ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Crystal Growth and Morphology of RS-Ibuprofen in Terms of its Intermolecular Synthons

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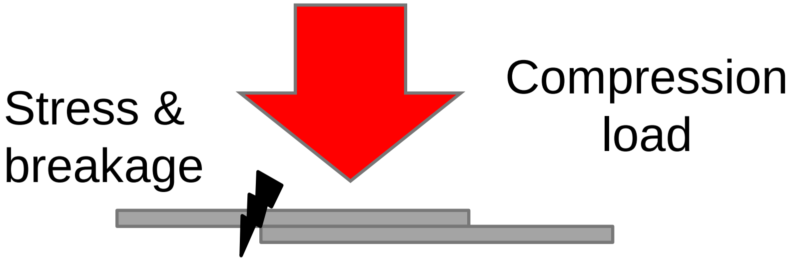
Context

The crystallisation of organic materials with anisotropic structures can result in a variety of anisotropic crystalline morphologies

Needle crystals are often the least desirable due to challenges associated with processing such crystal morphologies

- They often present undesirable physical properties when exposed to unit processes associated with pharmaceutical and fine chemical manufacture



- Can often be difficult to filter and they can block pipes
- The highly anisotropic shape can result in anisotropic dissolution profiles due to the difference in dissolution rates of the faces

Aims and Objectives

Aim

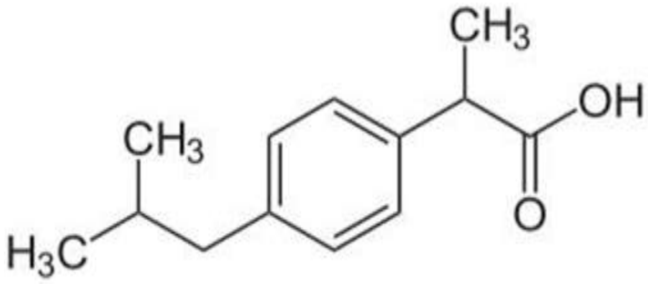
To understand the crystal growth, morphology and interfacial stability of the active pharmaceutical ingredient RS-ibuprofen in terms of it's intermolecular synthonic structure, surface chemistry and crystallisation solvent

Objectives

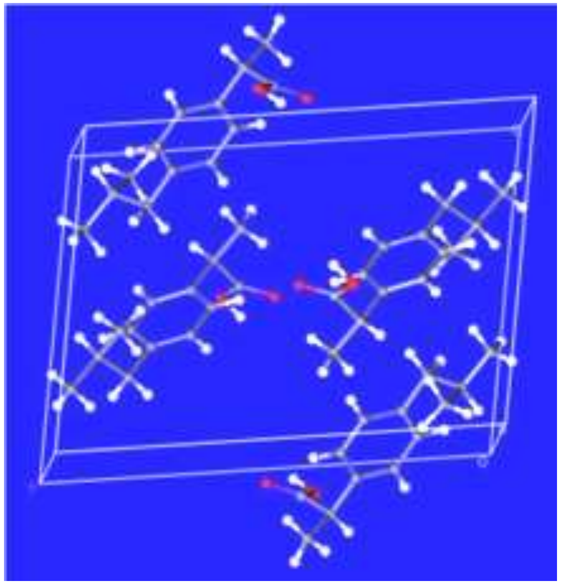
- Characterise the experimental crystal morphologies of RS-ibuprofen observed in solution
- Utilise molecular modelling to describe the intermolecular synthons in the bulk (intrinsic) and surface (extrinsic) of the material
- Rationalise the experimental morphology in terms of extrinsic synthons and solvent/surface interactions
- Characterise the interfacial stability of the material and relate to the crystal surfaces observed as a function of solvent and supersaturation

RS-Ibuprofen

The ibuprofen molecule contains a carboxylic acid group at one end and an aliphatic chain at the other, split by a phenyl ring



- Monoclinic crystal structure with a $P2_1/C$ space group
- Tetramolecular centrosymmetric unit cell



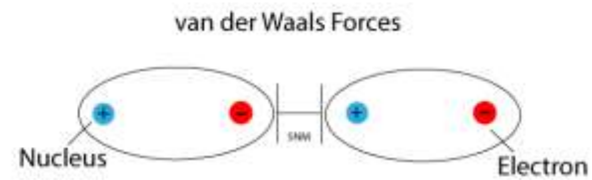
Ref Code	Space Group	A (Å)	B (Å)	C (Å)	β (°)
IBPRAC	$P2_1/C$	14.68	7.89	10.73	99.36

Calculating Intermolecular Force (Synthon) Strength

The forces can be calculated using potentials (forcefields) that calculate the attractive and repulsive forces between the atoms as a function of distance

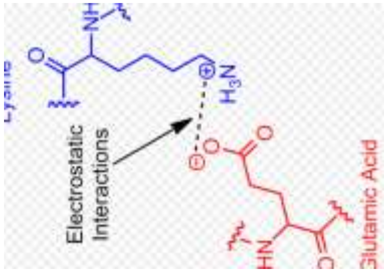
vdW

$$U_{NB}(r_{ij}) = \sum_{i=1}^{n}{}' \sum_{j=1}^{M}{}' \left({A^{k1}}/{r_{ij}}^{12} - {C^{k1}}/{r_{ij}}^{6} \right)$$



