Synthonic Engineering: Molecular-Scale QbD Tools for the Rational Design of Complex Particulate Materials for Pharmaceutical Formulation

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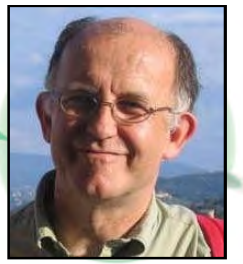


Professor Kevin J Roberts
Institute of Particle Science & Engineering
School of Process, Environmental & Materials Engineering

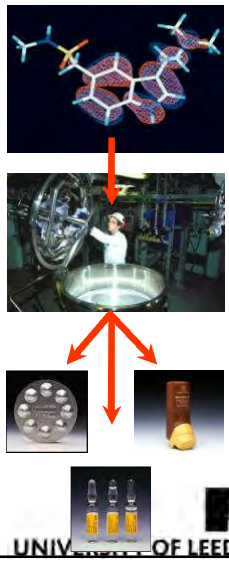
Fundamentals of Solid Formulation: Understanding & Measurement

Royal Society of Chemistry,
Burlington House, London - 11th March 2014

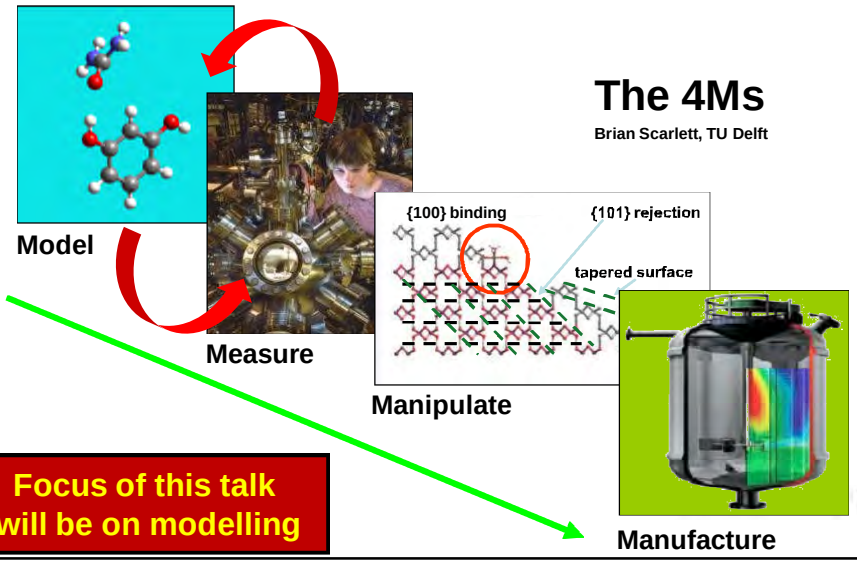
iPRD
Institute of Process Research and Development

Aims of Session & Presentation Plan

- **Application of molecular-scale predictive tools for use in pharmaceutical particle formation & formulation**
  - ❑ **Notably inter-molecular (synthonic) modelling for translating APIs into practical drug products**
- **Talk set this within an industrial QbD perspective**
  - ❑ **To improve quality, shorten lead times, cut costs, improve product profitability etc.**
- **Overview new synthonic engineering software tools & illustrate through case studies**
  - ❑ **Highlighting applications impacting at API/Drug Product interface**
- **Forward look perspective & vision drawing need for focus to be more on quality & not just cost**
  - ❑ **Particularly impact on development of new generation pharmaceuticals**
- **Finally, some closing remarks & acknowledgements**
  - ❑ **Hopefully staying on time!**



Manufacturing Molecules: Integrating Modelling, Measurement, Manipulation & Manufacture



Focus of this talk will be on modelling

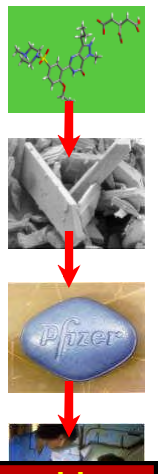
Critical Quality Attributes: Reducing Variability from Feedstock to Product

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 concomitant properties of formulated products made downstream**
  - ❑ **i.e. feedstock variability results in**



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

Example: Impact of Particle Size Engineering on Product's Critical Quality Attributes (CQA)

Product Feature	CQA	Particle Size	Impact on Product Performance
Safety	Content uniformity	Too large or too diverse	Variation in API uniformity of dose
		API size significantly different from excipients	Preferential segregation during processing & reduced dose uniformity
Efficacy	Dissolution behaviour	Too large	Reduced dissolution rate & reduced product bioavailability
Process al	Flow	Too small	Poor flow, lower than ideal

Need to design effective crystallisation processes to produced desired particle size & distribution (CSD)

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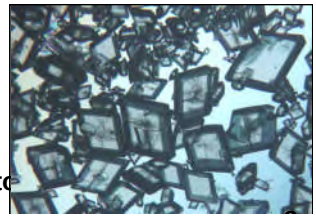
Future Pharmaceutical Science R&D: Open Innovation Based Collaborative Research, QbD & Design Space

- Pharmaceutical industry needs to work in partnership & adapt to meet future competitive challenges
- Current cultural change initiatives aim to promote detailed process understanding
  - From R&D through to manufacturing to improve product quality
    - ❑ moving from sigma 2.5 (0.5% variability) to
    - ❑ to sigma 6 (few ppb variability)

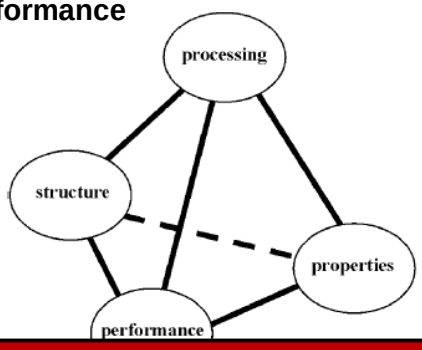


- Key need identified: improve science base implementing QbD methods
  - Moving from products pragmatically ENGINEERED TO WORK
    - ❑ PROCESS REGISTERED: - limited scope for process improvement
  - To MOLECULAR DESIGN of products manufactured via PAT

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

QbD for Drug Products Through Integrating Structure, Properties, Processing & Performance

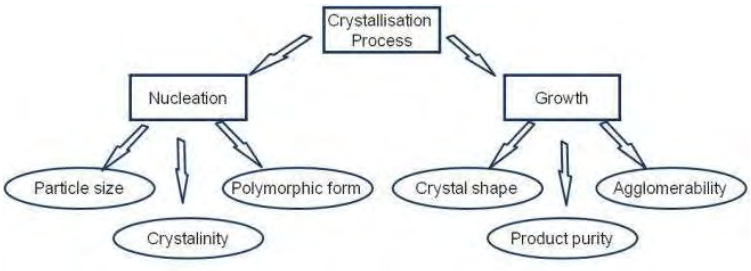
- Development of high added-value precision pharmaceutical products demands establishment of causal inter-relationships between a product's structure, properties, processing & performance



