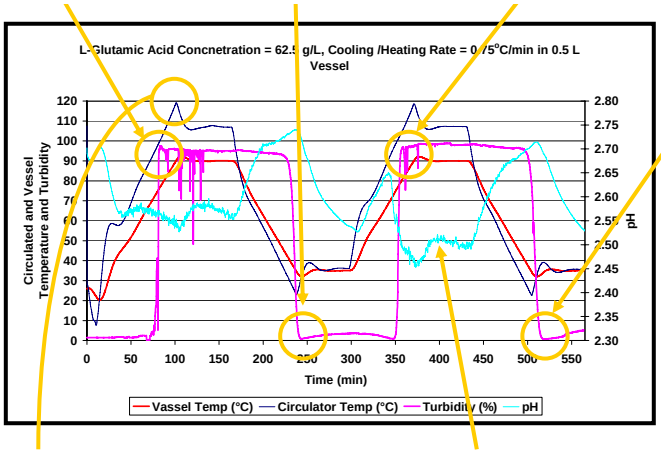
Slow Cool Data to Measure Meta-Stable Zone Width (MSZW)

Dissolve up raw materials

Crystallisation point

Dissolution point

Re-crystallise & harvest crystals for optical microscopy



Reactor jacket temperature overshoot

Variation in solution pH due to T, c change

Cross-check crystal morphology against that predicted

© European Compliance Academy (ECA)

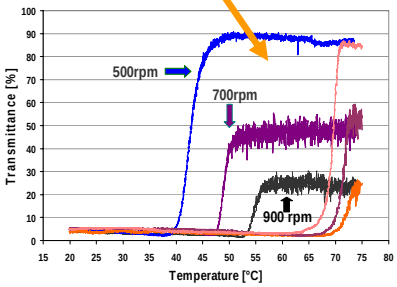
Nucleation Scale-Up

Nucleation promoted via sites within crystallisation reactor such as:

- **Walls of vessel & at liquid free surface**
- **Stirrer & reactor internals such as baffle surfaces & impellers**

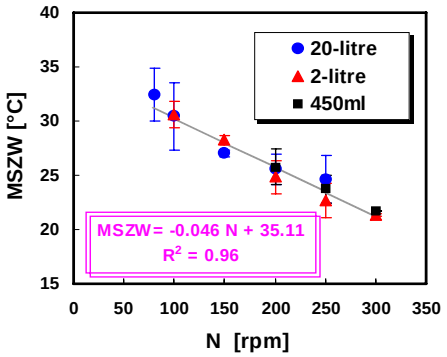
- **Heteronuclei, e.g. impurities, particulates, seeds etc.**
- **Particle/particle & reactor/particle collision attrition fragments**
- **Process inhomogeneities due**

LGA: stirrer speed effects MSWZ with nucleation being *enhanced* by greater mixing

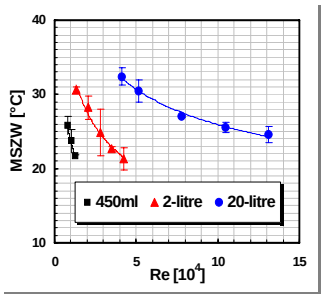


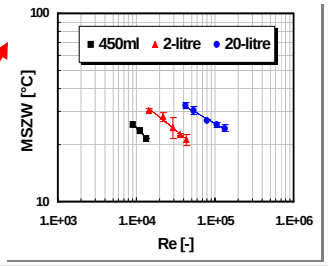
Fundamental understanding of nucleation processes vs reactor scale essential if NPI timescale to be met

Effects of Reactor Stirring & Scale Size on Nucleation



MSZW correlates to stirrer speed across several reactors scale sizes

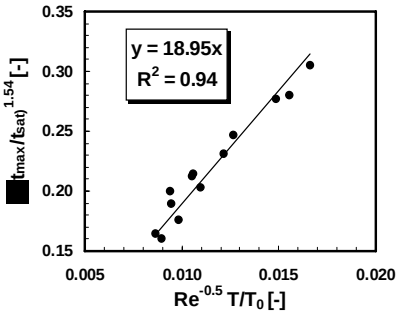




MSZW ∝ Re^a

© European Compliance Academy (ECA)