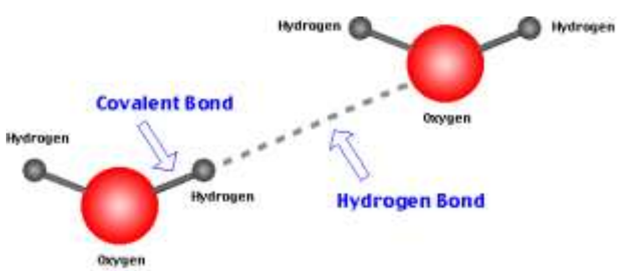
Coulombic

$$U_{e1}\,(r_{ij}) = \sum_{i=1}^{n} \sum_{j=1}^{M} {332.0qiqj}/{Dr_{ij}}$$

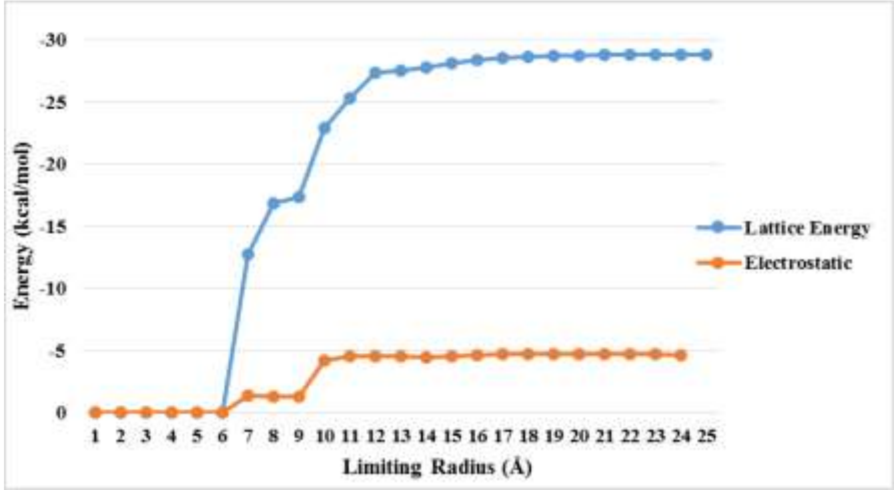


H-bonds

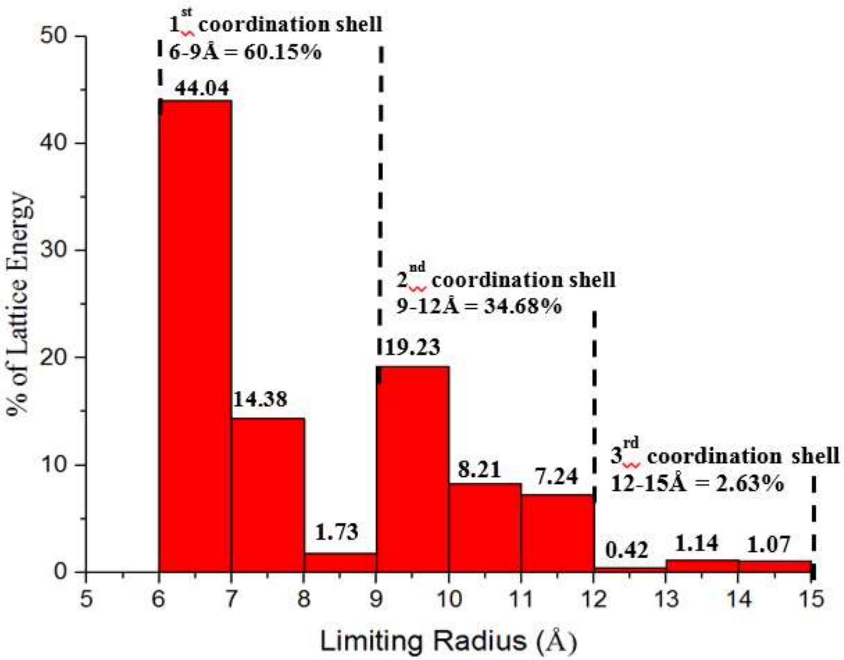
$$U_{GHB}(r_{H\ldots X}) = \sum_{i=1}^{n} \sum_{j-1}^{M} \left(A_{H\ldots X}/r_{H\ldots X}^{12} - B_{H\ldots X}/r_{H\ldots X}^{10} \right)$$



Lattice Energy Calculation

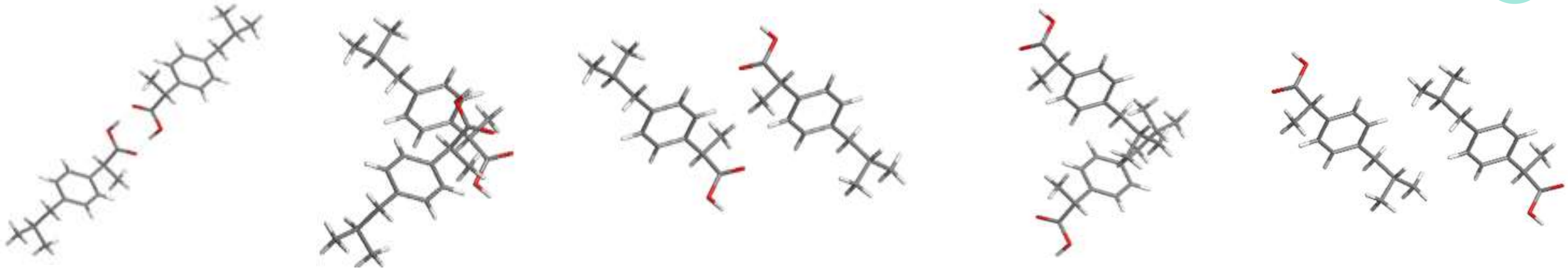


- Lattice energy was calculated as a function of distance from the central asymmetric unit using the Dreiding forcefield
- Electrostatic contribution to lattice energy relatively low
- Probably due to the COOH group being the only polar group capable of forming strong electrostatic interactions



- Over 60% of the lattice energy found within the nearest neighbours of the central asymmetric unit (6-9Å)
- Short range nature of interactions results in approximately 95% of the lattice energy converging by 12Å

Strongest Synthons



(A) (B) (C) (D) (E)

Synthon	Multiplicity	Interaction Energy (kcal/mol)	% Contribution to the Lattice Energy	Type of interaction		Nature of functional group involved		
				vdW + H-Bond %	Coul %	Aliphatic %	Phenyl %	COOH %
A	1	-5.2	18.1	44.0	56.1	4.7	0.5	94.8
B	2	-2.8	19.5	89.4	10.6	46.0	38.7	15.1
C	2	-2.4	16.8	99.6	0.4	63.1	34.7	2.1
D	1	-2.2	7.7	65.9	34.1	38.4	42.44	19.2
E	1	-1.5	5.1	97.3	2.7	46.7	48.5	4.8