- This requires linking the worlds of
  - ❑ Material science - structure/ property relationships
  - ❑ Chemical engineering - processing
  - ❑ Manufacturing - quality

Development of precision pharmaceuticals demands detailed understanding of SPP&P inter-relationships

Scientific Backdrop: Defining & Optimising API Properties for Optimal Performance in Formulation

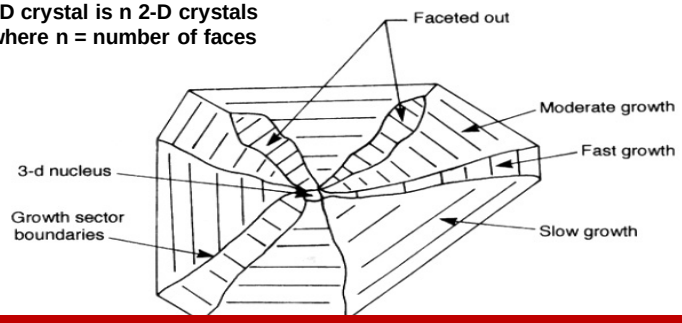


- Pharmaceuticals often delivered in crystalline form & crystallisation
  - ❑ Facilitates particle formation through nucleation & growth
  - ❑ Directs physico-chemical properties important to product performance
- **Particular focus on improving process R&D at drug substance (API) / drug product interface**

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

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

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



Key point: each crystal habit face has a different surface chemistry & hence different processing properties

Careful control of early crystallisation (nucleation, faceting & nano-scale crystal growth vital for highest crystal quality

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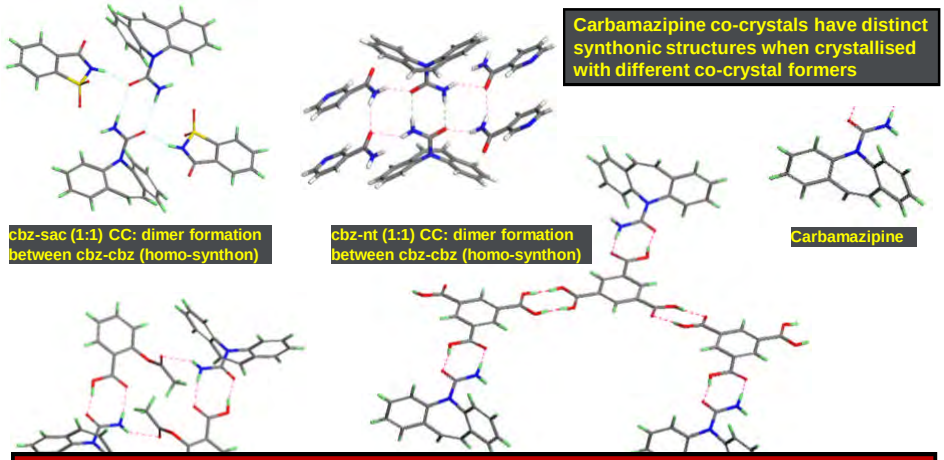
Synthonic Engineering: Design of Materials for Optimal Down-stream Processabiity

- Synthesis of molecules takes place via making/breaking of covalent bonds
  - Aided though formation of a transition state
- Condensed matter synthesis similar albeit "bonds" are inter-molecular interactions (synthons) defined as
  - *Homo*-synthons – same functional group
  - *Hetero*-synthons – different functional group
- Where inter-molecular interactions take place
  - Within material – can refer to as *intrinsic* synthons
  - At interfaces of material – can refer to as *extrinsic* synthons
- Synthons are vectors having both magnitude & direction who's properties can be

Synthonic modelling enables control of directed assembly process - providing capability for molecular-scale design

Supramolecular Chemistry - Intrinsic Synthons: Structure of Carbamazipine Co-Crystals



Opportunity: supra-molecular informatics for design, i.e. from crystal engineering to engineering crystallography

Sheikh, A.Y., Abd-Rahim, S., Hammond, R.B., Roberts, K.J., CrystEngComm, 11, 509. 2009

Extrinsic Synthons: Why are they Important in Particle Design?

- Extrinsic synthons on surfaces of crystalline particles are under-saturated with respect those in bulk
  - In terms of their expected co-ordination numbers (CN)
- CN for e.g. simple octahedral co-ordinated materials
  - 6 - bulk; 5 – surface; 4 – edge; 3 - corner
- These under-co-ordinated surface sites provide sites to initiate & direct a range of solid-state processes
  - Crystal growth
  - Material degradability
  - API/excipient binding/compatibility
- Knowledge of synthon strength, diffusivity, directionality, stereochemistry etc. can be exploited in particle design

Approach enables design & optimisation of high quality complex particulate-based processes & products

Determining Particle Surface & Interfacial Energies

- Degree of synthon under co-ordination together with its structural nature (i.e. hydrophobic versus hydrophilic)
  - ❑ Govern interfacial under co-ordination & surface energy
- Surface energy of a facetted particle can be broken down into summation of surface energies from constituent crystal forms

$$\gamma_{particle} = \frac{\sum_{i=1}^{N} M_{i(hkl)} A_{i(hkl)} \gamma_{i(hkl)}}{A_{total}}$$

Where: summation is over i; N - number of morphological forms; M_i - multiplicity/form; A_i - surface area/form; γ_i - interfacial tension/form; A_{total} - total crystal surface area

- Solvent selection can "tailor" surface properties of particle
  - ❑ Modelling solvent/surface synthons using SystSearch
  - ❑ Probing solvent binding to under coordinated surface sites

Net particle surface properties determined from summing those of its component crystal faces (hkl)

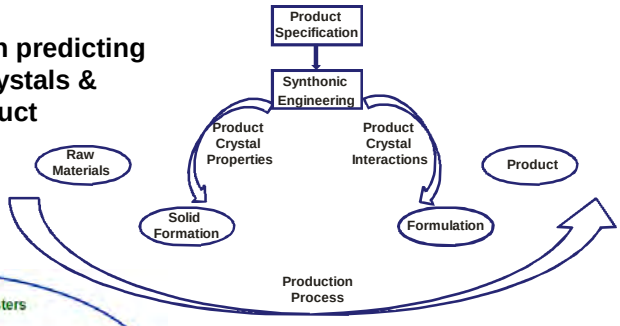
Particle Surface Engineering: Delivering Critical Quality Attributes (CQAs) needed for Product Design

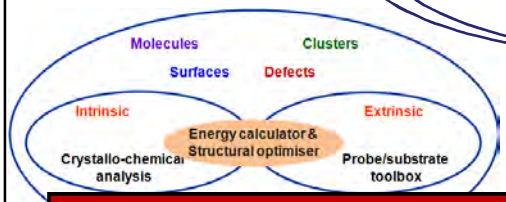
- Important parameter is number fraction of highly under coordinated edge/corner sites wrt those on flat habit surface
  - ❑ This increases with particle size reduction
    - Hence increases surface energy of particles
- Effect impacts through increasing
  - ❑ Solubility through Gibbs-Thomson effect
  - ❑ Particle surface energy due to breakage, e.g. as seen in iGC analysis of milled samples
- Breakage effect enhanced for fracture from rough rather than from smooth cleavage surfaces
  - ❑ Solid form selection issue, i.e. selecting crystal chemistry to have desired mechanical properties

