Towards Quality by Design: Modelling Nano-Particles & their Formulation in Relation to Product Physical Properties

UNIVERSITY OF LEEDS

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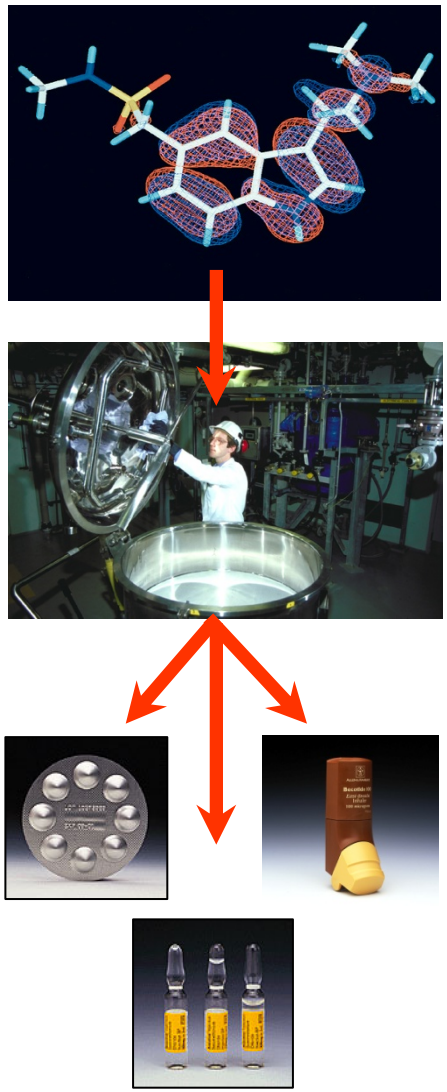
Scope of Presentation

- **Industry, regulatory & market pressures**
  - **Science-led QbD opportunities**
- **Particle formation & purification processes**
  - **Brief crystallisation science overview**
- **Crystallisation modelling**
  - **Crystal shape modelling, interface roughening & product purity control**
  - **Cluster modelling, polymorphic stability & crystallisability prediction**
  - **Crystal/crystal interaction modelling & formulation design**
- **Acknowledgement & Closure**



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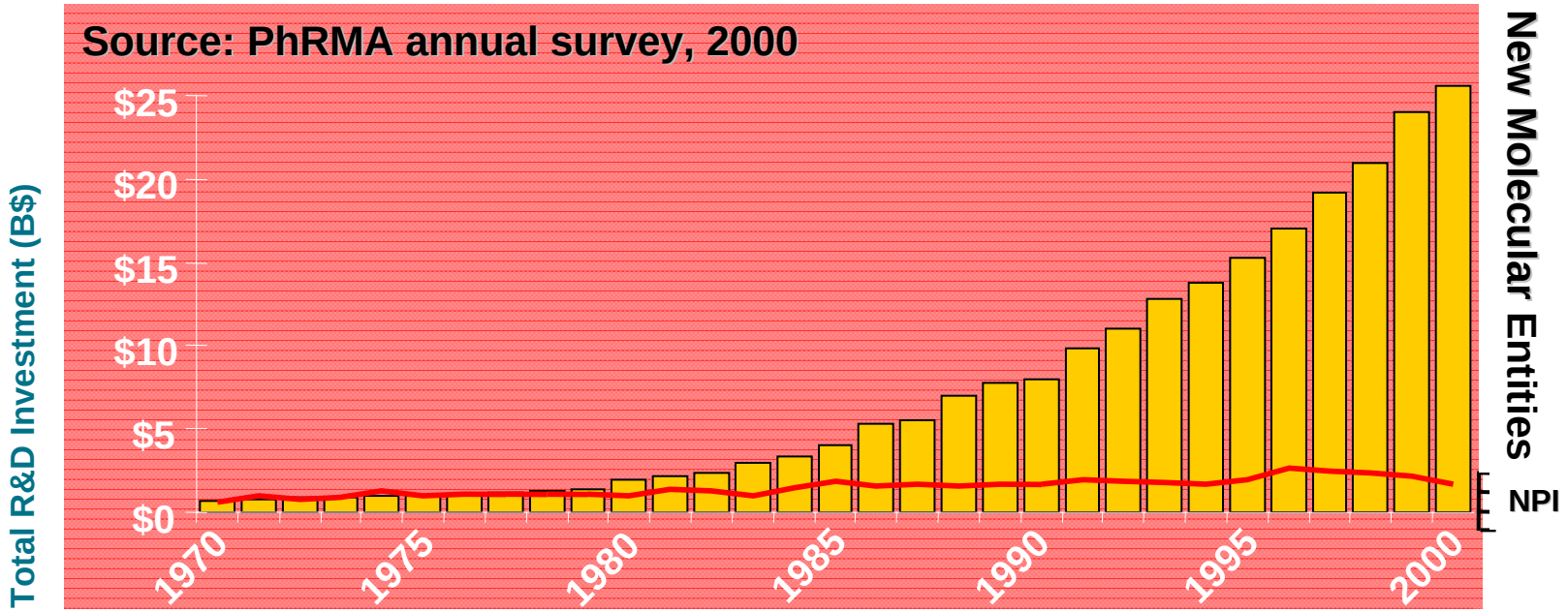
Productivity Paradox: Higher R&D Cost/Approved Product

Pharmaceutical industry getting more competitive but not any faster

Molecular complexity & solid form (solubility) challenges increasing



Emerging importance of material properties on production efficiency

Increasing expectations from patient on product performance

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Science-Based Manufacture: A Cultural Change to QbD

Where we are just now

Process Down

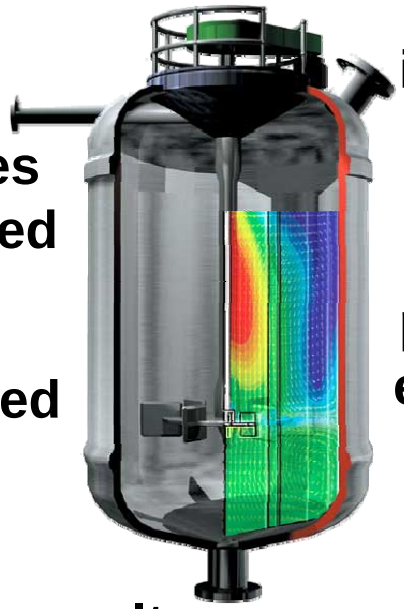
processes discovered

↓

engineered to work

↓

products result f



improvements incremental

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poor product enhancement potential

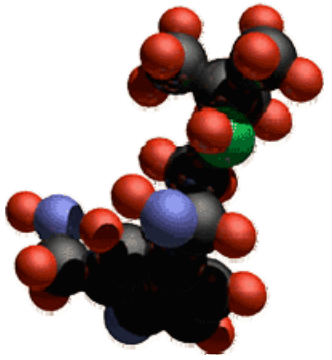
step change in capability

↓

dynamic control of properties

Where we need to be

Molecule Up



products built from molecules

↓

Much of this approach is routine in microelectronics, drug discovery etc. but not yet in process/product design

Quality Attributes: Reducing Variability - Feedstock to Product

- **Important to control solid-form properties to achieve high product quality, e.g.**
  - **physical properties: particle size/shape, density, hardness/plasticity**
  - **chemical properties: purity, polymorphic form, crystallinity, hygroscopicity**
- **Solid-form feedstock properties impact on their overall processability**
  - **hence on concomittant properties of formulated products made downstream**
    - ❑ **i.e. feedstock variability results in variability of products**

Drivers: API physico-chemical properties designed-in to ensure product quality & optimal formulation behaviour

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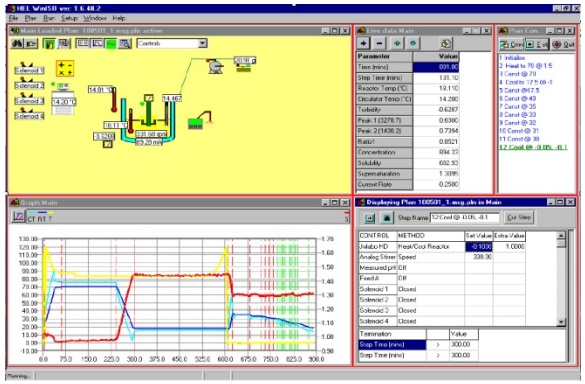
Innovation or Stagnation: FDA's 2004 White Paper

"… 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

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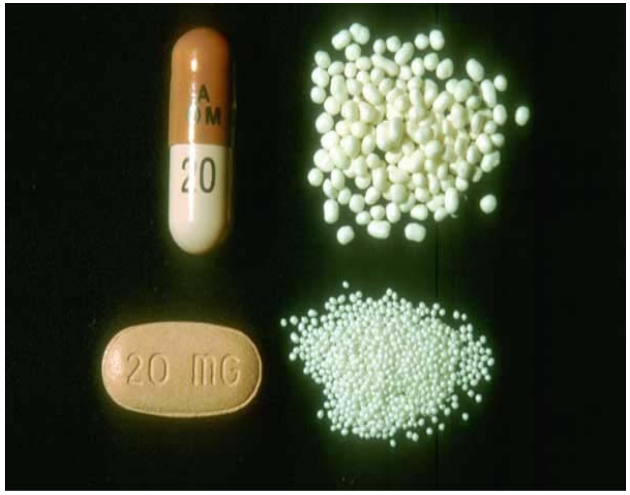
QbD Innovation, Design Space & ICHQ8

- **QbD is major regulatory driver, notably through ICHQ8 initiative stressing need for**
  - **more detailed process understanding from R&D to manufacturing**
  - **improved product quality moving culture**
    - ❑ **sigma 2.5 (0.1% variability) to**
    - ❑ **sigma 6 (few ppb variability)**



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

Challenge: developing & applying technical innovation & underpining science needed to deliver QbD

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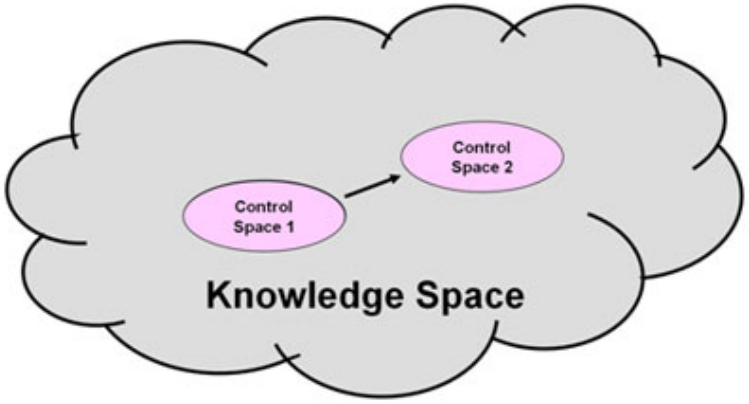
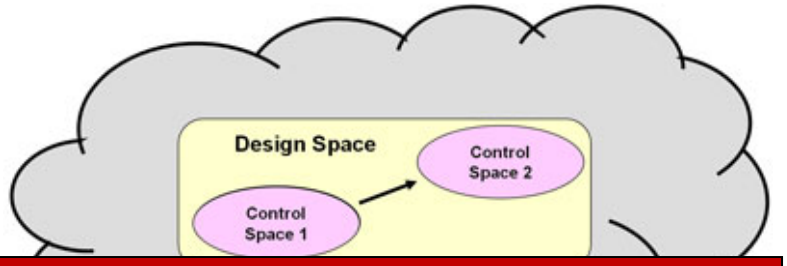
Quality by Design (QbD) & Design Space



Process R&D results in definition & approval of a "Control Space" for manufacturing process within a much wider "Knowledge Space" of possibilities concerning the process

As product matures many factors can require changes in process control scheme, moving it from Control Space 1 to a new Control Space 2 but expensive regulatory approval needed

ICHQ8 enables development of approvable Design Space in advance of commercial launch that anticipates & accommodates more