Glutamic Acid: Scale-up Correlations



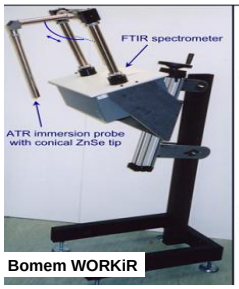
- **Physical properties of substance: *e.g. molecular weight (m)***
- **Physical properties of mother liquor: *e.g. viscosity (Re)***
- **Reactor internals: *e.g. stirrer materials & surface roughness (m)***

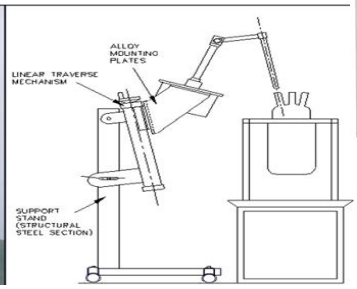
$$J \propto \left(\frac{\Delta t_{max}}{t_{sat}}\right)^{1.54} = 18.95\,\mathrm{Re}^{-0.5}\left[\frac{T}{T_0}\right]$$

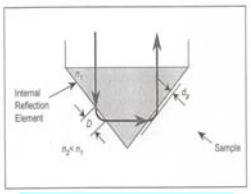
© European Compliance Academy (ECA)

Using ATR-FTIR & Turbidity to Examine Crystallisation On-set

- **Control of API nucleation vital to avoid variability downstream in product formulation with concomitant QA problems**
- **Supersaturation measurements cross-correlated with measuring crystallisation on-set during processing**







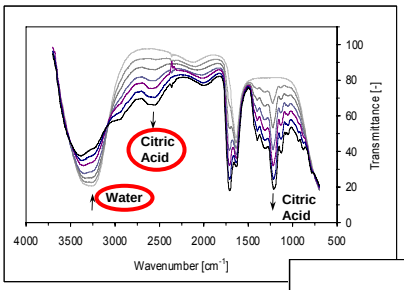
$$d_p = \frac{\left(\frac{\lambda}{n_2}\right)}{2\pi\left[\sin\theta - \left(\frac{n_2}{n_1}\right)^2\right]^{1/2}}$$

Portable ATR FTIR with Direct Data Logging to HEL AUTOLAB

© European Compliance Academy (ECA)

ATR-FTIR Spectra Calibration vis Peak Ratio Method

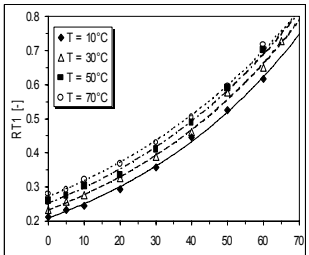
in-situ ATR FTIR spectra at 10 °C



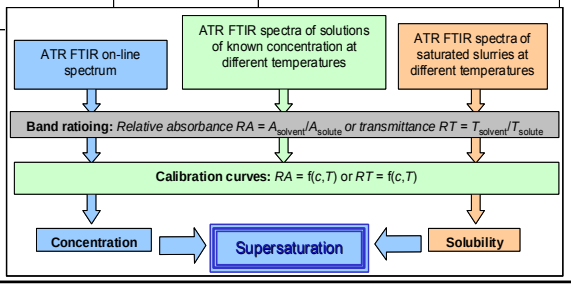
Solubility curve

RT1: ratio of trans mittance for 3279 cm^{-1} & 2611 cm^{-1} IR bands

RT1 Calibration of at 10, 30, 50, 70° C

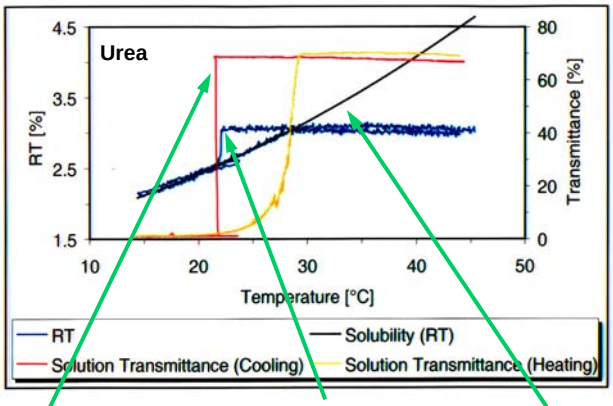


In-situ Supersaturation Measurement & Calibration: Overall Strategy



© European Compliance Academy (ECA)