Solid-form & particle engineering approach enabling delivery of CQAs, e.g. drug product dissolution

Applications of Synthonic Engineering Tools: VisualHABIT & SystSearch

Application of SE tools in predicting physical properties of crystals & potential impact on product formulation

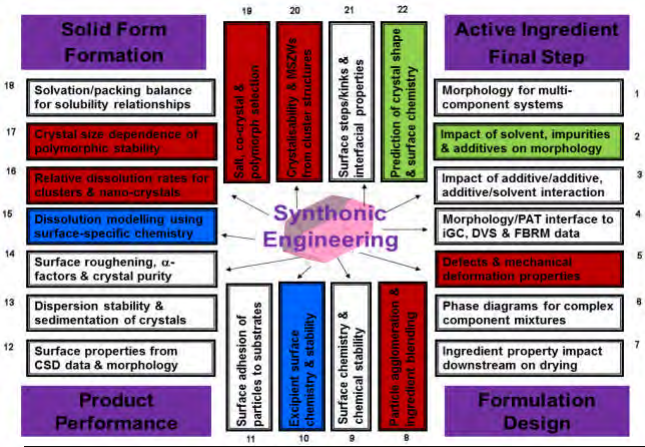




Main components of scientific software kernel

Key aim: flexible & easy to use molecular-scale tools for direct application in process R&D workstreams

Synthonic Engineering: Industry-Led Research Strategy & *The Clock Diagram*



- Develop molecular-based simulation tools for utility in process R&D
- Enhance process understanding of formation, development & aggregation steps important in crystallisation & formulation design
- Develop predictive tools & integrate them within routine pharmaceutical development work-flow situations

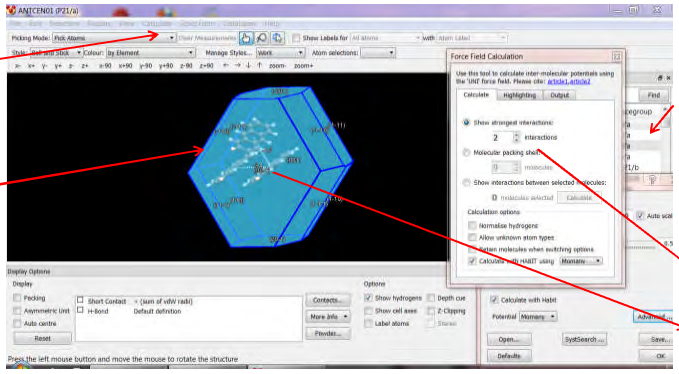
Cross-industry team brainstormed capability gaps (clock diagram above) & evolved strategy to address these

VisualHABIT in Context of CCDC Mercury

3 Steps for energy/morphology calculations:

- **Choose desired structure from database**
- **Click Calculate> BFDH morphology or**
- **Click on Calculate > BFDH > HABIT**

HABIT within Calculate



Morphology of anthracene calculated using HABIT

Database window to choose structure from

Molecules with 2 strongest interactions are displayed

Intrinsic Synthons: Graphical User Interface (GUI) for VisualHABIT

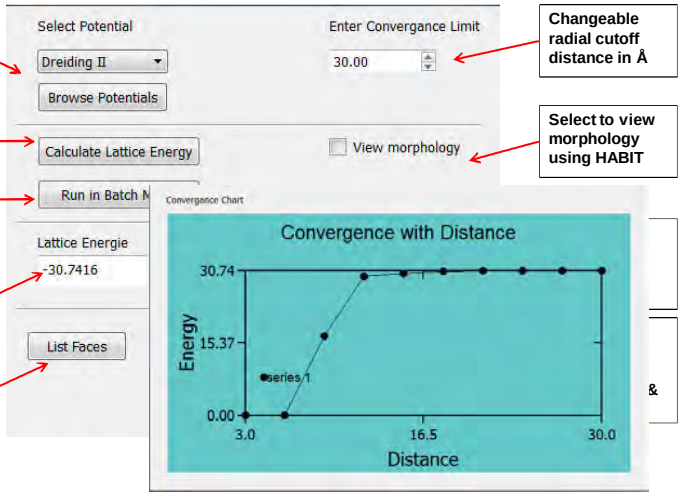
Choice of Forcefield/potential from a list of 4

Click to get lattice energy

Run lattice energy calculations for a number of structures

Lattice energy is displayed & convergence plot pops up

Lists faces taken from BFDH for which attachment energies are calculated

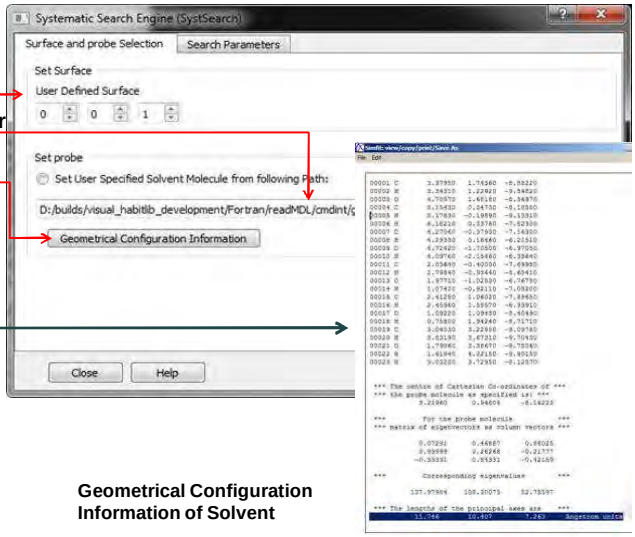


Changeable radial cutoff distance in Å

Select to view morphology using HABIT

Extrinsic Synthons: Graphical User Interface for SystSearch

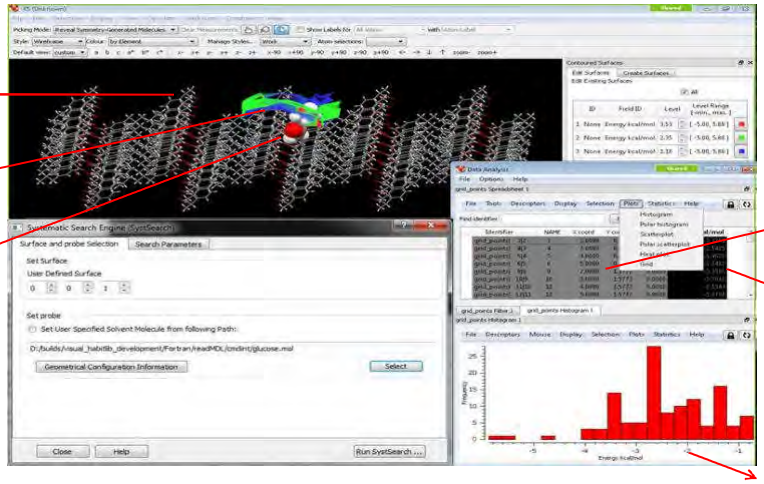
- Choose desired surface
- Select solvent from a folder
- Click on Geometrical configuration info button
- Generates geometrical configuration information of probe (solvent)
- User can adjust search parameters accordingly