- Strongest synthon comprised of OH…O H-bonds between adjacent COOH groups (A)
- Rest of the interactions dominated by vdW interactions between apolar groups
- No obvious close stacking of phenyl rings, probably precluded by molecular conformation
- Energy of synthon A dominated by COOH group
- Rest of strong synthons energies dominated by phenyl and aliphatic groups

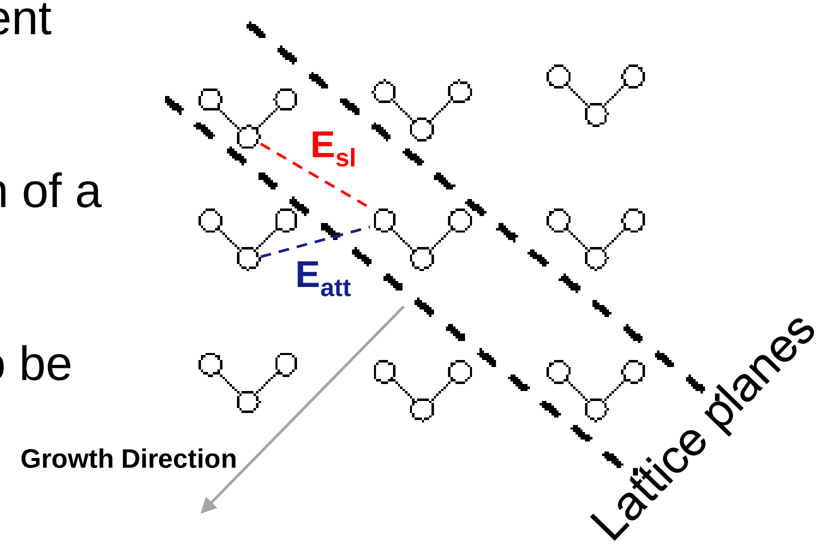
Crystal Morphology Prediction: Attachment Energy

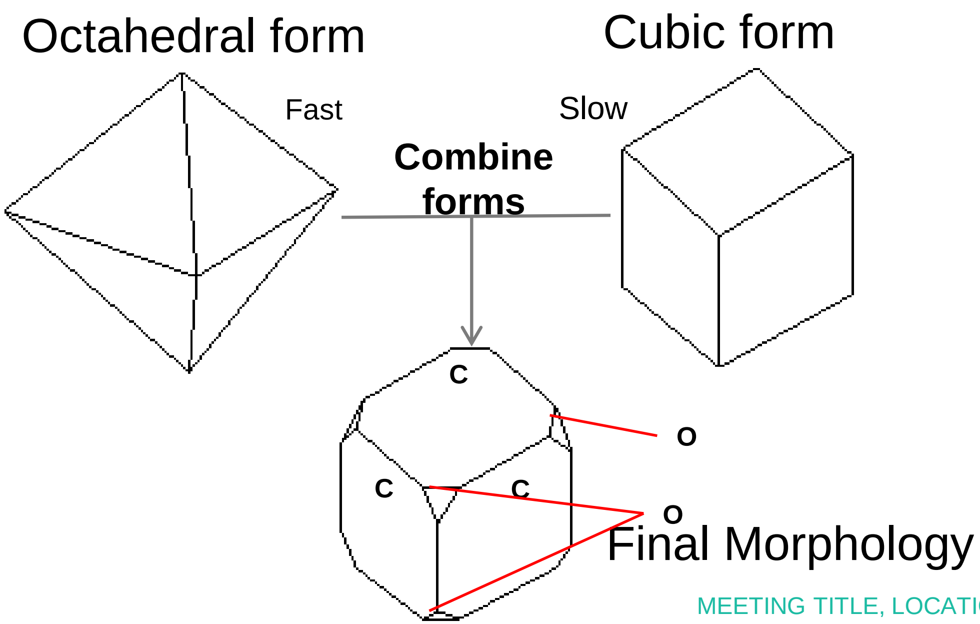
- Lattice energy split into slice and attachment energy

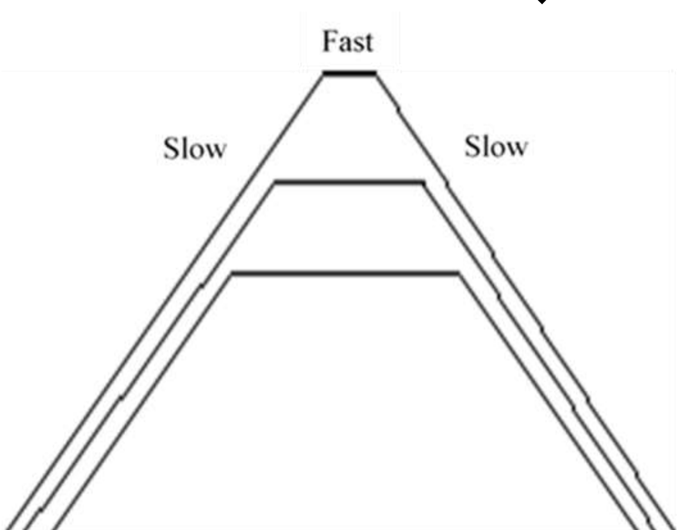
$$E_{cr} = E_{sl} + E_{att}$$

- Attachment energy released upon addition of a slice of molecules d_{hkl} thickness in a crystallographic direction
- Growth in that direction is approximated to be proportional to attachment energy