ATR-FTIR Combined with Turbidimetric Measurements



Crystallisation on-set via turbidity

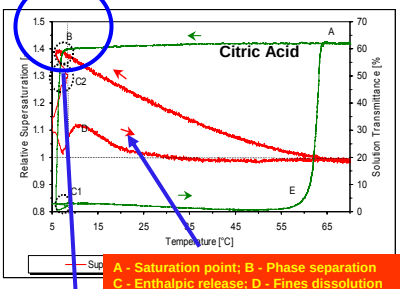
De-supersaturation following nucleation

Equilibrium solubility

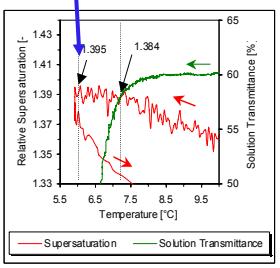
Temperature programmed studies reveal, as expected, ATR FTIR detects crystallisation on-set ahead of turbidity probe (size limit ca. 1µm)

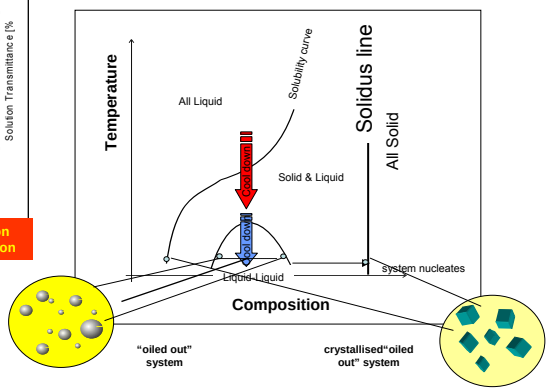
ATR-FTIR & Turbidimetric Studies of Citric Acid

Temperature programmed studies reveal phase separation prior to nucleation (wide MSZW)



A - Saturation point; B - Phase separation
C - Enthalpic release; D - Fines dissolution

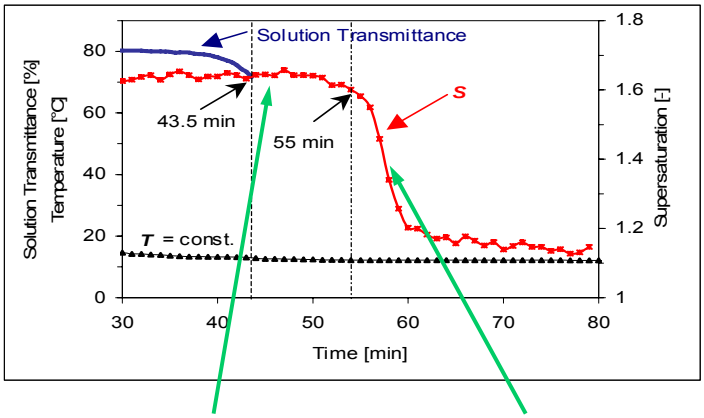




Note: Poorly nucleating materials with wide MSZWs tend to oil-out particularly when process scaled up

Significant problem in crude crystallisation post synthesis when hetero-impurity content is high

Phase Separation in Citric Acid Prior to Nucleation



Constant supersaturation prior to nucleation

Rapid de-supersatruration after on-set of nucleation

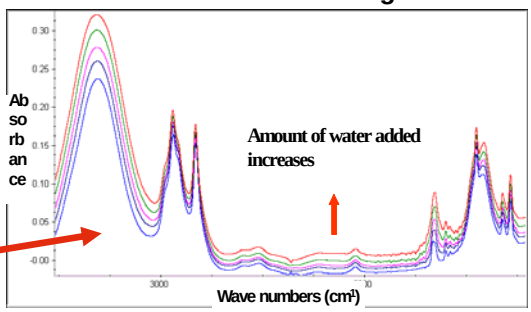
© European Compliance Academy (ECA)