Geometrical Configuration Information of Solvent

Solute/Solvent Binding: Acetonitrile on Ibuprofen (0 0 2) surface

Extrinsic synthonic analysis data displayed as energy iso–surfaces on slab of host & probe molecule & as histogram simultaneously



Aspirin: Solvent-Mediated Interfacial Tension as Function of (hkl) & Solvent Type

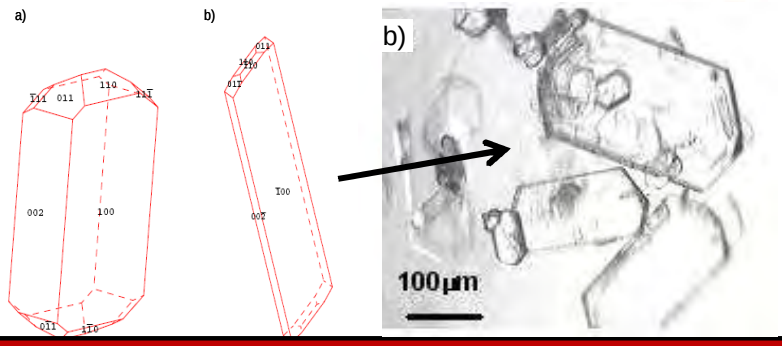
- Attachment energies modelled for crystal habit faces of aspirin
  - Together with their recalculation through solvent binding calculations using grid-based modelling
  - Example: predicted morphologies for water, ethanol & 38%/62% ethanol-water (mixed) solvents

Habit Plane / (hkl)	Face Multiplicity	Slice Thickness / Å	Solvent Dependant Attachment Energy / kcal mole^{-1}		
			Water	Ethanol	Ethanol/Water
(100)	2	11.4	0.27	0.37	0.20
(002)	2	5.66	3.64	9.97	1.19
(011)	4	5.69	11.75	12.94	11.90

Grid-based modelling methodology enables morphology prediction as function of crystallising solvent

Aspirin: Solvent-Mediated Morphology Predictions

(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)



More plate-like crystal morphology from solution crystallisation than predicted using attachment energy

Supersaturation Direction of Polymorphic Form: L-Glutamic Acid (LGA)

- 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

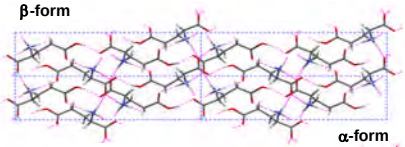
$$2\gamma v$$

Hypothesis: meta-stable forms more thermodynamically stable at small cluster sizes, i.e. high supersaturation

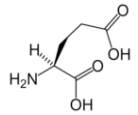
Crystallisation-Directed Polymorphic Forms & their Conformational Transition Pathways

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

β-form

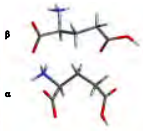


α-form

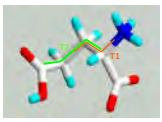


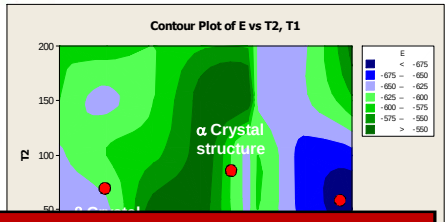
L-Glutamic acid

- Polymorphs have different molecular conformations defined by torsion angles
  - ❑T1 reflects position of amino group
  - ❑T2 reflects conformation of carbon chain



Conformation transition pathway probes polymorphic propensity

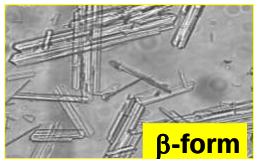


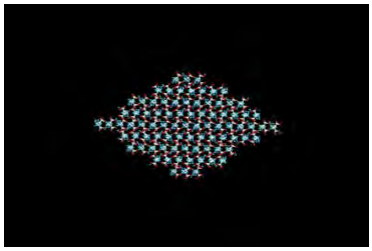


Focus point: LGA crystallisation & polymorphic transformation involves change in molecular conformation

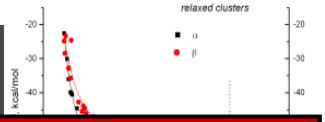
Facetted Clusters of L-Glutamic Acid (LGA): Polymorphic Stability as a Function of Size

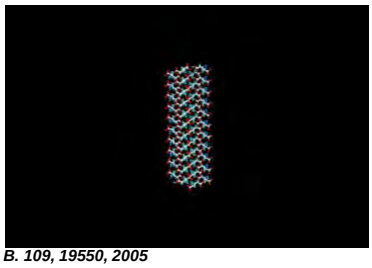
Predicting early growth stage using shaped molecular clusters





Meta-stable α-form stabilises at small



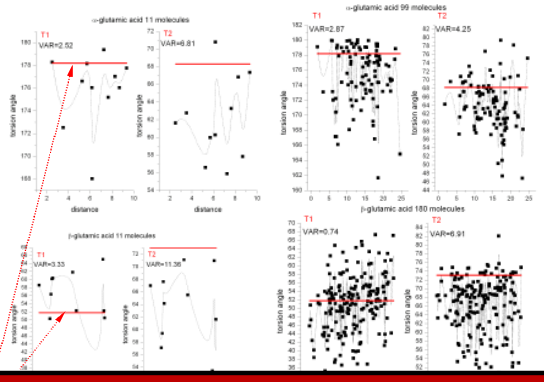


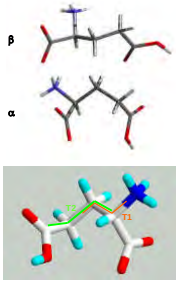
"Meta-stable" form more stable at small crystal sizes i.e. higher supersaturation

Hammond, R.B., Pencheva, K., Roberts, K.J., J. Phys. Chem. B. 109, 19550, 2005

Probing CrystalisAbility: LGA Cluster Conformation Analysis

Cluster Conformation Analysis of L-Glutamic Acid: Probing Crystalisability

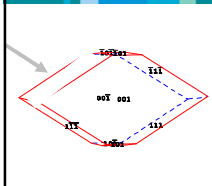


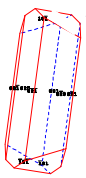


T1 reflects position of amino group
T2 reflects conformation

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

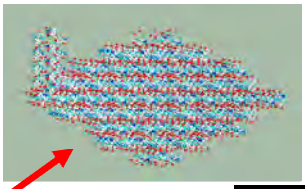
Predicting Inter-Particle Binding Associated with Polymorphic Conversion: LGA