Opportunity: secure knowledge-intensive manufacturing science to ensure future industrial competitiveness

Neway, Aegis Analytical Corporation 2008

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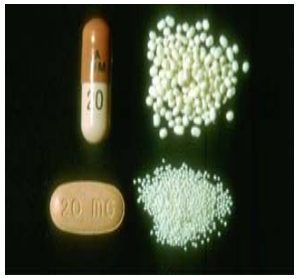
Engineering Science for Advanced Pharmaceutical Manufacturing

- **Holistic approach needed to optimise & control crystallisation processes**
  - **Molecule-centred understanding**
  - **New unit processes & strategies**
  - **Process analytics - R&D to manufacturing**
  - **Over-arching high level framework**

- **Enablers for improving crystal technology science base**
  - **Multi-scale computational modelling**
  - **Precision controlled particle formation processes**
  - **PAT, advanced chemometrics & control**
  - **Systems engineering & informatics**



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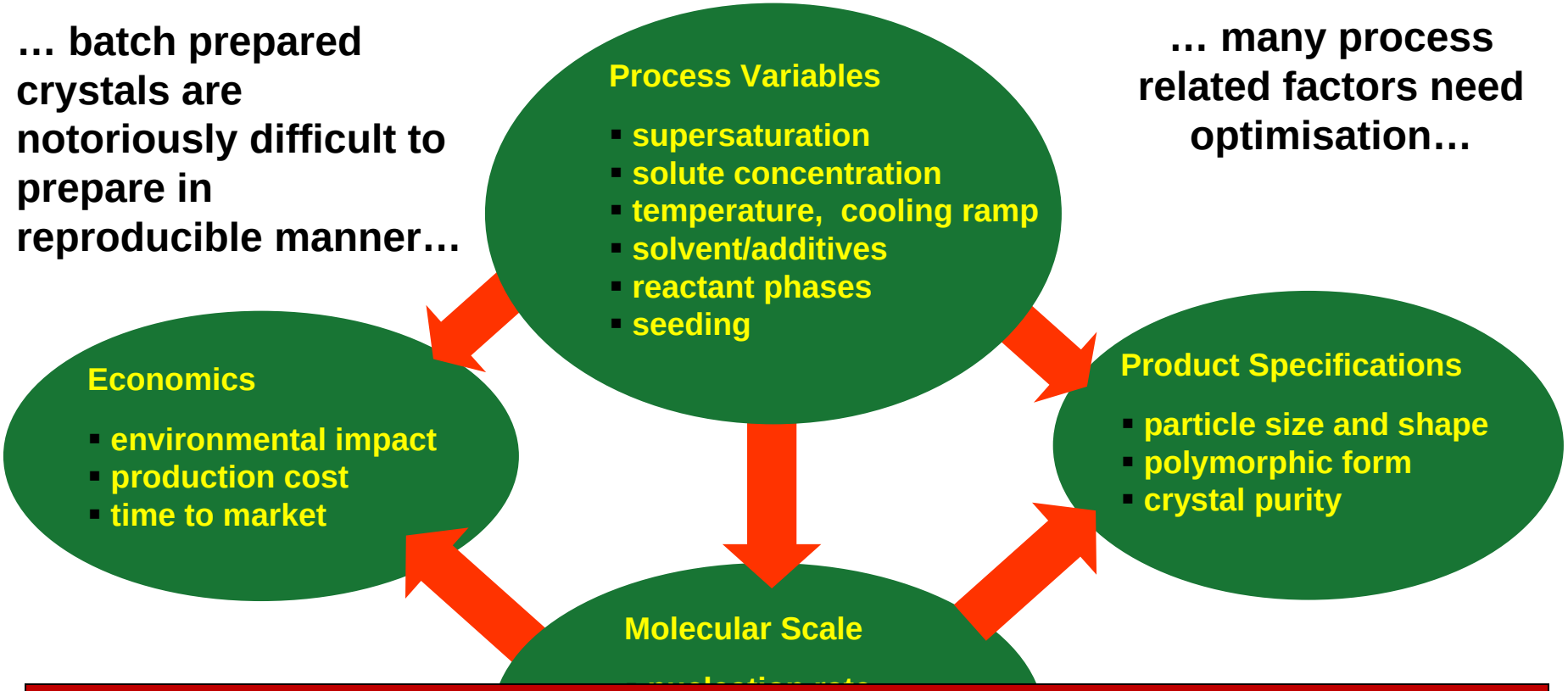
Batch Crystallisation Process Science

… batch prepared crystals are notoriously difficult to prepare in reproducible manner…

… many process related factors need optimisation…



Integrated approach critical - encompassing multi-scale/phase analysis

4M – Model, Measure, Manipulate, Manufacture

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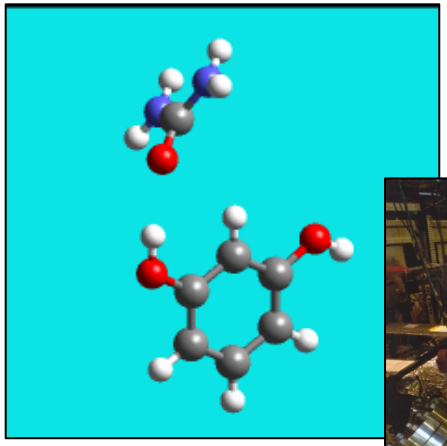
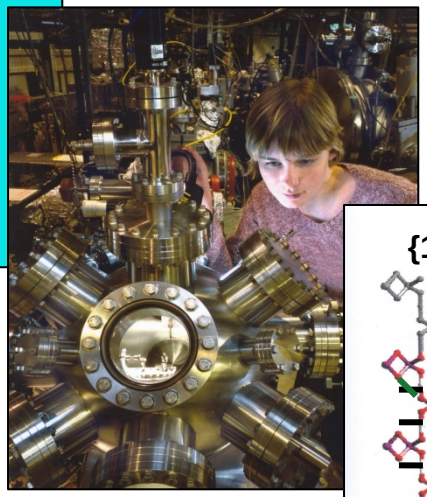
Manufacturing Molecules
An Integrated Approach

The 4Ms

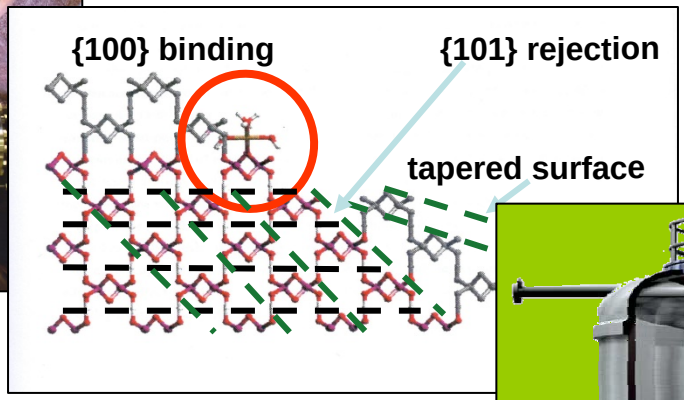
Brian Scarlett, TU Delft



Model



Measure



Manipulate

Manufacture

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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 crystal surfaces
    - ❑ through which growing crystal recognises host & rejects impurities
- Two main fundamental steps
  - Nucleation - molecular assembly 3-D clusters (10-1000 molecules)
    - ❑ dominant step - many small crystals
  - Growth - 2-D growth on atomically smooth crystal surfaces (hkl)
    - ❑ dominant step – fewer larger crystals

Controlling competing demands of nucleation & growth Is key issue for process design & scale-up

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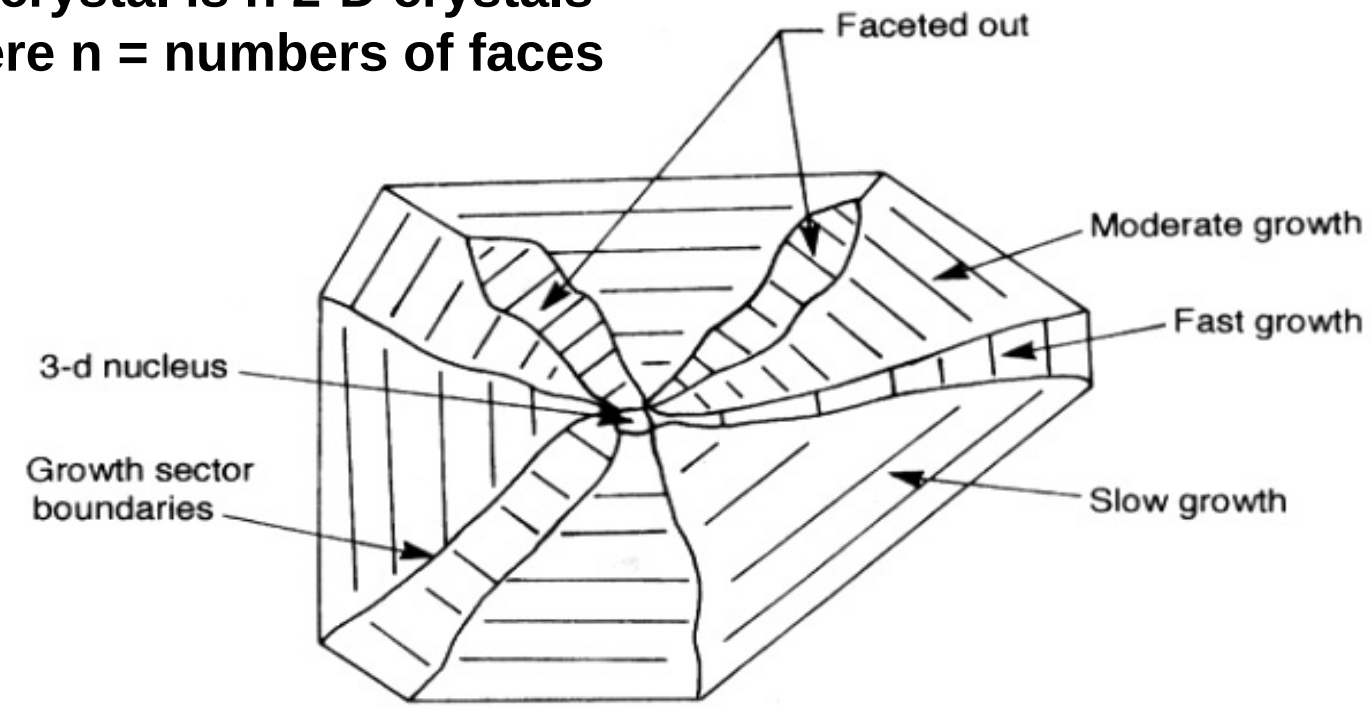
Shape: 3-D Nucleation & 2-D Growth Outcome