Benzophenone via Aqueous Drown-out

- Use of ATR FTIR to monitor on-line concentration & supersaturation in drowning-out process
- Building calibration model for Benzophenone concentration in Water/Methanol solutionOn-line monitoring of drowning-out of Benzophenone in Water/Methanol
- Studying effect of antisolvent addition rate on drowning-out process

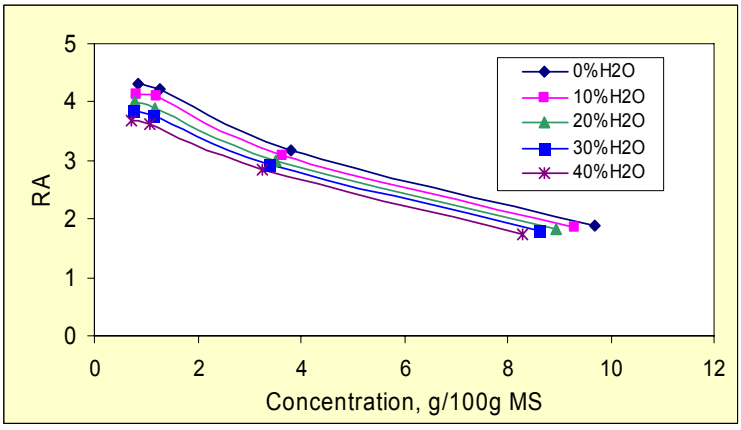
ATR FTIR spectra of benzophenone in water-methanol solutions at 20C & different amount of water added

IR peaks: methanol at 2942 cm-1 & benzophenone at 1281 cm-1



© European Compliance Academy (ECA)

ATR-FTIR Calibration for Aqueous Drown-out Studies

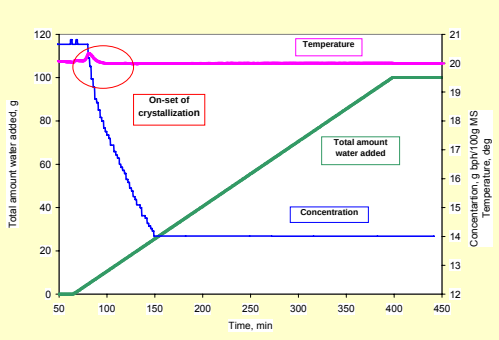


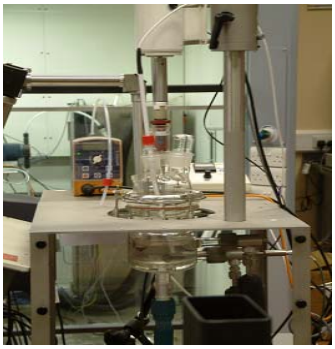
RA calibration curves for benzophenone in water-methanol solution at 20ºC as f (Conc)

© European Compliance Academy (ECA)

48

Aqueous Drown-out of Benzophenone from Methanol

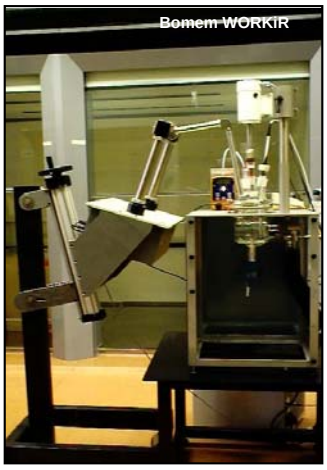




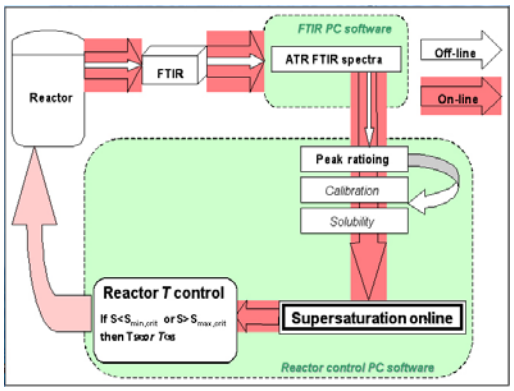
Benzophenone solute concentration decreases from 20.65 to 14.02 g/100g via aqueous drown-out from methanolic solutions