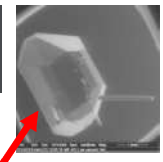




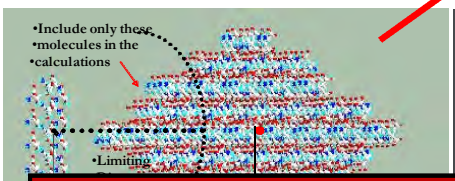
Predicted morphologies of α- & β - L glutamic acid with interacting faces highlighted

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

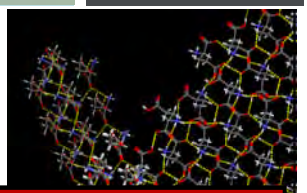




Experimental data (Ferrari & Davey, Cryst Growth Des 4 (2003) 1061)



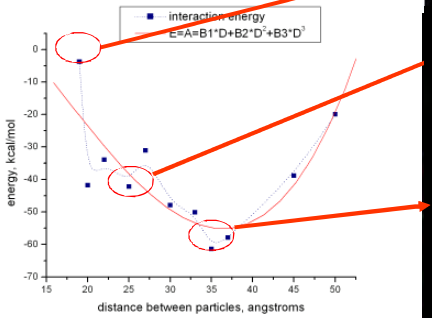
Inter-particle H-bonding revealed - route for design of optimal formulation of

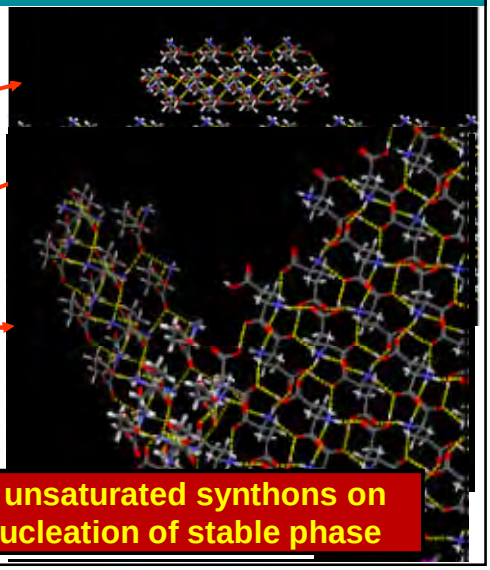


Molecular modelling correctly predicts structural nature of binding between particles (extrinsic hetero-synthons)

Energy Ranking of Inter-Particle Hydrogen Bonds Mediating α to β Transformation in LGA

Interfacial characterisation: key to understanding & controlling Inter-Particle Binding Strength

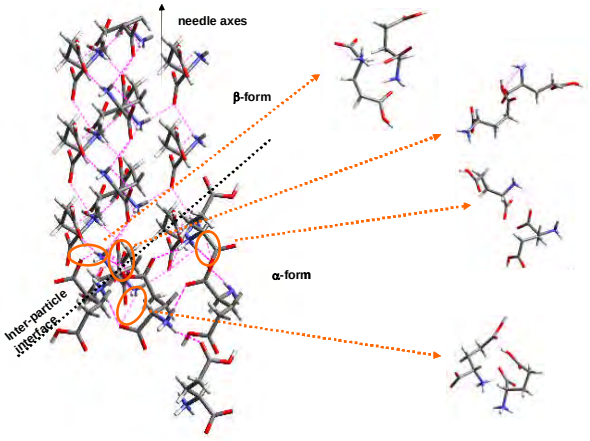




Examining structural interfacial

H-bonds associated with unsaturated synthons on (111) surface direct the nucleation of stable phase

Characterising Extrinsic Hetero-Synthons Associated with Inter-Particle Hydrogen Bonding



Details of interfacial hydrogen bond structure at interface between (111) face & (101) face

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

Can use synthonic analysis to reverse engineer this approach using to predict materials properties

Understanding Inter-Particle Nucleation Template Involved

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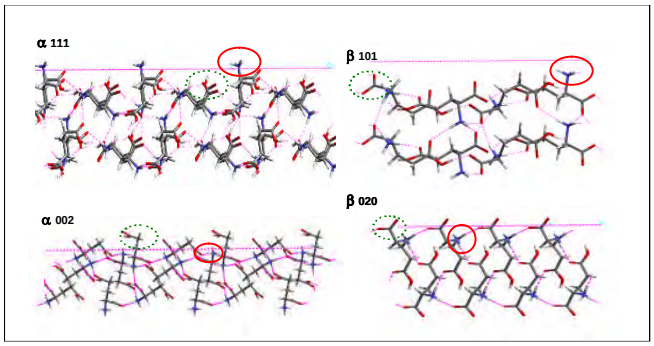
L-Glutamic acid: interfacial templating of β-form on crystal surfaces of α-form

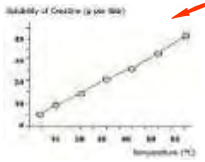


Examining surface chemistry of (111) α & (101) β interacting surfaces
- Amino group exposed on surface not involved in bulk hydrogen bonding & available

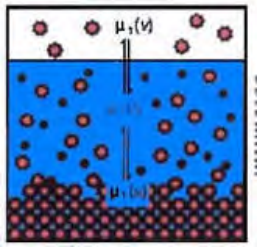
Generic feature: active sites for polymorphic transitions are minor but highly reactive fast growing faces

Solubility Enhancement from Crystal Size Reduction & Habit Modification

Poor solubility of a drug candidate is a major challenge for pharmaceutical scientists

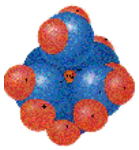


Temperature



$$\ln \frac{c(r)}{c^*} = \frac{2M\gamma}{\nu RT\rho r}$$

Gibbs-Thompson effect



Molecular nature of solute & solvent

Solubility enhanced when particle size (r) is reduced

Reliable data on solid/solution interfacial tension (γ) needed

Solubility Enhancement & Solvent Composition

Ethanol

Water

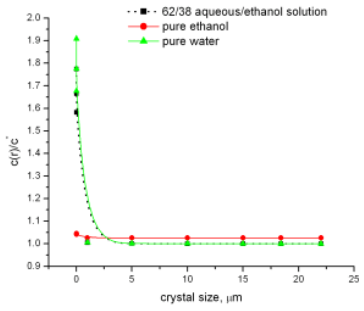
25.15 10^{-3} J/m² **47.20 10^{-3} J/m²**

Poor solubility

Solvent	38% ethanol	Pure ethanol	Pure water
Solubility, g/100ml	15.5	20	0.33

Solubility enhancement	38% ethanol	Water	Ethanol
0.01 µm	58%	67%	4.1%
0.1 µm	4.6%	5.3%	2.6%