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

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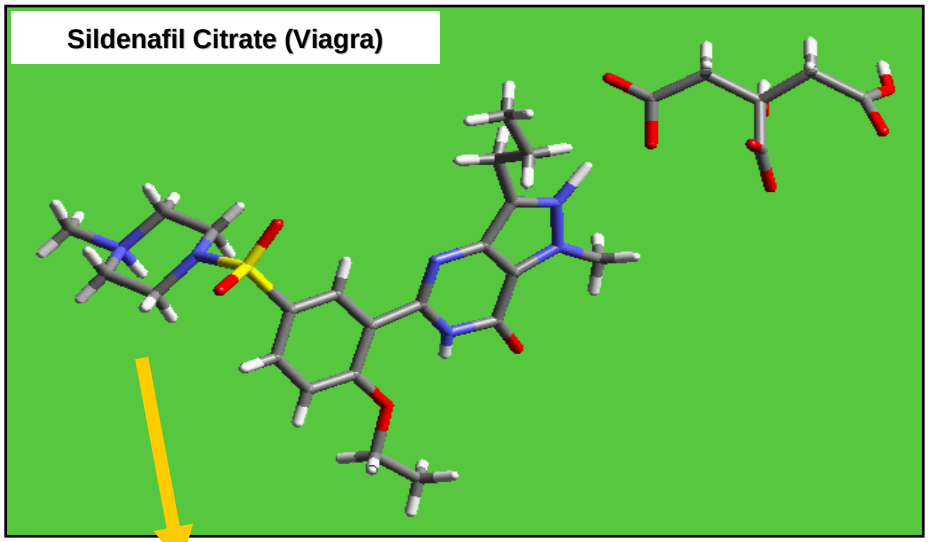
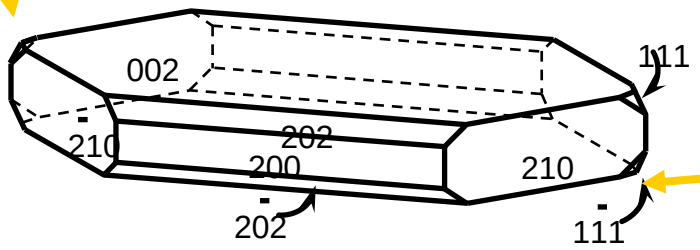
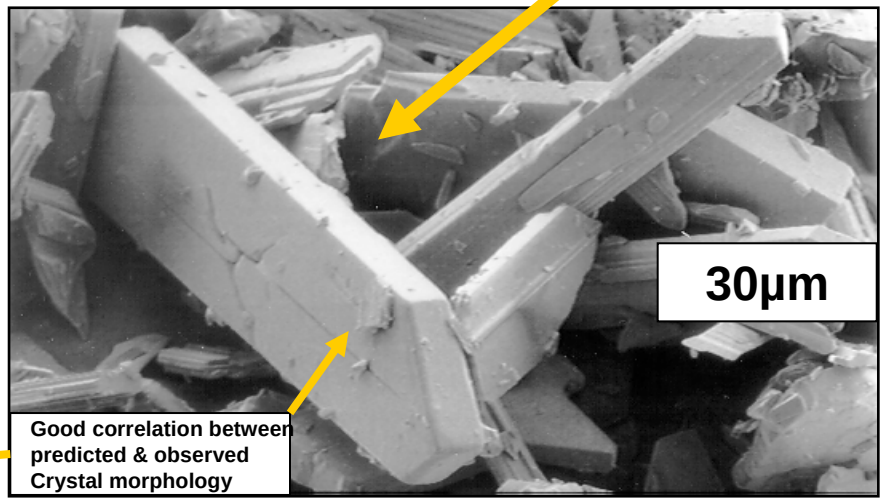
Predicting & Understanding API Crystal Morphology





Typical API morphology, i.e. plate like with a wide range of particle sizes & shapes



Focus: Little known about surface & interfacial chemistry of pharmaceutical APIs despite their importance in formulation design & product performance

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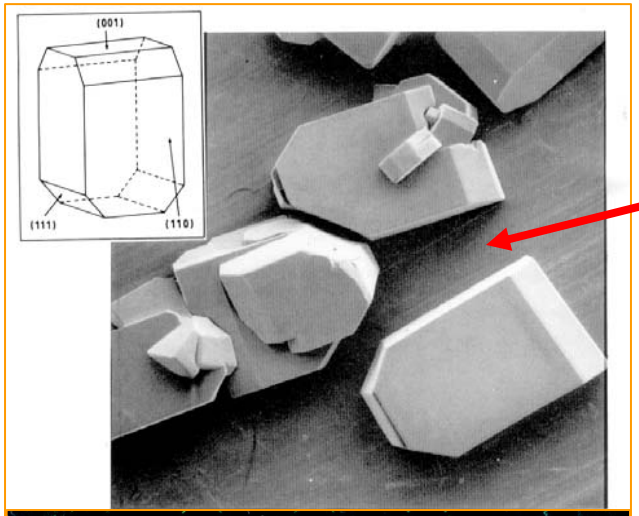
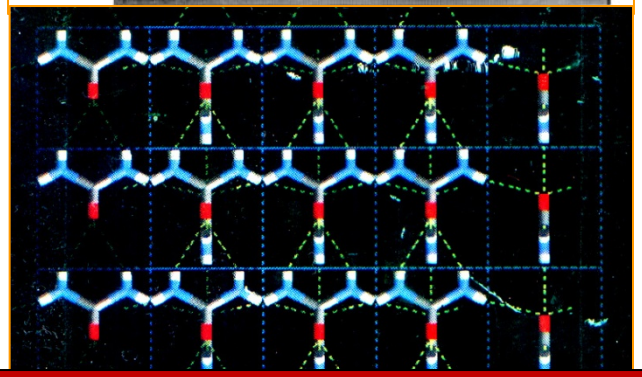
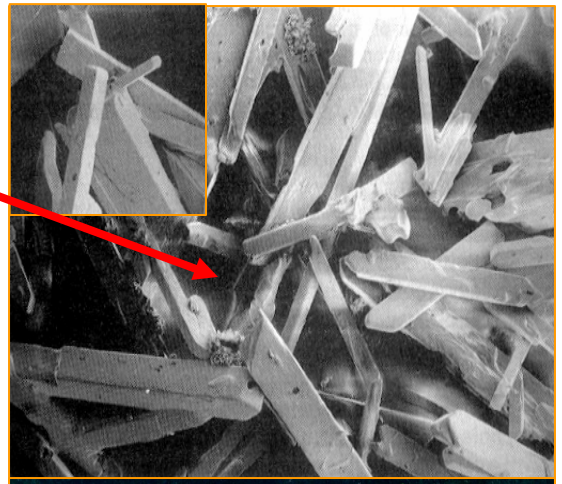
Crystal Chemistry, Morphology & Solvent: e.g. Urea

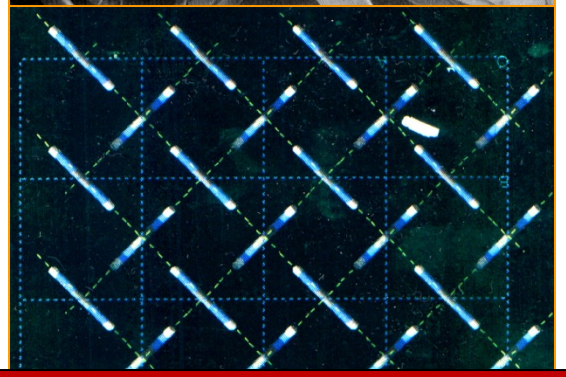




Different growth environments *vapour vs methanolic solutions yields different morphologies*

Crystal morphology relates to crystal surface chemistry





Solvent binds to different crystal faces

Solvent selection impacts on crystal form, notably particle morphology which effects product separation, e.g. filtration

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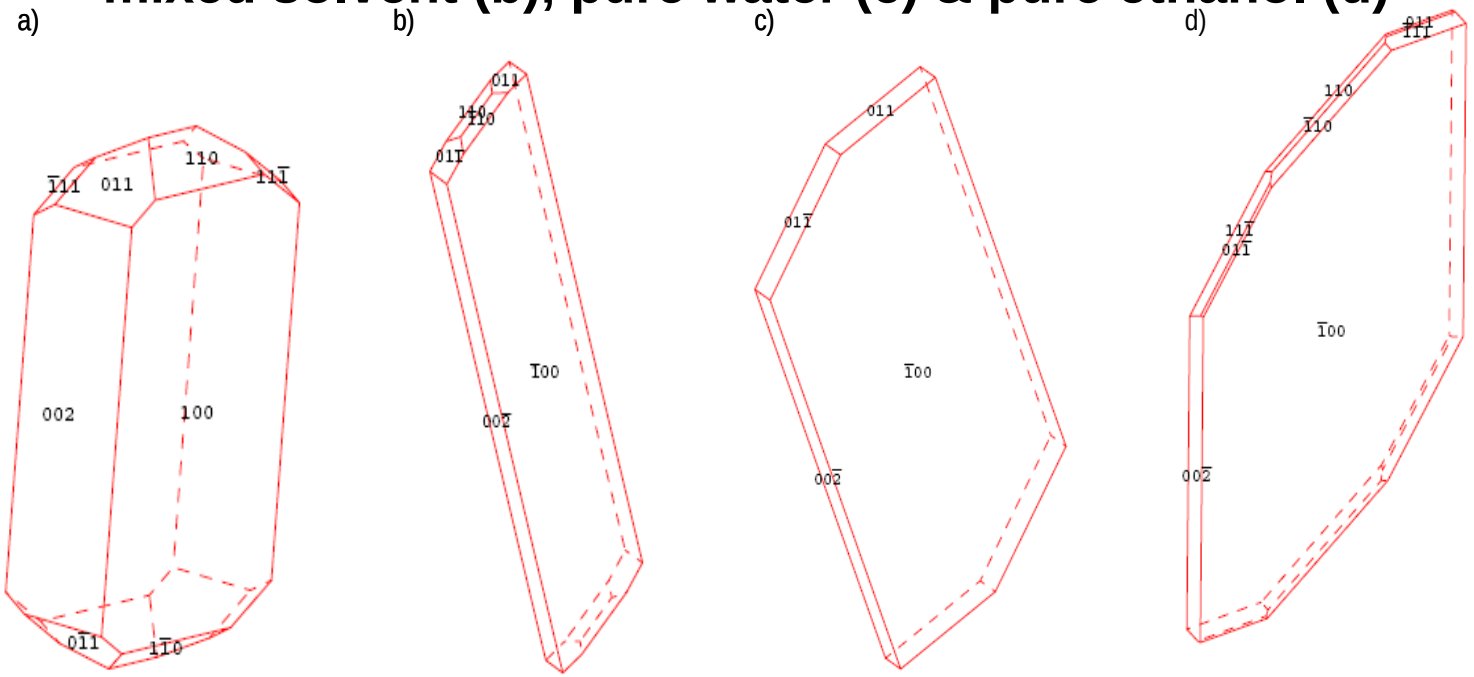
Modelling Solvent-Mediated Morphologies

(a) Crystal habit for aspirin as predicted via attachment energy model (b-d) Simulated crystal habits, using modified surface energies for mixed solvent (b), pure water (c) & pure ethanol (d)



Experimental data provides more plate-like crystal morphology than predicted using a simple attachment energy calculation

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Process Ability: Impact of Molecular Complexity

- **Well-known Murphy's law:**
  - **high value-added products e.g. pharmaceuticals are much harder to prepare**
- **Often drug molecule molecular flexibility tends to make materials difficult to self-assemble & crystallise**
- **Process understanding is key to achieving control of complex drug compound formation**
  - **process compounded by many new drugs having very poorly solubility & hence bioavailability**
- **Nano-particles and/or formulations offer key opportunity for delivering enhanced physical & chemical properties**

Need to understand & inter-relate molecular & incipient solid-form structures with their physical properties

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Crystallization: Nucleation & Polymorphism

- **Controlling balance between nucleation & growth reflects on crystal size**
  - **i.e. high nucleation rate result from high solution supersaturation leading to small nucleation cluster sizes**
- **Structure & thermodynamic stability of post nucleation product clusters important in**
  - **understanding inter-relationship between process conditions & product properties**
- **Hence, controlling crystallization supersaturation could enable direction of product polymorphic form, through**
  - **Supersaturation-control of cluster size at nucleation**
    - **i.e. via homogeneous nucleation theory**

$$r^* = \frac{2\gamma v}{}$$

Hypothesis that meta-stable forms are more thermodynamically stable at small cluster sizes shown for L-glutamic acid & D-mannitol

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POLYPACK Cluster Building Programme

System-specific molecular modelling program for size, shape & structural anisotropy dependency characterization of particles

- **Calculation of Cartesian coordinates of polyhedral corners with shape corresponding to crystal morphology**
- **Calculation of volume & surface area of crystal polyhedron & defining the size of crystal polyhedron**
- **Building facetted shaped molecular cluster**
- **Determination of surface & bulk characteristics of molecular clusters such as**
  - **Crystallinity & radial distribution function (RDF)**
  - **Surface/bulk molecular ratio & surface area/unit volume**
  - **Surface properties, roughness, surface charge, reactivity**
  - **Molecular disorder wrt reference structures**