$$R_{hkl} \propto E_{att}$$

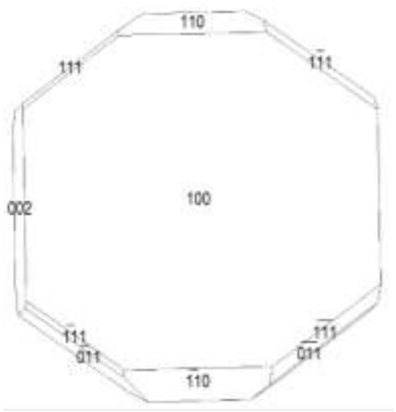




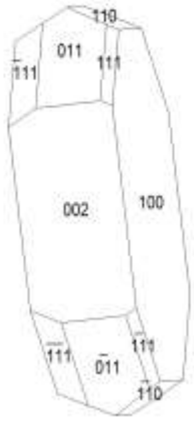


Crystal Morphology Prediction: Attachment Energy

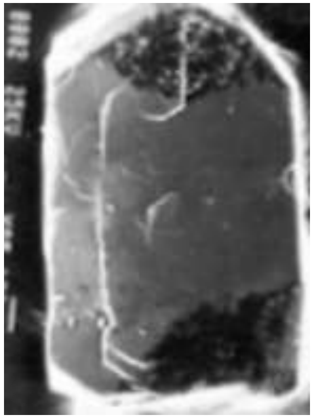
The crystal morphology of ibuprofen was predicted using the attachment energy theory assuming a monomer growth unit



(a)



(b)

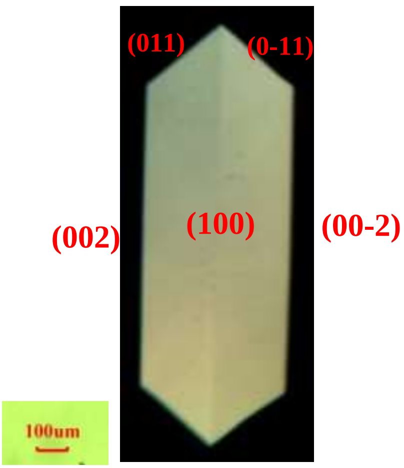


(c)

- Attachment energy morphology prediction gives good match to general shape of vapour grown morphology
- (100) predicted to dominate morphology, along with smaller side (002) faces and fastest growing (011) faces, in good agreement with experimental data

Crystal Morphology in Solution

Ibuprofen was grown from ethanol, ethyl acetate, acetonitrile and toluene at varying supersaturation



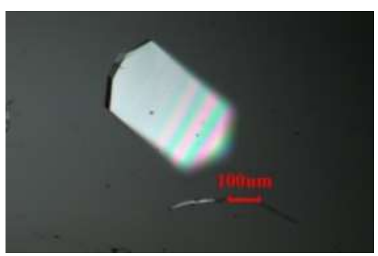
EtOH

Ethyl acetate

Acetonitrile

Toluene

- Solution grown morphology in general more needle-like than attachment energy predicted morphology
- Morphology from ethanol much less needle like than the crystal morphology produced from other solvents
- Must morphologies appear to contain the (100), (002) and (011) faces predicted

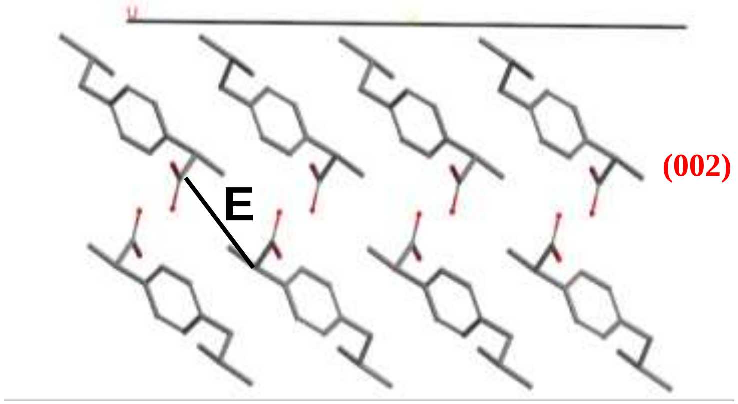


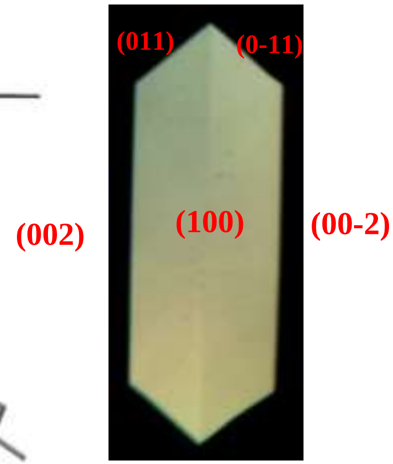
EtOH

- Crystals observed from ethanol are very thin
- Suggesting that the (100) face grows very slowly

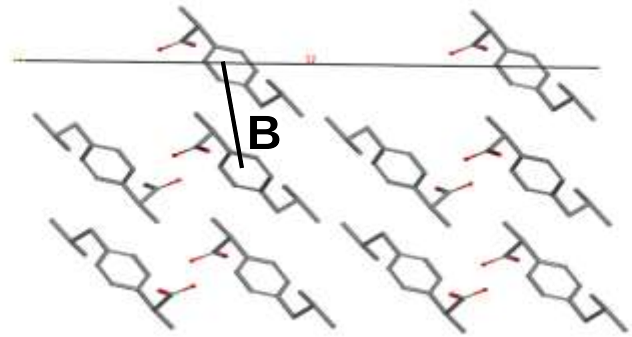
Surface Chemistry of Ibuprofen

(100)

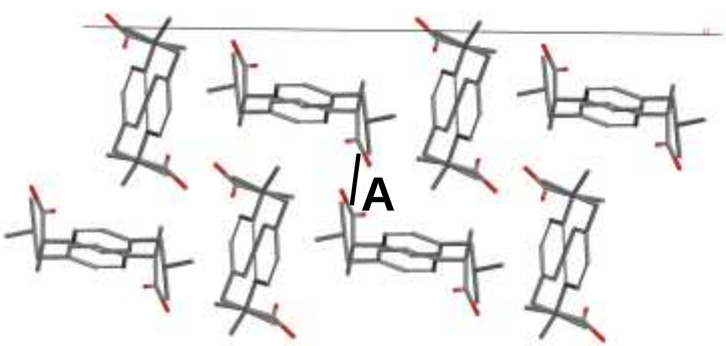




(002)