Negligible enhancement > 5 µm size

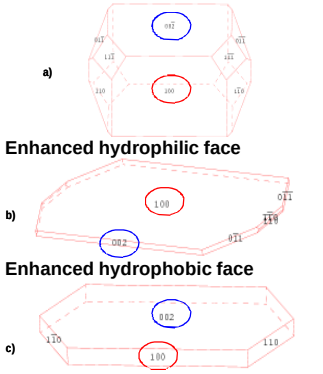


R B Hammond, K Pencheva, K J Roberts and T Auffret, Journal of Pharmaceutical Science 96 (2007) 1967-1973

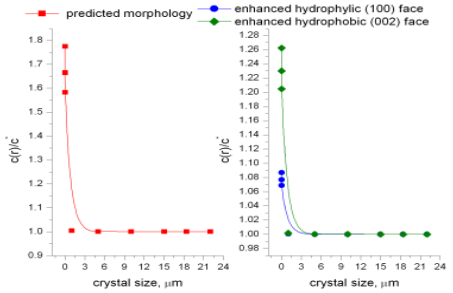
Solubility Enhancement & Crystal Morphology

Predicted Morphology

hydrophilic hydrophobic



$$\ln\frac{c(r)}{c^*}=\frac{2M\gamma}{\nu RT\rho r}$$

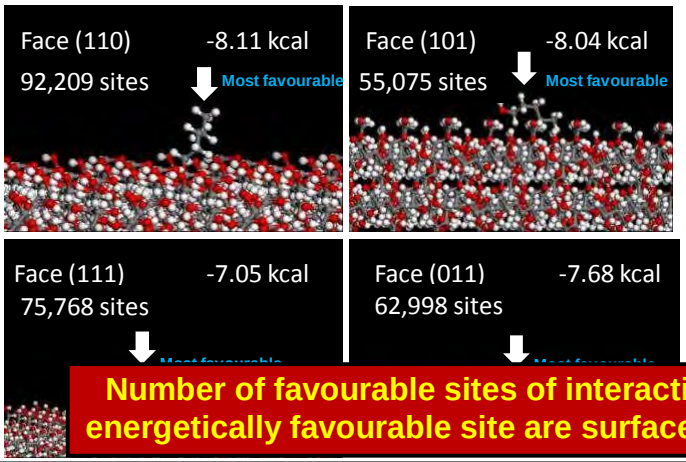


Size / µm	Enhancement hydrophilic	Enhancement hydrophobic
0.01	0.6%	66%
1	0.067%	0.2%

Negligible enhancement > 10 µm size

In-silico IGC Studies: 1-Pentanol on Mannitol Crystal Surfaces (EPSRC/GSK)

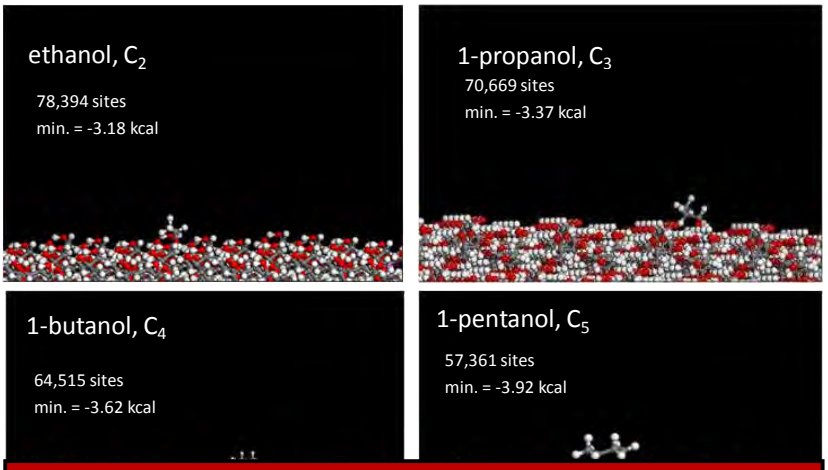
Objective: rationalise & understand chromatographic performance for probe / substrate combination in IGC



- Predict retention characteristics from number of favourable interaction sites
- Determination without recourse to actual experiment ('IGC in-silico')
- Resource saving for e.g. new APIs
- Test use "probes" which might not be practically convenient

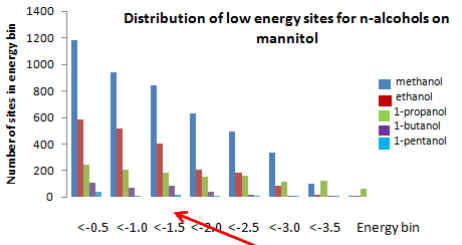
Number of favourable sites of interaction & most energetically favourable site are surface dependent

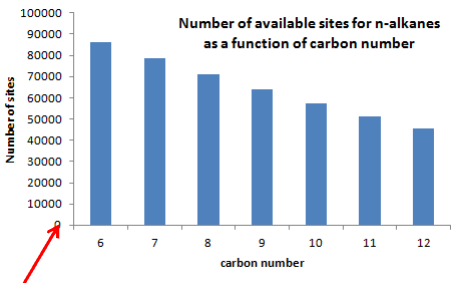
In-silico IGC Studies: Homologous Series of *n*-Alcohols on Xylitol (111) Surfaces (EPSRC/GSK)

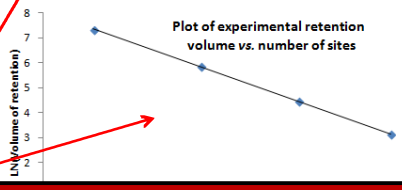


Binding energy increase & number of binding sites decrease with molecular weight of probe species

Comparison of SystSearch Modelling Predictions with Experimental IGC Data



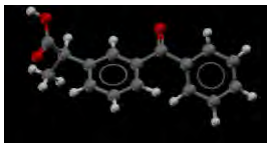




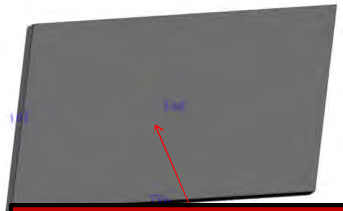
- Systematic grid based searching used to determine number of low energy sites available to a probe molecule, e.g. an *n*-alkane, alcohol, ketone etc.
- Used to establish relationship between number of sites & carbon number
- Note: linear relationship between Ln V_N (IGC retention volume) & Ln (number of

As probe molecular weight increases, number of binding sites decreases & retention time increases

API/Excipient Compatibility & Selection for Oral Formulation Development



Ketoprofen ($C_6H_{14}O_3$) is the chosen API



- Aerosil
- Avicel
- Corn starch
- β-D-glucose
- α-lactose monohydrate
- β- lactose
- Magnesium stearate
- d-mannitol
- Methocel
- Natrosol
- Palmitic acid
- PEG 6000
- PVPP

- Excipients used as probe systems
- 3 conformations of each excipient was considered for systematic search study
- Conformation with most stable energy is considered for comparison with other excipients