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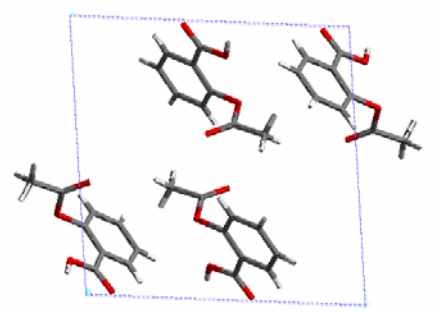
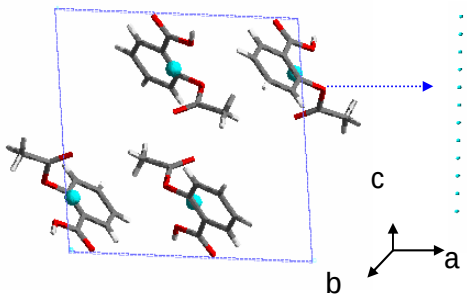
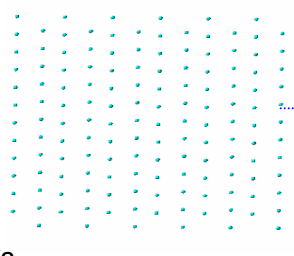
Building Facetted Clusters: Example Aspirin



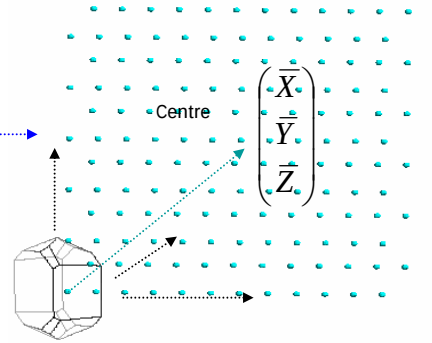
Crystal unit cell



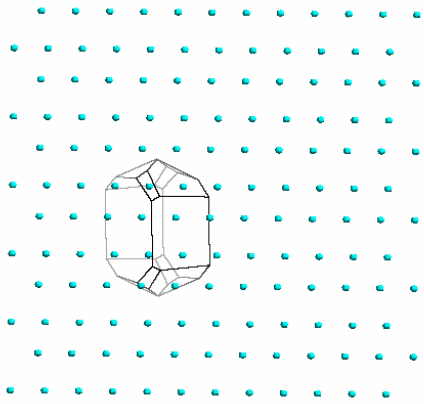
Unit cell with calculated centres of gravity



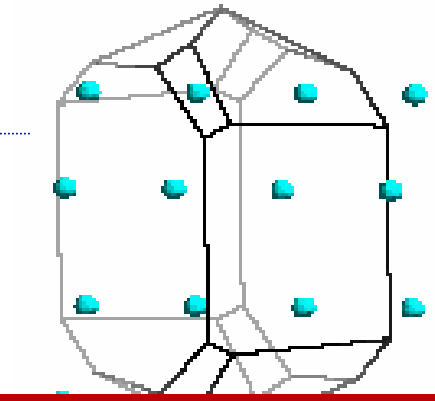
Lattice grid of centres of gravities

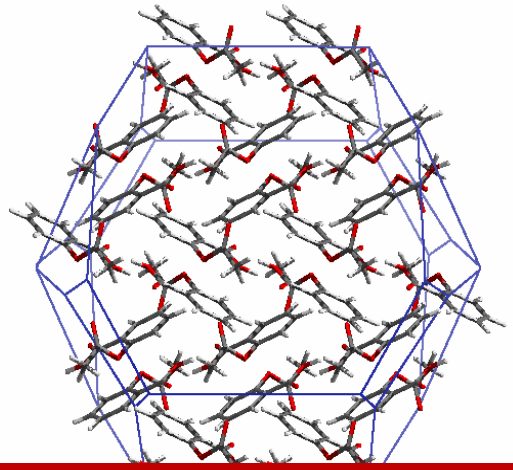


Location of polyhedron at the coordinate system origin



Shift polyhedron to the middle of





Molecular model for a crystalline particle produced enabling particulate processing properties to be predicted

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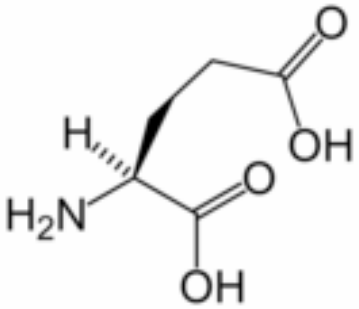
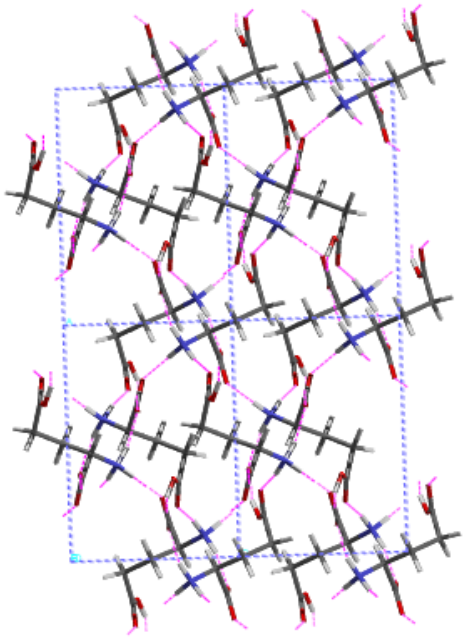
Cluster Stability: L-Glutamic Acid

L-Glutamic acid

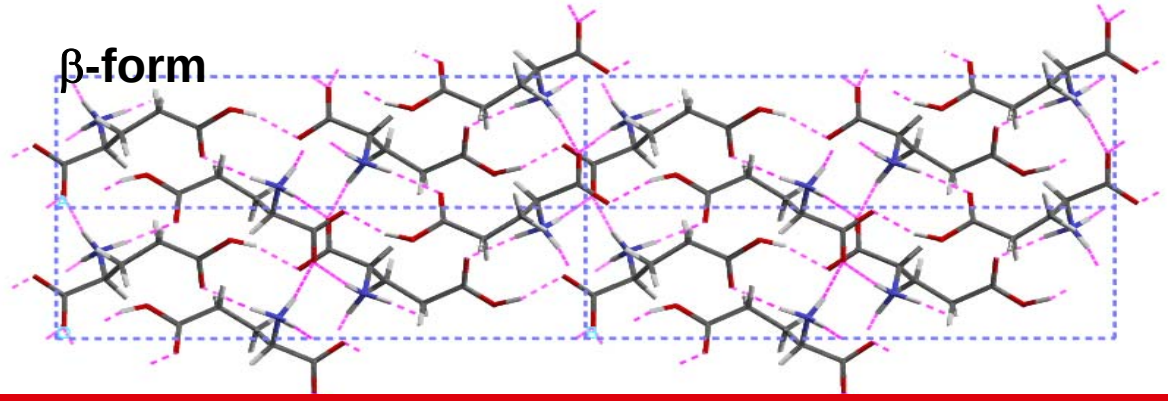


α-form



- **L-glutamic acid has two polymorphic forms: α & *β***
- **Meta-stable α-form: produced under kinetic control**
- **Transformation form α to b occurs in solution**

β-form



Different molecular conformations & hence inter-molecular packing between these two polymorphic forms

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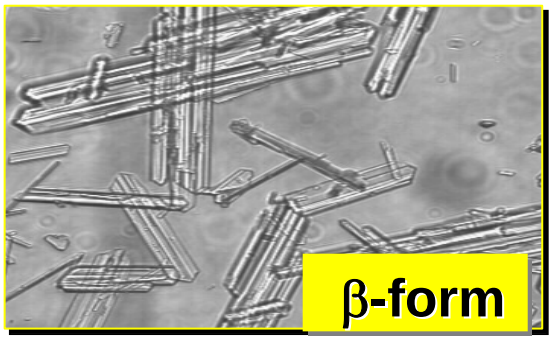
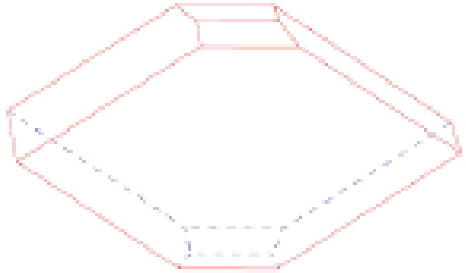
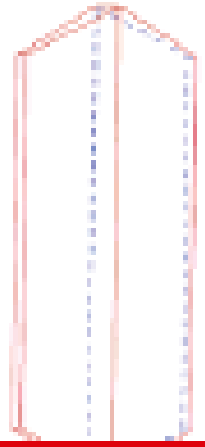
L-Glutamic Acid Facetted Clusters