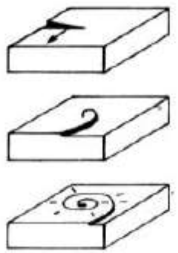
(011)



- (100) face has the weakest interactions at the surface, hence slowest growing and dominant surface
- (002) extrinsic synthons dominated by vdW interactions
- Capping (011) surface dominated by hydrogen bonding interactions

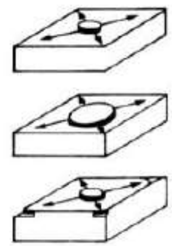
Growth Interface Stability and Mechanism

The crystal growth mechanism is thought to greatly influence the growth rate of a surface[1]



BCF: The incorporation of growth units onto the stepped surface provided by protrusion of dislocations leads to the formation of a growth spiral over the crystal surface creating a permanent source of growth steps at the crystal surface.

$$R_{hkl} = A\sigma^2 tanh\left(\frac{B}{\sigma}\right)$$



B & S: In the absence of steps surfaces develop through the nucleation (birth) and growth (spread) a monolayer. After nucleation, further molecules can absorb and integrate into the existing monolayer thus enabling it to spread over the surface followed, in turn, by further 2D nucleation events when the surface layer has fully spread over the surface.

$$R_{hkl} = A_1\sigma^{5/6}exp\left(\frac{A_2}{\sigma}\right)$$

RIG: At high supersaturation, the growth interface undergoes surface roughening providing through this abundant sites for surface integration with a lot more step and kink sites thus resulting in a much higher growth rate.

$$R_{hkl} = A\sigma$$

1. Bourne and Davey, J.Cryst Growth, 1976, 36, 278-286

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Surface Entropic α-Factors

The surface entropic α-factors can be used to predict how rough a surface may be[1,2]

Enthalpy of fusion

$$\alpha = \xi\left(\frac{\Delta H_f}{RT} - \ln X_{seq}\right)$$

Anisotropy factor

Equilibrium mole fraction of solute

	Predicted growth mechanism
$\alpha < 2$	The interface is rough so all growth units can incorporate onto the growing surface (continuous growth).
$2 < \alpha < 5$	The interface is smoother and the most probable mode of growth is B&S
$\alpha > 5$	The surface becomes very smooth and growth generally proceeds by screw dislocation (BCF).

1. K.A Jackson, Mechanism of Growth in Solidification of Metals, 1958
2. Bourne and Davey, J.Cryst Growth, 1976, 36, 278-286

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Interfacial Stability of Morphologically Important Surfaces

The interfacial roughness of the morphological important surfaces can be measured by α-factor calculations

	Face specific α-factors between 15°C-35°C			
Face	**Ethanol**	**Ethyl acetate**	**Acetonitrile**	**Toluene**
{100}	9.4 – 10.6	9.3-10.4	10.3 – 12.1	9.3-10.5
{002}	5.0-5.5	4.8-5.4	5.3-6.2	4.8-5.4
{011}	4.6-5.0	4.4-4.9	4.8 – 5.7	4.4-4.9

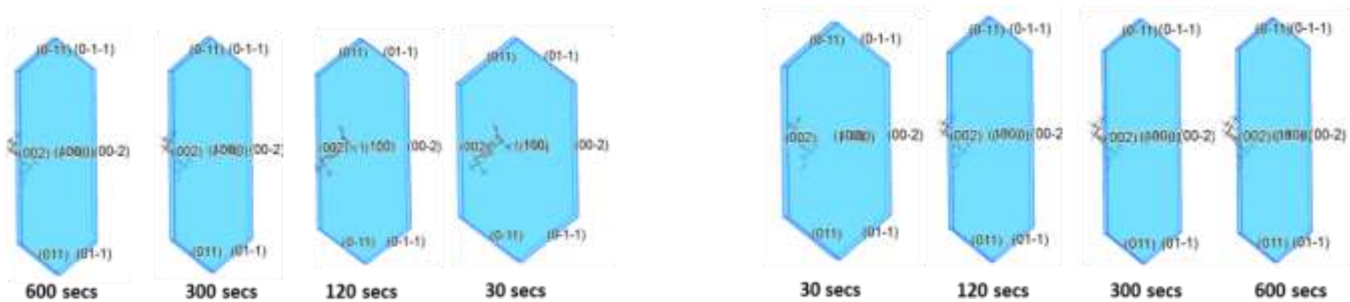
- The capping (011) surfaces have the lowest α-factors
- Suggests greater interfacial roughening on the molecular level
- Hence greater instability at the capping faces compared to (002) and (100) faces

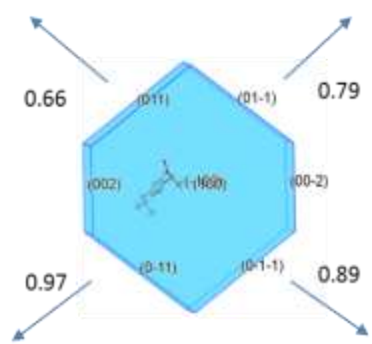
	{011}		**{002}**	
Solvent	**Predicted Growth Mechanism from α-factors**	**Experimentally Measured Growth Mechanism**[2]	**Predicted Growth Mechanism from α-factors**	**Experimentally Measured Growth Mechanism**[2]
Acetonitrile	BCF or B&S	B&S	BCF	B&S
Ethanol	B&S	BCF/B&S	BCF or B&S	BCF/B&S
Ethyl Acetate	B&S	B&S	BCF or B&S	B&S
Toluene	B&S	B&S	BCF or B&S	B&S