© European Compliance Academy (ECA)

Crystalliser Supersaturation in Closed-loop Control via ATR-FTIR

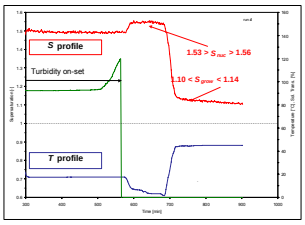
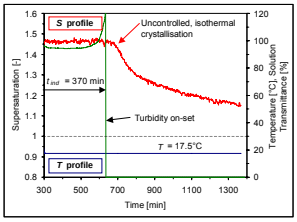
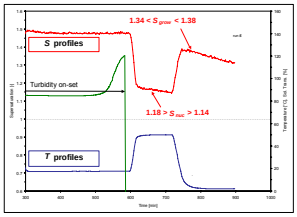
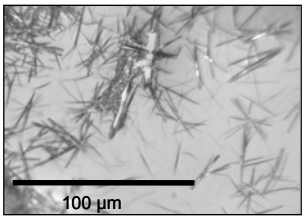
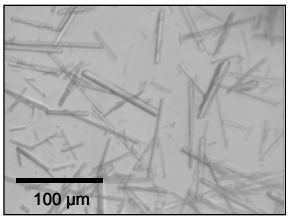
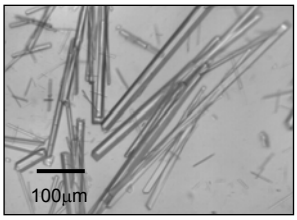


Batch reactor with ATR FTIR probe



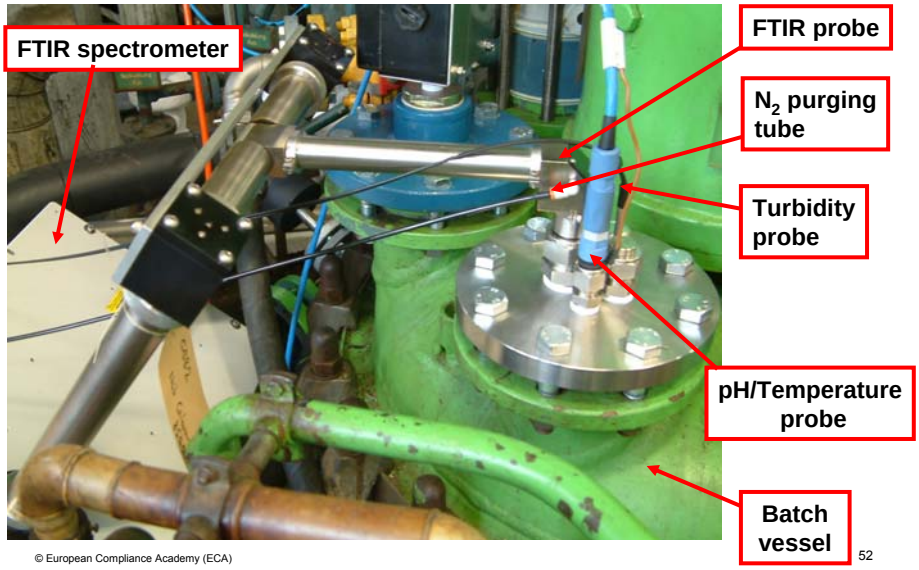
Control system including FTIR peak ratio based calibration matrix