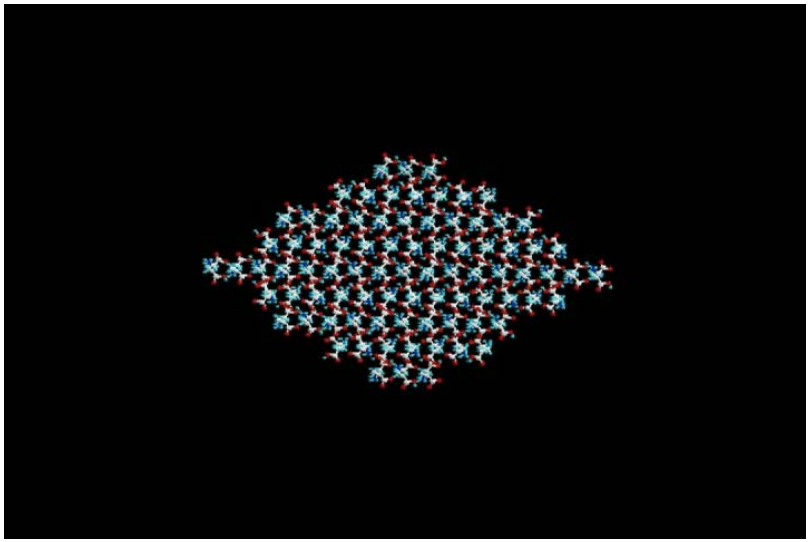
Experimental morphologies

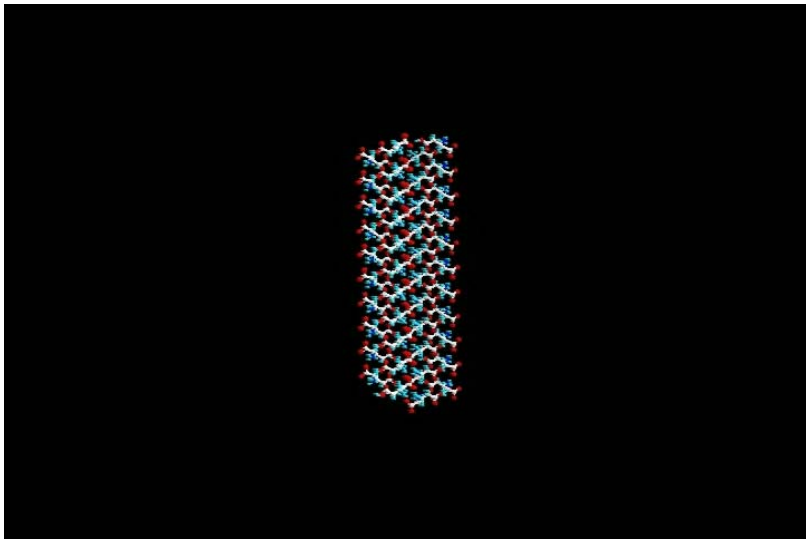


Predicted morphologies









Shaped molecular clusters built on basis of predicted crystal morphologies

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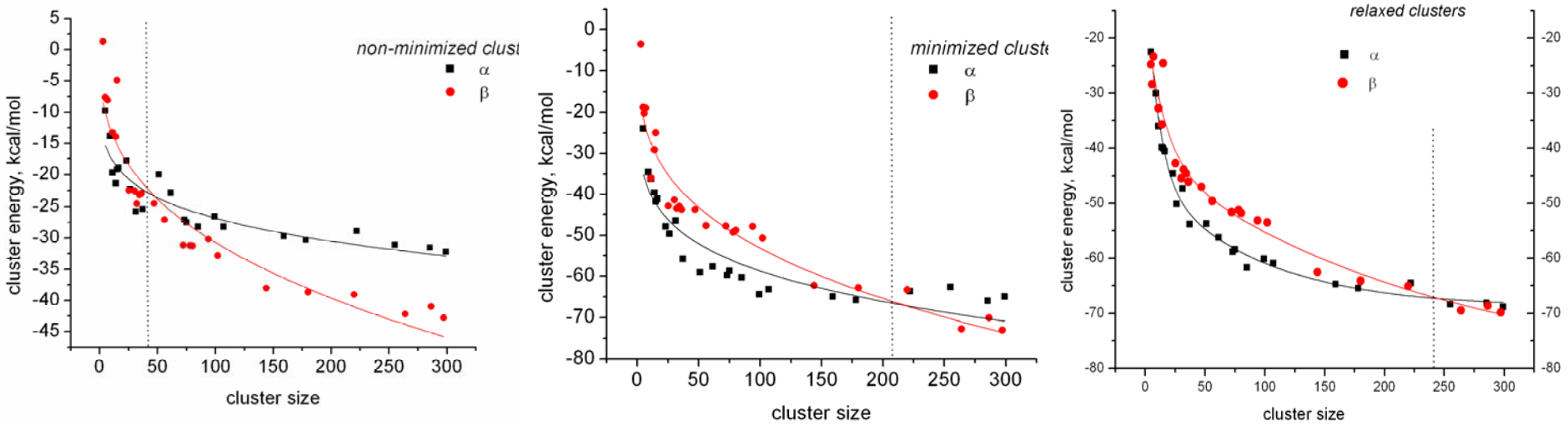
Energetic Stability of Facetted L-Glutamic Acid Clusters

Journal of Physical Chemistry B 109 (2005) 19550



Meta-stable form is more thermodynamically stable at small cluster size

Homogeneous nucleation theory

$$r^* = \frac{2\gamma v}{kT\sigma^2}$$

Controlling crystallization supersaturation enables control of critical cluster size therefore directing the final product polymorphic form

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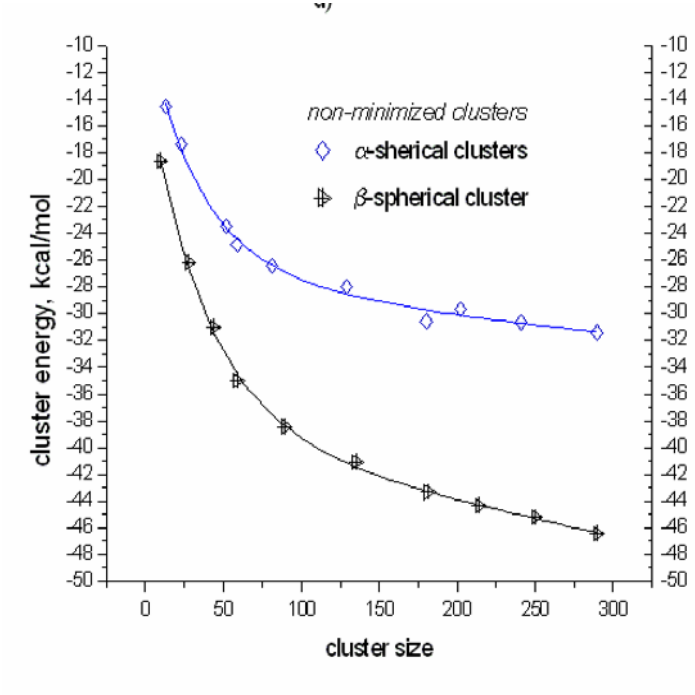
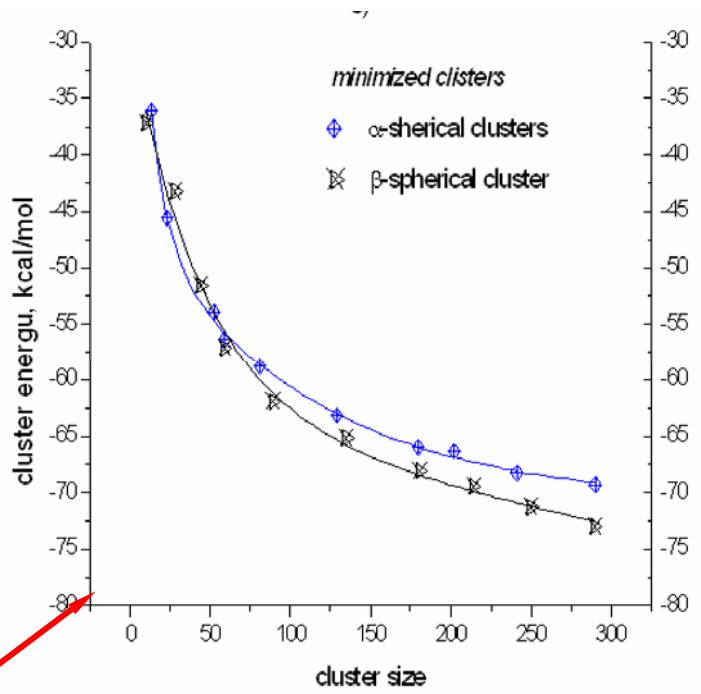
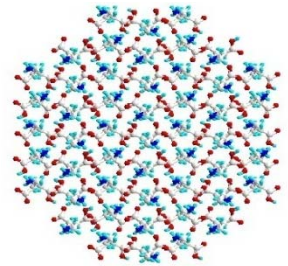
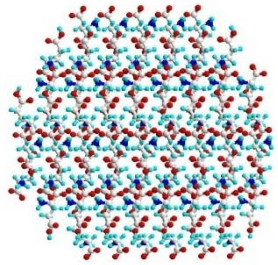
Energetic Stability of Spherical L-Glutamic Acid Clusters



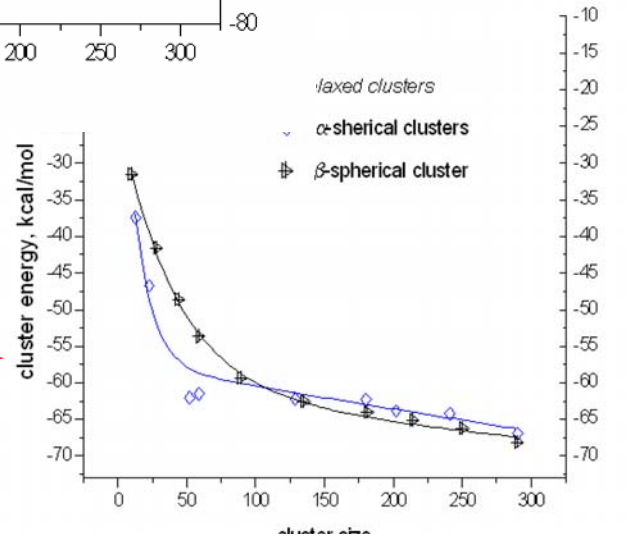






Meta-stable form more energetically stable at small cluster size for minimized & relaxed clusters but effect not so strong as for facetted clusters

Overall effect is a combination of both shape & size



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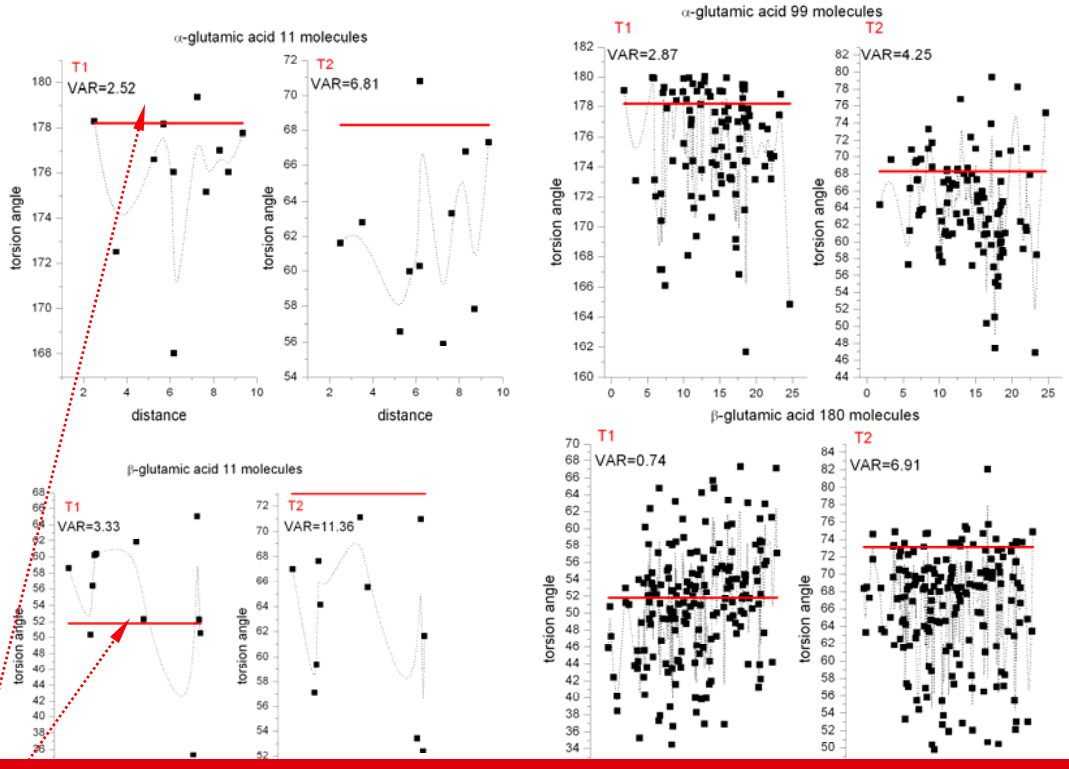
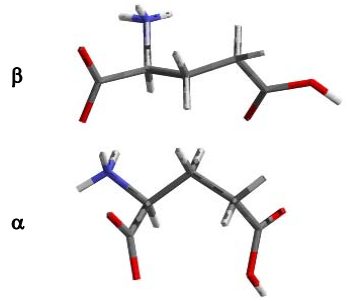
Cluster Conformation Analysis of L-Glutamic Acid

Cluster Conformation Analysis of L-Glutamic Acid





T1 reflects position of amino group
T2 reflects conformation

Nano-size cluster disorder links to ease of nucleation as assessed via crystallisation measurements

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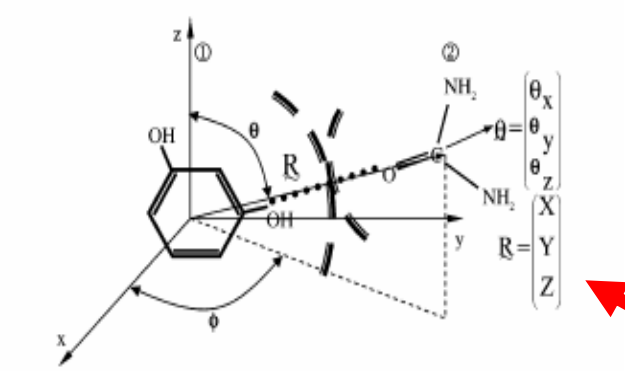
Grid Search: Exploring Inter-Molecular Packing Space