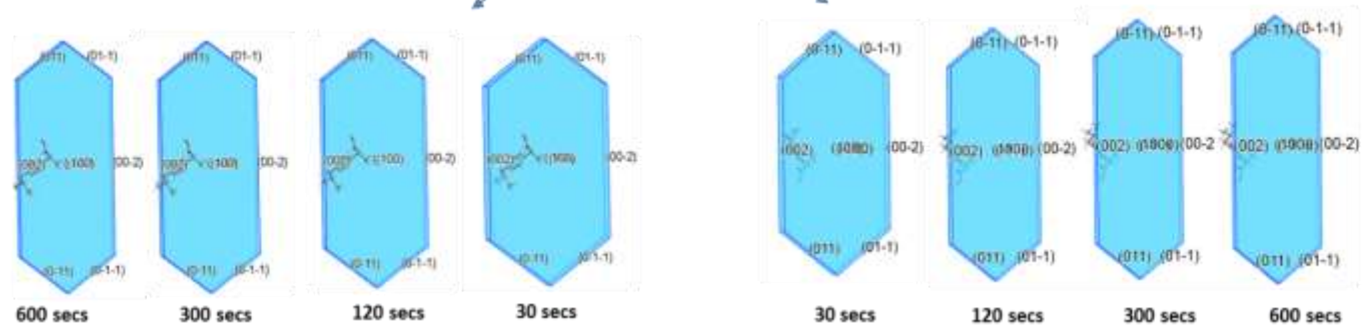
α-factor predicted growth mechanisms in good agreement with experimental work

Morphological Development of Ibuprofen in Ethanol

Using the measured growth rates[1], an estimation of the morphological development over time of ibuprofen in ethanol was derived



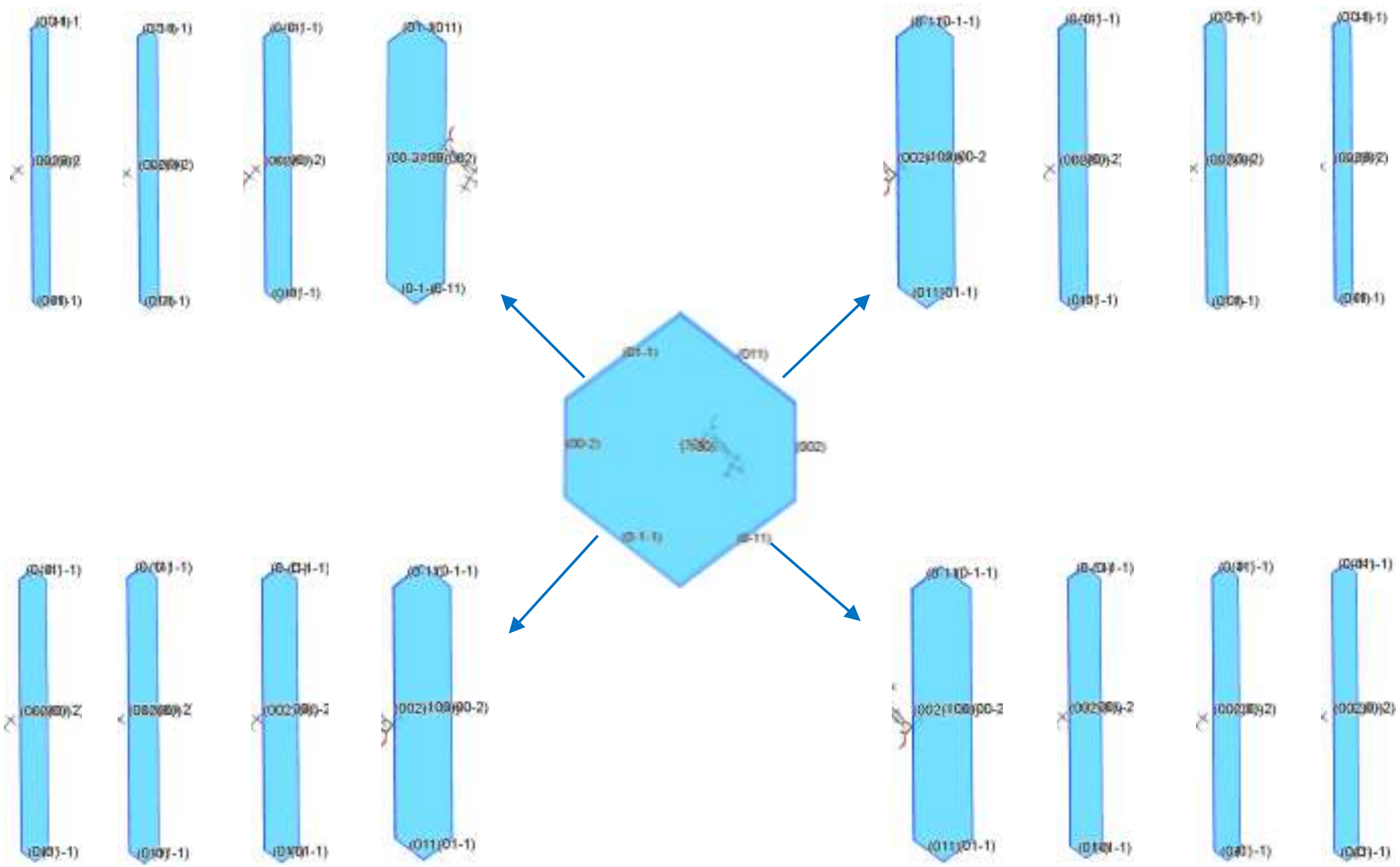




- Morphology remains relatively plate-like even at enhanced supersaturations
- Side and capping faces have similar growth mechanisms