Close-loop Supersaturation Control: MSG Crystals Made to Measure

High S_{nuc} and low S_{grow}	*No S control*	*Low S_{nuc} and high S_{grow}*
		
		
… lots of small crystals…	… mixed size crystals…	… few bigger crystals…

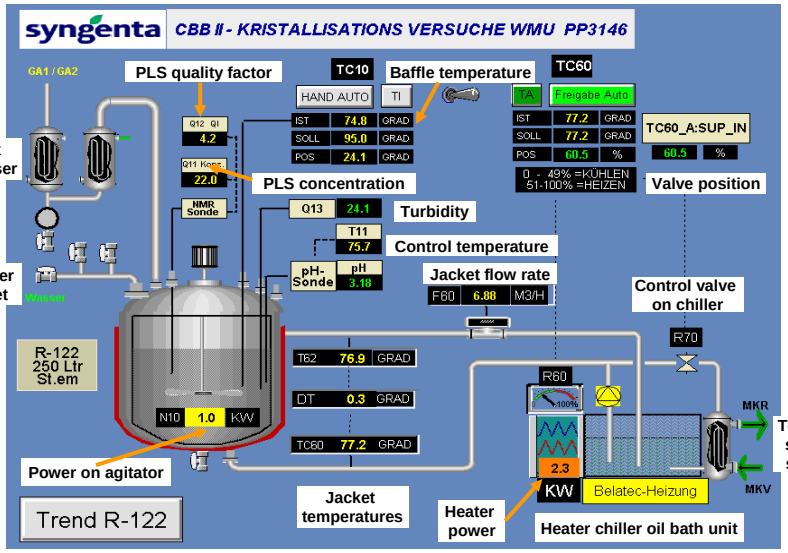
© European Compliance Academy (ECA)

Supersaturation Control on 250 Litre Reactor



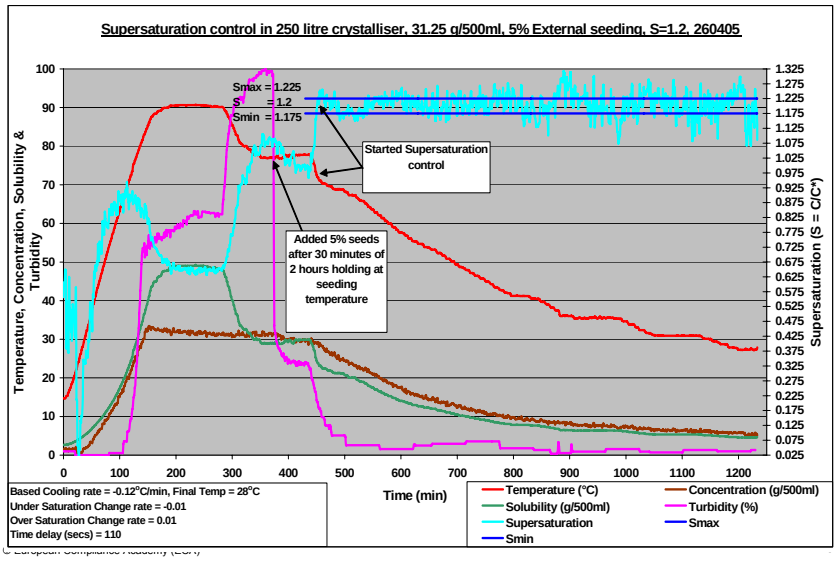
© European Compliance Academy (ECA)

Foxboro System Control System on Syngenta 250 Litre Reactor



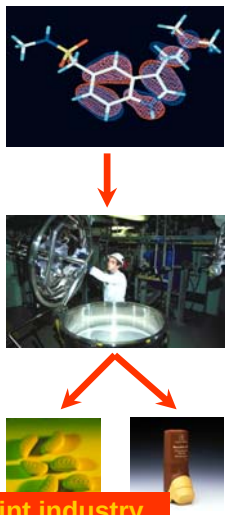
© European Compliance Academy (ECA)

ATR FTIR Supersaturation Control Data: Syngenta 250 Litre Reactor



Need for Better Industry/University Linkages

- Academic research is curiosity-based
  - ➢ not very focussed on needs of industrial product manufacture
- Industrial research is very delivery-based
  - ➢ not too focussed upon fundamental science unless it impacts on product performance
- Both academic & industrial approaches are highly complementary
  - ➢ strong synergy & each has a lot to learn from the other
- Strong EU academic research base poorly connected to needs of speciality materials industry
  - ➢ key current industrial objective to cross-