Mobile molecule Fixed molecule

$$\begin{pmatrix} x_i' \\ y_i' \\ z_i' \end{pmatrix} = \mathbf{M}\begin{pmatrix} x_i \\ y_i \\ z_i \end{pmatrix} + \lambda \underset{\sim}{\mathbf{R}}$$

$M(\theta_x, \theta_y, \theta_z)$-rotational matrix

R-position vector

λ-translational magnitude

- Pair of molecules considered treated as rigid bodies
- First molecule fixed - other subjected to grid search
- Search defined by 6 degrees of freedom of second molecule (3 translational & 3 rotational)
- Intermolecular search defined by 2 angles & a radial distance
- Configuration accepted or rejected based on intermolecular pair energy
- Typical van der Waals radii used to define minimum separation distance between centres of two molecules

* Hammond et al Journal of Physical Chemistry B 107 (2003) 11820

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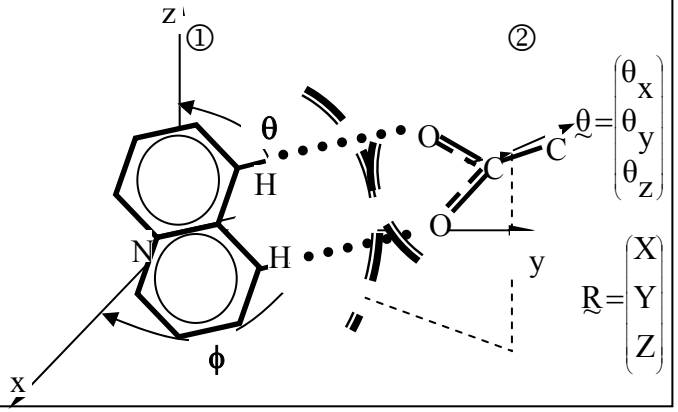
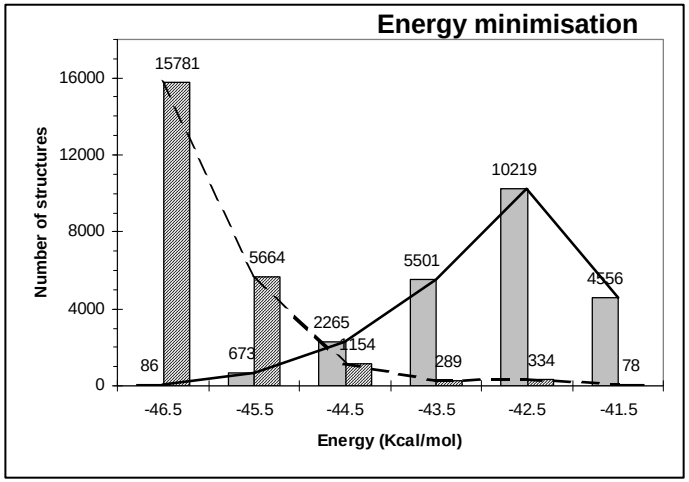
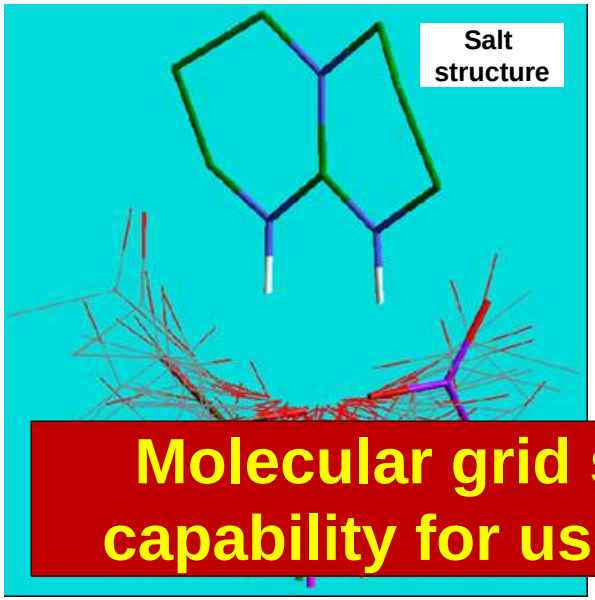
Grid Search: Salt Selection

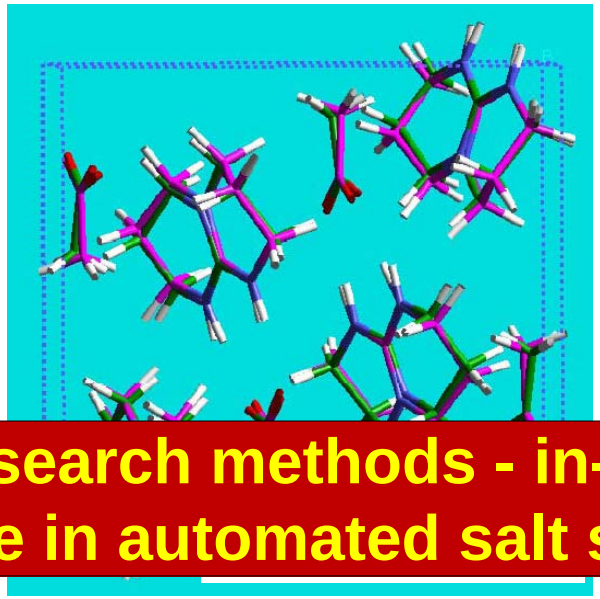
SYSTSEARCH: Dimer intermolecular search

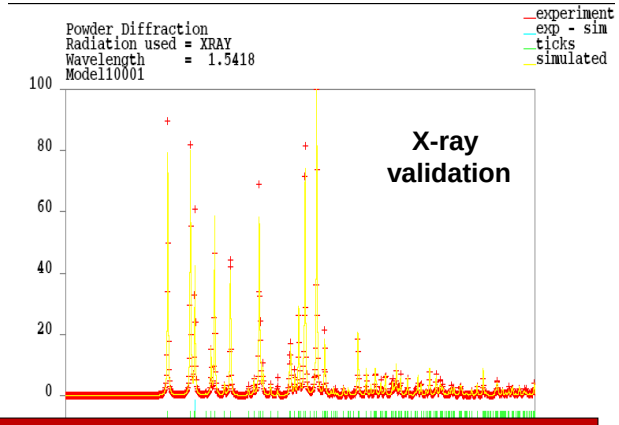


1,3,4,6,7,8-hexahydro-2H-pyrimido [1,2-a] acetate









Molecular grid search methods - in-silico predictive capability for use in automated salt selection process

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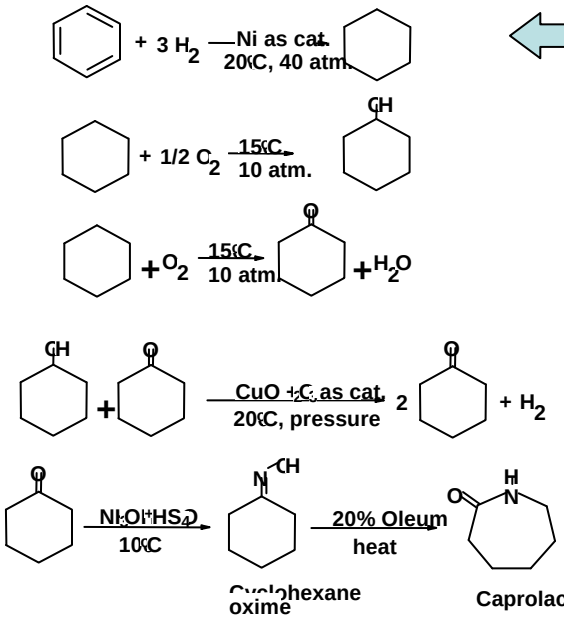
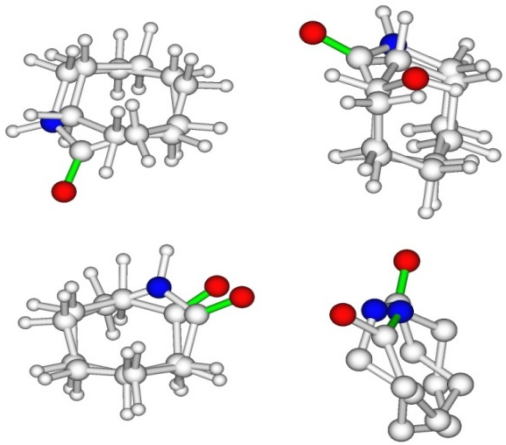
Impurity Segregation in Solid Caprolactam

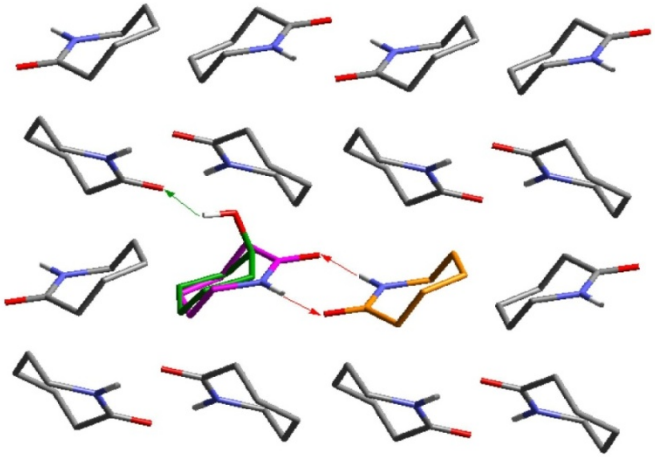
- Caprolactam precursor in production of nylon-6.
- Polymerization process influenced by presence of impurities
- Molecular modelling used to study crystal impurity incorporation



Synthesis of Caprolactam: Source of Impurities



Impurity molecules overlaid in context of host crystal lattice: a)



Optimal position of impurity cyclohexanol in ε-caprolactam

Ease of Impurity incorporation predicted hence enabling direction the synthetic route to optimise product purity

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Crystal/Crystal Interfaces & Product Formulation

- **Processes involving solid phases tend to result in more manufacturing problems**
  - **reflecting heterogeneity & high molecular density of solid phases compared to gaseous or liquid phases**
- **Reactions between solid phases dominated by**
  - **surface properties of interacting particles**
  - **inter-particle contact area**
- **Molecular shape/size factors yield pharmaceuticals crystallising in low symmetry structures producing**
  - **highly anisotropic physical & chemical properties**
    - ❑ **notably facetted particulate products**
- **Also, inherent heterogeneity in production-scale p**
    - ❑ **creating problems for product formulation**

Molecular scale modelling tools are needed to predict particle-particle interactions