Morphological Development of Ibuprofen in Toluene

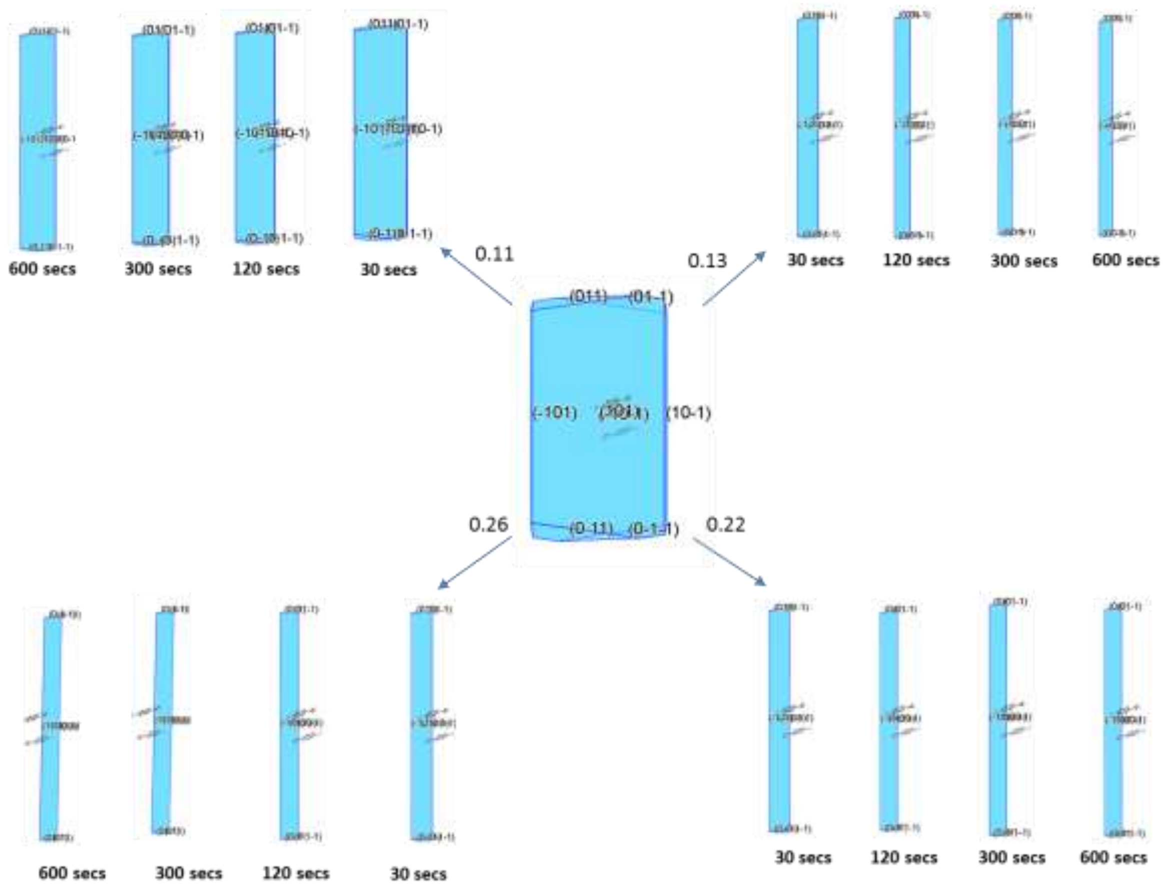
Measured growth rates in toluene were also used to show morphological development



- Crystals quickly become much more needle like compared to ethanol
- Low growth rate of side (002) surface

Comparison to α-*p*ABA

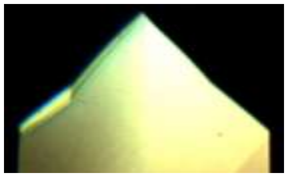
The capping face of α-*p*ABA was found to have a rough interfacial growth mechanism at the capping (01-1) face, and a birth and spread mechanism at the side (002) face



- Crystal morphology rapidly becomes much more needle-like, even at much lower supersaturations
- Instability of capping face, compared to side face results in much faster growth
- Ibuprofen crystals in ethanol show much more stable growth and less needle-like morphologies

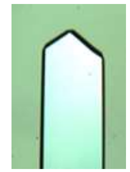
Re-Entrant Facet

An extra re-entrant facet appeared between the (011) and (01-1) facets in all solvents examined



EtOH

ACN



EtOAc

Toluene

Re-entrant face dependent on supersaturation and the critical supersaturation derived for each solvent

	Ethanol	Ethyl acetate	Acetonitrile	Toluene
Critical supersaturation σ	0.66	0.69	> 0.79	> 0.79

EtOH $\sigma = 0.66$ $\sigma = 0.79$ $\sigma = 0.97$

Enhanced supersaturation resulting in increased flux of growth units to the surface, resulting in enhanced roughening and re-entrant morphological instability

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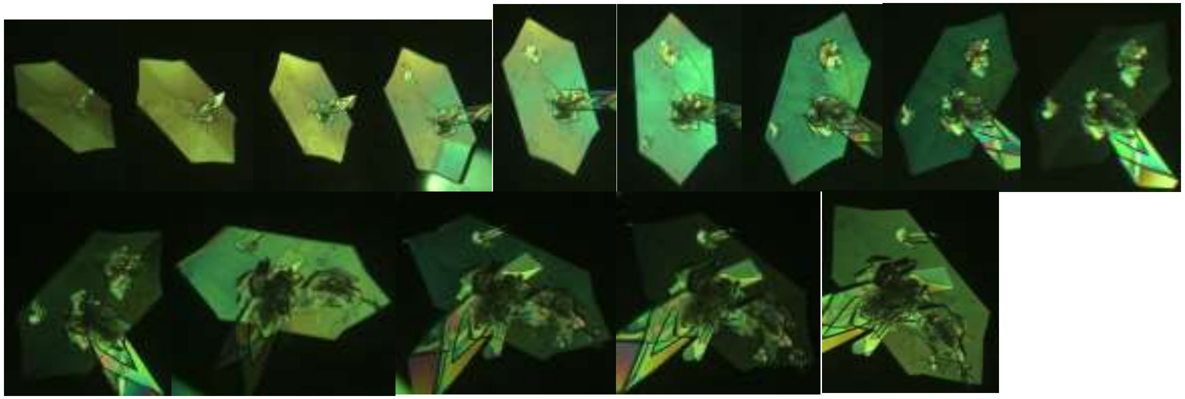
Re-Entrant Facet