Aim: excipient selection based on ranking binding strength on ketoprofen crystal habit surfaces

Compatibility of Excipients on Ketoprofen from DSC Study*

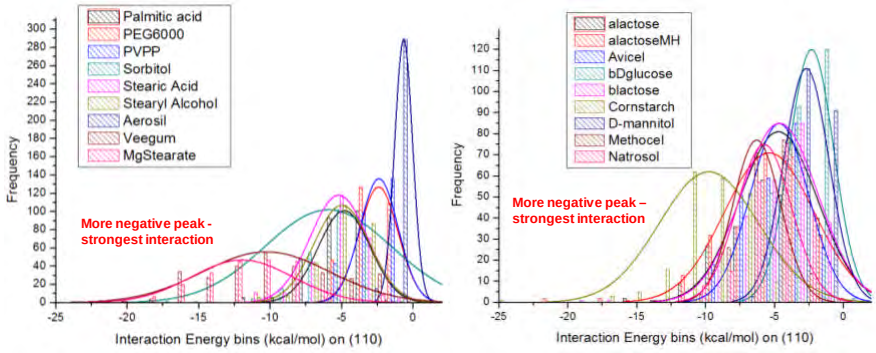
Table 1
Peak temperature and enthalpy values of ketoprofen after co-mixing with

Excipient	Peak temperature (°C)			
	Physical mixture	Ground mixture	Compressed mixture	Kneaded mixture
Corn starch	92.6	89.9	93.2	91.8
Arabic gum	90.9	87.7	87.1	87.3
Natrosol	91.4	89.4	90.3	89.4
Methocel	93.5	90.5	92.0	–
Avicel	92.8	90.4	92.0	92.3
Veegum	93.6	92.1	92.7	93.1
Aerosil	95.1	93.4	94.5	–
Lactose	95.7	93.3	95.3	95.6
Glucose	95.4	93.7	95.2	95.2
Mannitol	95.6	93.6	94.9	95.2
Sorbitol	94.8	93.3	93.8	93.1
PVP K30	–	–	–	–
PVPP	88.0	–	85.2	–
PEG 6000	–	–	–	–
Palmitic acid	85.3	84.3	84.6	84.6
Stearic acid	87.6	86.6	87.9	87.5

- Peak MP temperature of ketoprofen 95.8^0 C
- If mixture has peak temperature < 95.8^{0}C, excipient is compatible
- Table shows all excipients are compatible with ketoprofen
- Peak temperatures are very close & therefore difficult to rank compatibility of

Synthonic modelling provides an effective alternative method to DSC for ranking of API/excipient compatibility

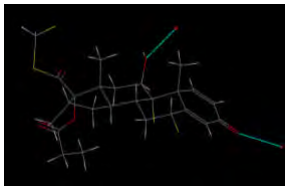
Modelling API/Excipient Compatibility: Ketoprofen



- Similar plots for (100) surface albeit interaction less than for fast growing (110) surfaces
- Conclusions are made from data on both surfaces

Magnesium stearate, veegum, corn starch, natrosol more compatible (stronger binding) than other excipients

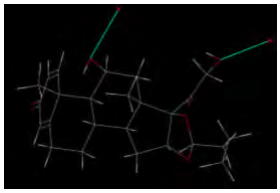
API/API Cohesivity Prediction for Inhalation Drug Delivery



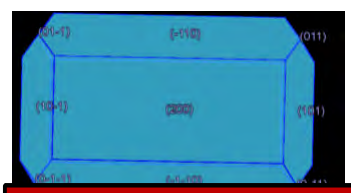
Fluticasone Propionate (FP) ($C_{25}H_{31}F_3O_5S$) used as probe API

Physical interactions between API particles impact on:

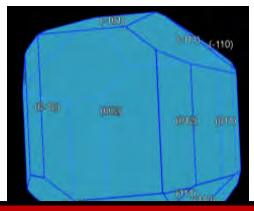
- Powder cohesivity
- Ease of de-agglomeration
- Pre-formulation model to assess drug dispersibility



Budesonide (BUD) ($C_{25}H_{34}O_6$) used as probe API



From predicted morphology, (200), (110) , (101) & (011) surfaces selected



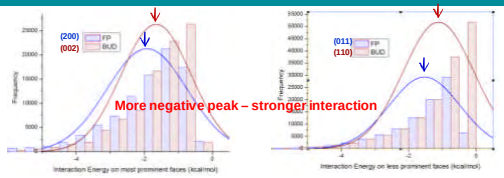
From predicted morphology, (002),

Aim to characterise inter-particle interactions & optimize agglomerate strength versus ease of disintegration

BUD on BUD vs FP on FP – Analysis of Average & Distribution of Cohesive Interaction Energy

FP on FP		BUD on BUD	
Faces	Minimum Energy (kcal/mol)	Faces	Minimum Energy (kcal/mol)
(2 0 0)	-12.960	(0 0 2)	-8.693
(1 1 0)	-9.263	(1 0 1)	-10.747
(1 0 1)	-13.224	(0 1 1)	-9.268
(0 1 1)	-10.605	(1 1 0)	-11.111
Average (over 4 faces)	**-11.513**		**-9.955**

More negative – stronger interaction



Mode of interaction energy from distribution of interaction energy: on slower growing surfaces (left) & faster growing surfaces (right) show FP agglomerates strongly than BUD

"…….from low to high cohesivity as follows: SB **< Bud** = LH300 < BDP < **FP** = Tof < SX'.

The linearity (R^2), primary pressure for 50% de-agglomeration (DA_{50}), maximum degree of de-agglomeration (DA_{max}) and critical primary pressure (CPP) of the powders deduced from dry dispersion laser diffraction.

Powder	R^2	DA_{50} (Bar)	DA_{max}	CPP (Bar)
BDP	0.9990	0.44	1.11	2.5
Bud	0.9995	0.32	1.08	2.0
FP	0.9049	1.15	1.13	3.0[a]
LH300	0.9997	0.23	1.06	2.0

FP's higher cohesivity evident from average energy & distribution on faster as well as slower growing surfaces

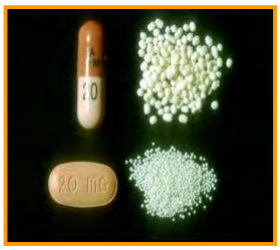
Direct Compression as Default Option in Formulation Route Selection

- **3 options**
  - ❑ **Wet granulation (5 step)**
  - ❑ **Dry granulation (4 step)**
  - ❑ **Direct compression (2 step)**
- **Route selection approach varies from company to company being based on**
  - ❑ **Physical & chemical properties of API**
  - ❑ **Potency of drug determining its concentration in formulation**
  - ❑ **Cost (HR, production materials, capital assets, R&D/validation)**
  - ❑ **Timescale, i.e. throughput which influences ROI & profitability**
- **Simplicity & economy, i.e. fewer unit operations**

Flowability	Compressability	
	High	Low
High	Direct compression	Wet granulation
Low	Dry granulation	Wet granulation