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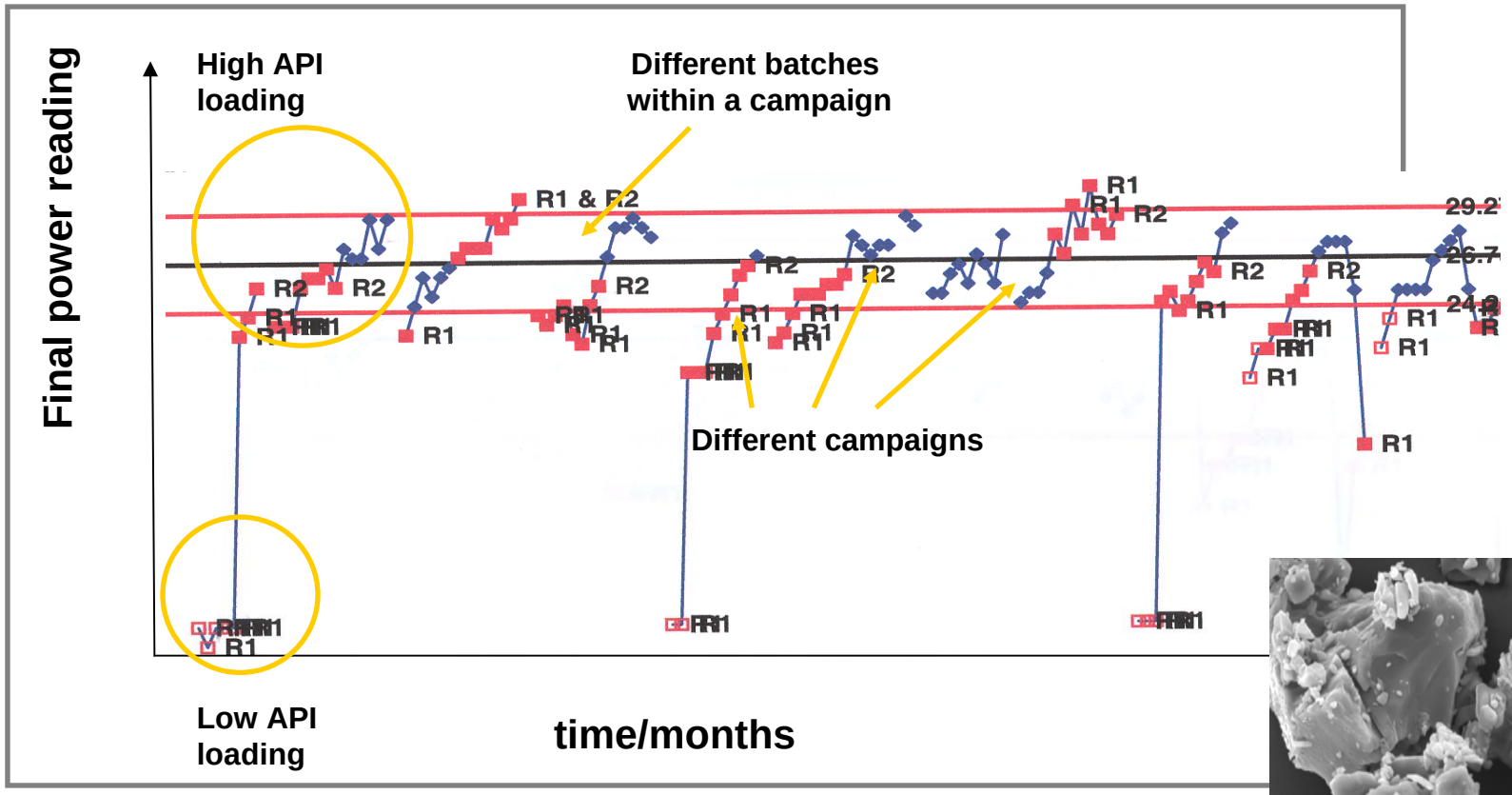
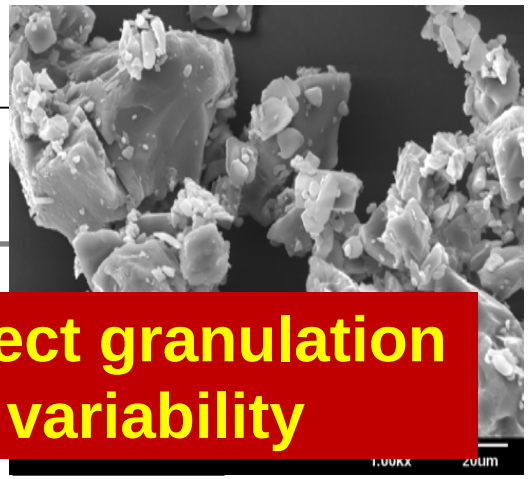
Morphology, Crystal/Crystal Interfaces & Formulation





- **High API loading: physical properties effect granulation**
- **Batch-to-batch, & hence product quality, variability**

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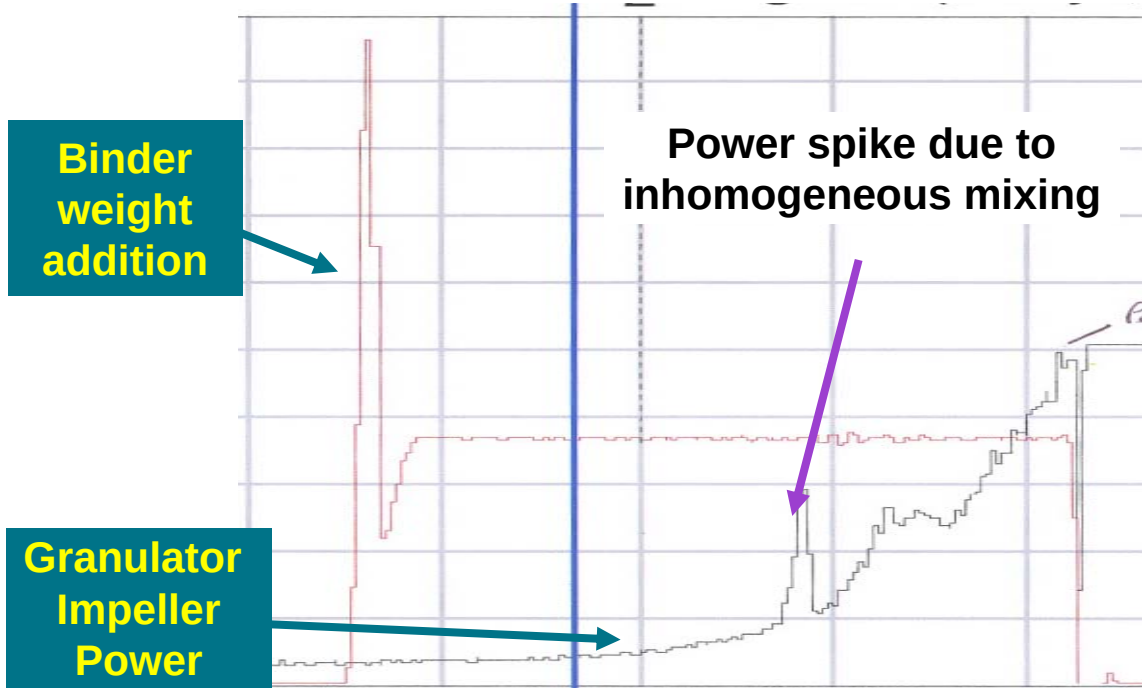
Granulation Performance Manufacturing Variability

In-process monitoring of granulation Process (power & water addition)



Batch to batch variability related to API physical particle properties

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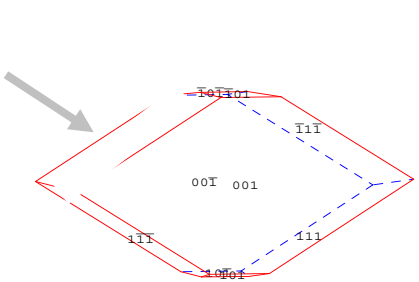
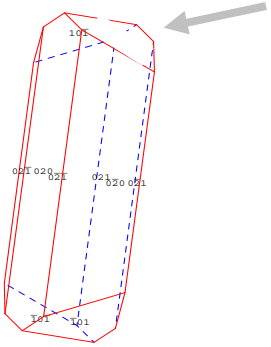
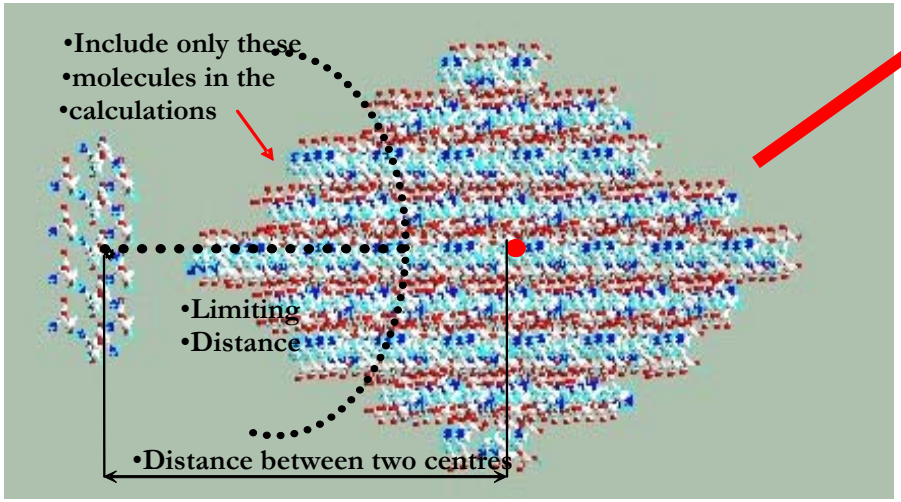
Modelling Binding Between Crystal Particles

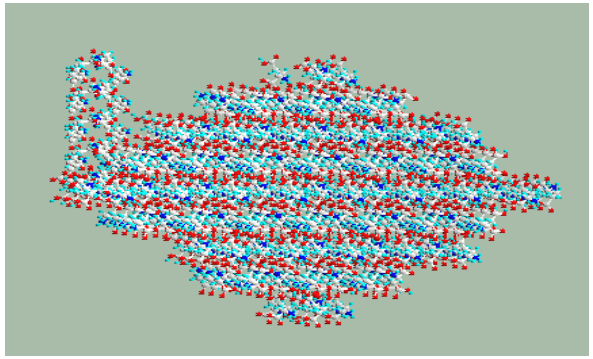




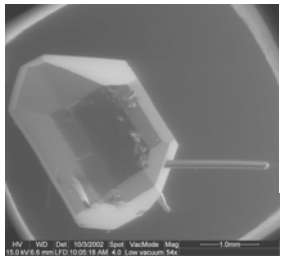
Most stable configuration at distance 35Å show interaction between (101) face β- form with (11-1) face of α-form

Predicted morphologies of α- & β- L glutamic acid with interacting faces highlighted