Major challenge for sector: how to build-up joint industry academic teams to deliver against strategic needs

© Eur

Acknowledgements

I would like to gratefully acknowledge

Royal Academy of Engineering & AstraZeneca for supporting my industrial secondment from which I gained a greater insight into current needs of the speciality chemical sector

- **particularly hosts Simon Ruddick & Mark Hindley**

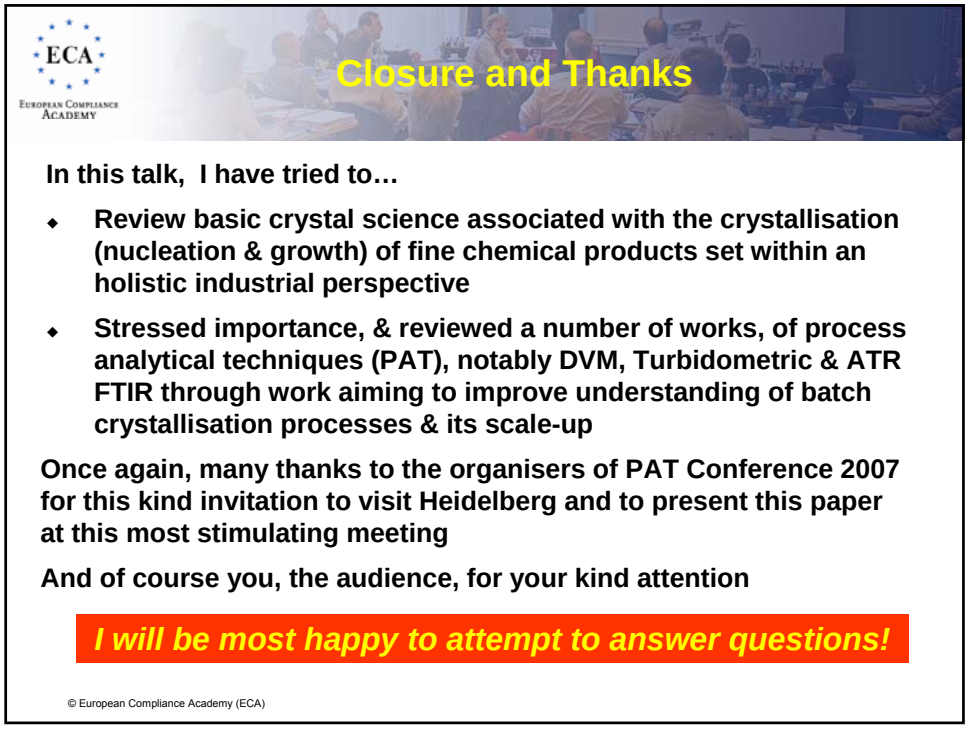
PAT studies of crystallisation processes involved collaboration* with Heriot-Watt & Newcastle Universities with funding from DTI, EPSRC, AEA, AstraZeneca, BASF, Bede, BNFL, Clairet, GSK, HEL, ICI, Malvern Instruments, Pfizer & Syngenta

Numerous researchers in the Institute of Particle Science & Engineering at University of Leeds

- **Xue Wang & Jorge Calderon de Anda – Video-microscopy**
- **Tariq Mahmud, Antonia Borrisova, Shahid Kahn & Heidi Grön – ATR FTIR**
- **Lesley McCalman & Richard van Gelder – Turbidometic studies**

*** Chemicals Behaving Badly Project**

© European Compliance Academy (ECA)


ECA
European Compliance Academy
Closure and Thanks
In this talk, I have tried to…
Review basic crystal science associated with the crystallisation (nucleation & growth) of fine chemical products set within an holistic industrial perspective
Stressed importance, & reviewed a number of works, of process analytical techniques (PAT), notably DVM, Turbidometric & ATR FTIR through work aiming to improve understanding of batch crystallisation processes & its scale-up
Once again, many thanks to the organisers of PAT Conference 2007 for this kind invitation to visit Heidelberg and to present this paper at this most stimulating meeting
And of course you, the audience, for your kind attention
I will be most happy to attempt to answer questions!
© European Compliance Academy (ECA)