Requirements: solid form selection process providing drug candidates with high flowability & compressibility

Mechanical Deformation of Pharmaceutical Crystals: Key Concepts for Direct Compression



- Highly anisotropic molecular & crystallographic structures
  - ❑ Complex molecular shape
  - ❑ Reduced symmetry crystal structures
- Weak intermolecular forces giving rise to
  - ❑ Low elastic moduli , hence soft materials
- Slip planes for plastic deformation
  - ❑ Characterised by low surface energy & rugosity
- Plastic deformation restricted by
  - ❑ Low multiplicity of slip planes & Burgers' vector
  - ❑ Limited combinations of these to create active slip systems
- Fracture behaviour depends on balance between

Potential: selecting solid forms with good mechanical properties for formulation by direct compression

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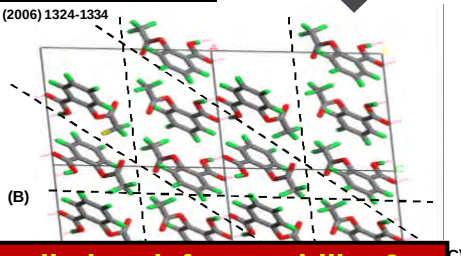
Crystallographic Analysis of Potential Slip Systems in Aspirin

(hkl)	Surface* Energy mJ/mm²	Slip Plane Rugosity	Interlocking of Slip Planes?	Slip system with b= [010]	Slip involving hydrogen bond breaking	Surface Cleavage Likely?	Plastic Deformation Likely?
(100)	-0.0829	Very low	N	Y	N	Y	Y
(001)	-0.0904	low	N	Y	N	Y	Y
(011)	-0.1550	high	Y	N	Y	N	N
(110)	-0.1430	high	Y	N	Y	N	N
(101)	N/A	low	N	Y	Y	N	Possible

Analysis of key structural factors related to likely slip due to (plastic) mechanical deformation

* R B Hammond, K Pencheva & K J Roberts, Crystal Growth & Design 6 (2006) 1324-1334

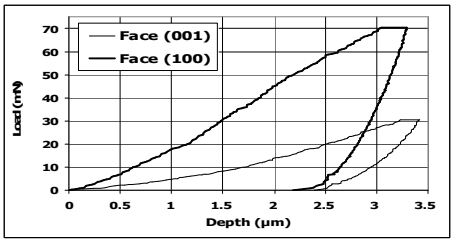
- (001) projection showing comparatively easy slip possibilities on (100) (A) crystal planes & less so at (001) (B).
- Note slip on (101) (C) would involve breaking dimer hydrogen bonds.
- Red & green parts of molecule represent

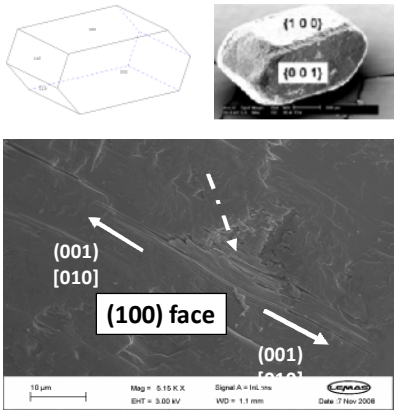


Solid form selection tool - predicting deformatability & enabling direct compression as default formulation route

DS

Nano-Indentation Studies on Surfaces of Aspirin (100) & (001) Surfaces: Load vs Depth Data





- Load-displacement curves (above) from indentation on Aspirin (001) & (100).
  - ❑ These carried out at loading rates of 5 mN/s & at similar depths.
  - ❑ 'Pop-ins' due to plastic deformation can be observed on both curves.

Nano-indent on (100) face revealing

Nano-indentation studies consistent with prediction of dominant [010](001) Slip System for Aspirin

Precision 6σ Quality Pharmaceutical Ingredients & Formulated Products

- Developing & manufacturing to specification will always carry concomitant risk of failure
  - ❑ Better to "raise the bar" & process to highest (economically feasible) ingredient & product quality
- Pharmaceutical industry should take opportunity to lead field in
  - ❑ Design (QbD with digital definition)
  - ❑ Supply (advanced manufacture)

  of precision 6σ quality ingredients (APIs & excipients) & formulated products
- Pharmaceutical ingredients would be
  - ❑ Prepared through (greener) reactions & physical processes
    - Much better designed, understood & controlled

Advantages of Precision 6σ Quality Pharmaceuticals

- Pharmaceutical ingredients would also be
  - ❑ Assembled, purified & formulated producing
    - Precision drug products of ultra-high purity & ultra-low variability
- Resulting precision designed drug ingredients & formulated products will have
  - ❑ Lower cost basis & environmental burden
    - Hence be much more competitive
  - ❑ Improved long term stability
    - Enabling much longer shelf life & streamline supply chains
  - ❑ Better pharmacological response
    - Enabling drug delivery at much lower doses

Overall - Safer Medicines Faster!

I'm Just Presenting: So Who Did The Work Then?

I would like to gratefully acknowledge

- Numerous researchers in Institutes of Particle Science Engineering & Process R&D at University of Leeds & its associated industrial & academic collaborators
- National & industrial funding bodies & collaborators
  - ❑ DTI, EPSRC, TSB
  - ❑ AEA, AstraZeneca, BASF, Bede, Boehringer-Ingelheim, BNFL, CCDC, Clairet, GSK, HEL, ICI, Infineum, Malvern Instruments, Novartis, Pfizer, Pliva, Sanofi, Syngenta & Unilever
- Colleagues involved in synthonic engineering research projects overviewed here, notably:
  - ❑ Syarifah Ab Rahmin, Graham Clydesdale, Jason Cole (CCDC), Bob Docherty (Pfizer), Yulong Ding, Neil George (Syngenta), Mojtaba Ghadiri, Robert Hammond, Ken Lewtas (Infineum), Ivan Marziano (Pfizer), Lee Mason, Paul Meenan (Pfizer), David Merriefield, Patricia Mougin, Thai Nguyen, Dolapo Olusanmi, Klimentina Pencheva (Pfizer), Jonathan Pickering, Elna Pidcock (CCDC), Vasuki Ramachandran & Majeed Soufian

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Closing Remarks & Thanks

In this talk, I have tried to…

- **Highlight opportunities of pharmaceutical industry's QbD agenda**
  - ❑ **Particularly in particle formation & formulation**
- **Stress value of molecular-scale (synthonic) tools in process R&D**
  - ❑ **Focussing on those needed for development of precision pharmaceutical ingredients & products**
  - ❑ **Highlighting this through a number of case studies at the API/DP interface**
- **Drawn attention to opportunities provided through a greater focus on product quality rather than simply cost**
  - ❑ **Highlighting potential opportunities resulting from development of 6σ processes, products & culture**

Once again, many thanks to RSC's Formulation Science &Technology Group for the invitation & also to you for your kind attention

I will be happy to attempt to answer questions!