***Experimental data (Ferrari & Davey) Crystal Growth & Design* 4 (2003) 1061**



Modelling Correctly Predicts Binding Between Particles

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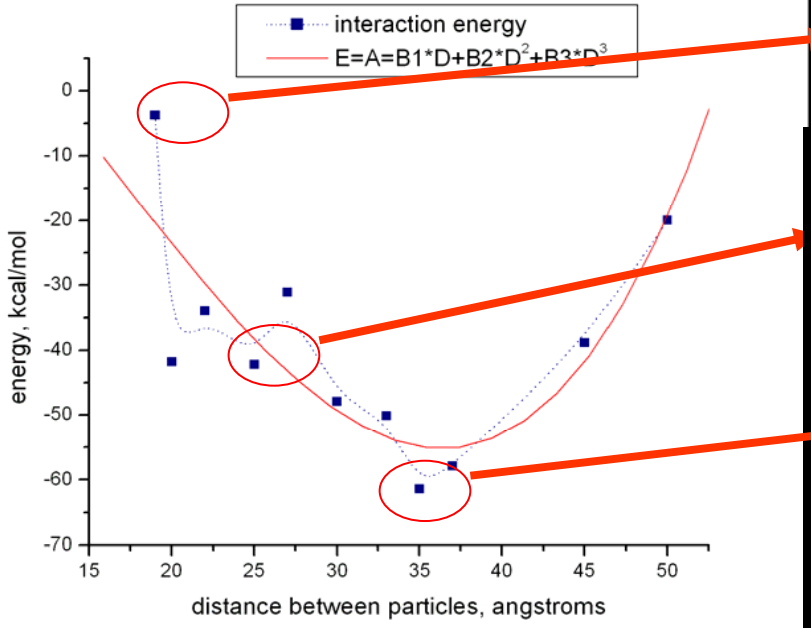
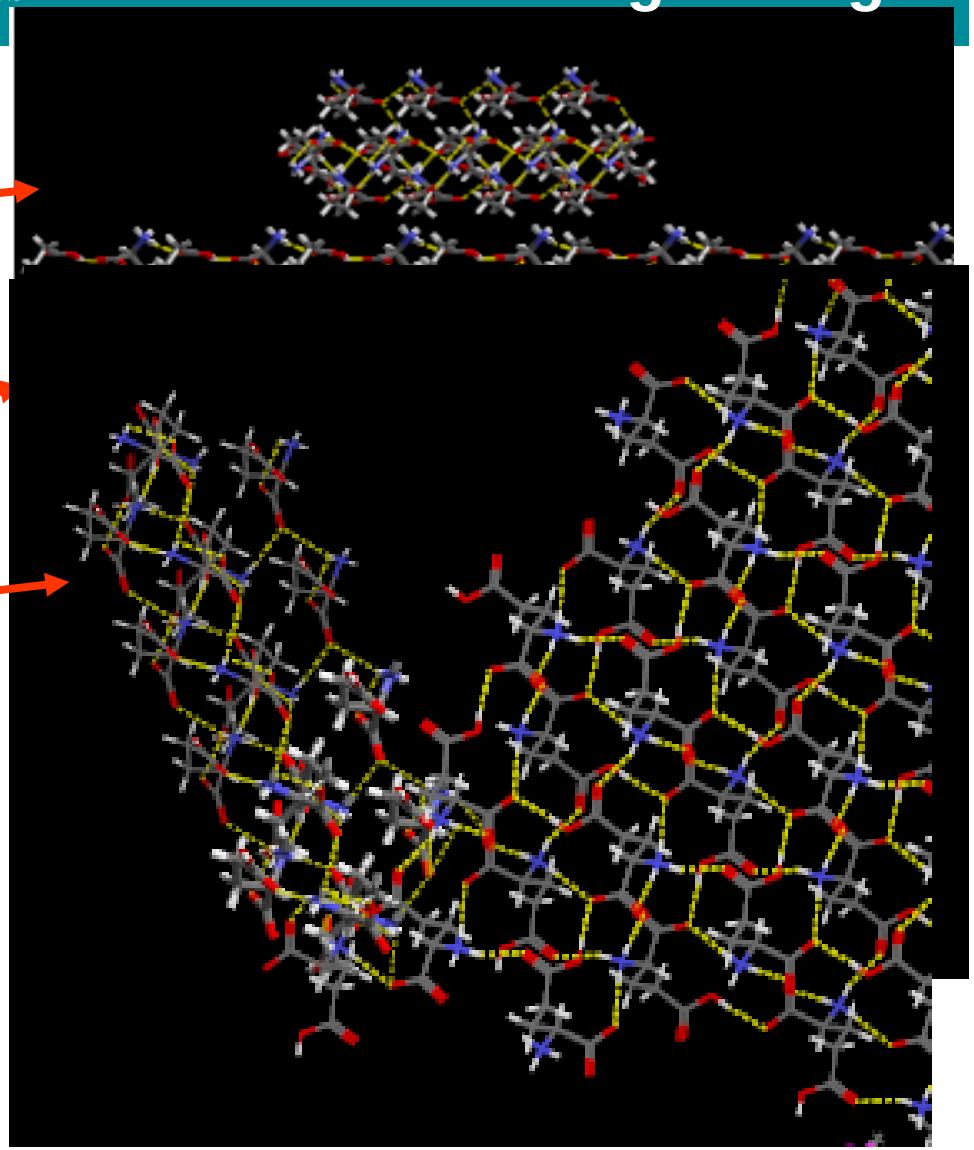
H-Bonding & Understanding Inter-Particle Binding Strength





Examining structural interfacial chemistry for various stable inter-particle interactions for different inter-particle distances

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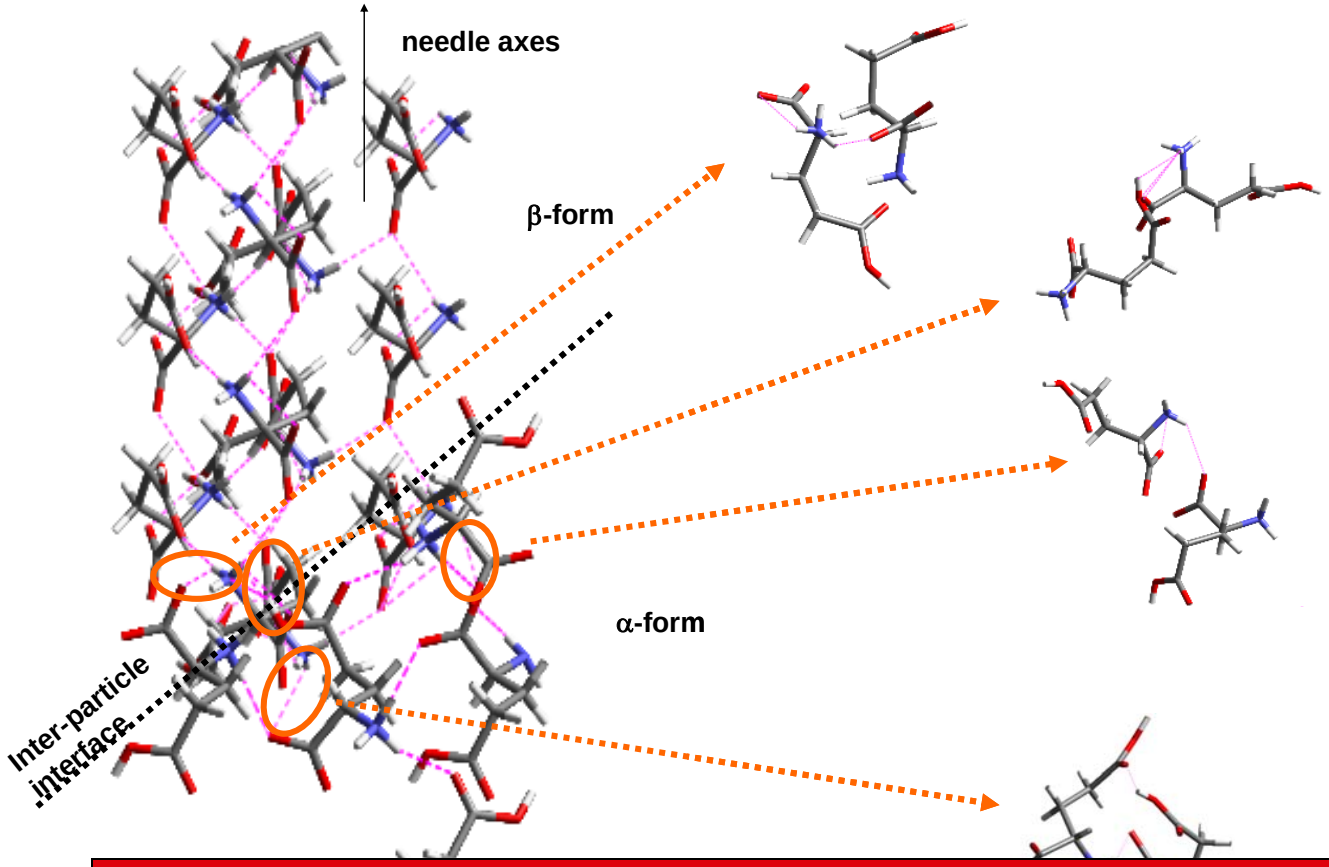
Inter-Particle H-Bonds at (111)/(101) Interface



Amino group found to be most important functional group in hydrogen bond pattern between the interacting surfaces

Challenge: to reverse engineer this approach to provide reliable predictive capability ab-initio

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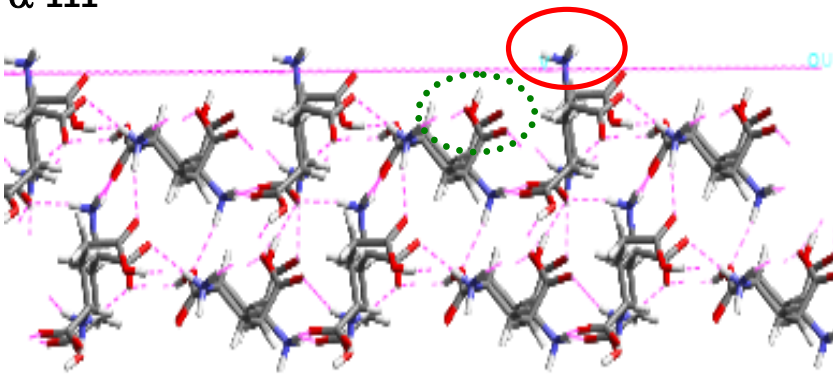
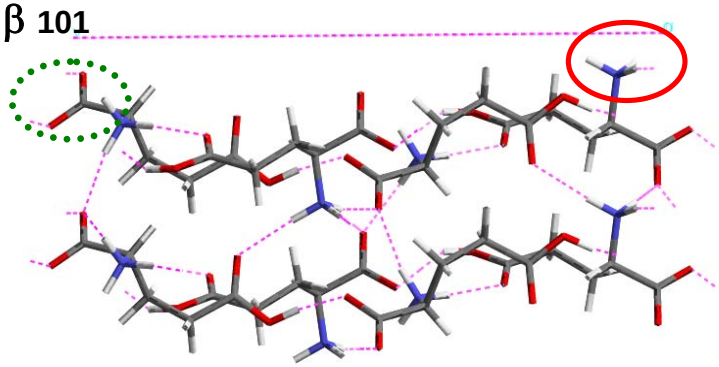
LGA Surface Chemistry & Interacting Crystal Surfaces

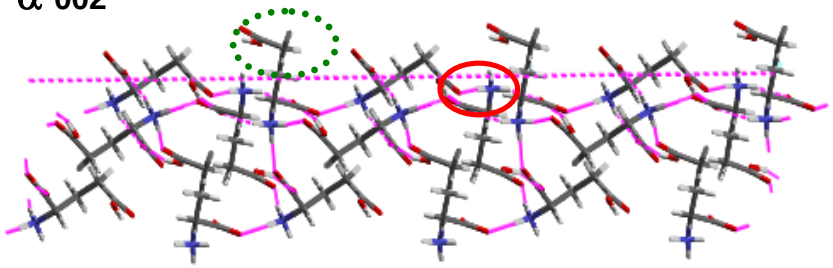
α 111



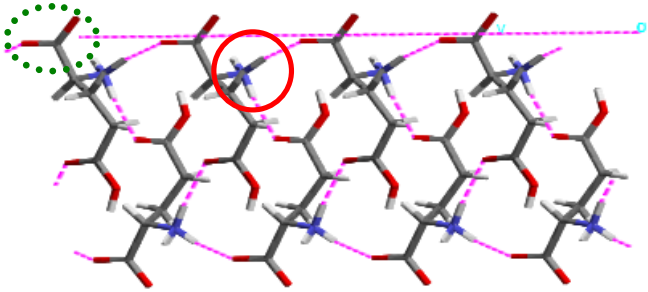
β 101



α 002



β 020



α (111) & β (101) show surface amino group (circled in solid line) not actively involved in H-bonding hence available molecular with agglomerating particles

***α (002) & β (020), in contrast, have amino group fully H- bonded* & not available for inter-particle binding**

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Very Grateful Thanks & Acknowledgements

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**

Molecular & crystal modelling studies for particle design involved collaborations with Durham & Strathclyde Universities with funding from EPSRC, AstraZeneca, GSK, Pfizer & Sanofi

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

- **particularly Klimentina Pencheva & Robert Hammond for their work on cluster modelling**

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Closure and Thanks

In this talk, I have tried to…

- **Overview industrial need for science-based process technology to maintain the EU's chemicals manufacturing sector's competitive position**
- **Given a very indecent "head-up" on crystallisation science theory, notably achieving balance between 3-D nucleation & 2-D growth processes**
- **Describe some recent modelling-based research**
  - **Morphological modelling for predicting particle shape**
  - **Modelling crystal precursor molecular clusters relating their structure to polymorph selection & crystallisability**
  - **Predicting down-stream product formulation via modelling crystal/crystal interactions**

Once again, many thanks to EMEA for the invitation to visit, for the opportunity to present this talk & also for your kind attention

I will be most happy to attempt to answer questions!