Polarised microscopy confirmed that re-entrant facet not due to twinning

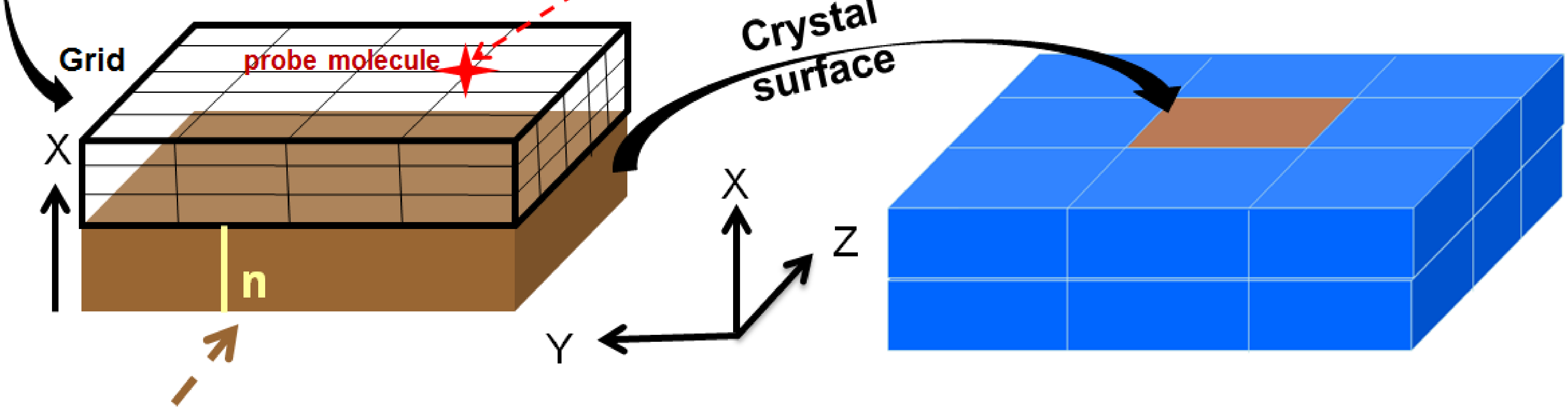
Though a relatively rare observation, a re-entrant facet is not forbidden by morphological theory[1,2]

Face	Anisotropy Factor (ζ)	Ethanol	Ethyl Acetate	Acetonitrile	Toluene
(012)	26.4	3.1-3.3	2.9-3.3	3.2-3.8	2.9-3.3
(112)	30.6	3.5-3.9	3.4-3.8	3.8-4.4	3.4-3.8

Re-entrant facet provisionally identified as (012) or (112). Both have low α-factors suggesting high degree of interfacial roughening and hence morphological instability

Systematic Search of Crystal Faces

- 3 dimensional grid near surface under study
- One probe molecule (red star) explores every grid point on a reticular area



- Volume of crystal considered for simulation is defined in input
- Slice thickness (n) is multiple of d_{hkl}

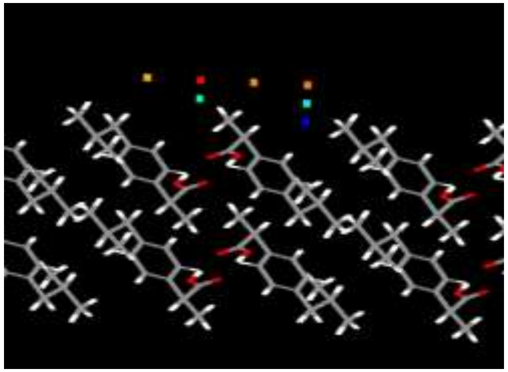
- It is oriented in three degrees of rotation (θ, γ, δ)
- For every set of X, Y, Z, θ, γ, δ, interaction energy of probe molecule is calculated

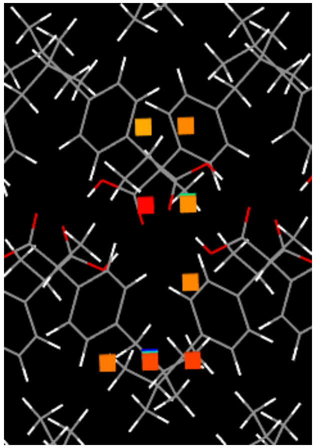
- Surface embedded in a 3 x 3 x 2 matrix to overcome edge effects on simulation

SystSearch of Capping and Side Faces of Ibuprofen

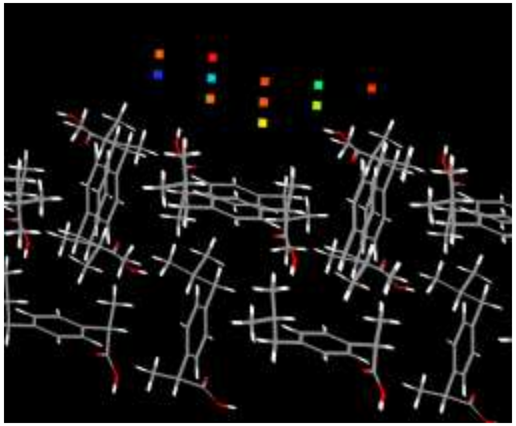
Capping (01-1) and side (002) faces were searched with ethanol and toluene

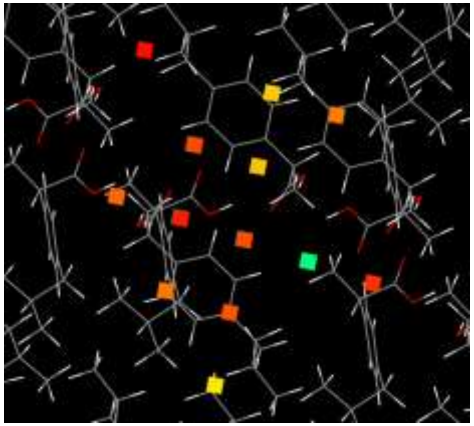
EtOH **(002)**





(011)

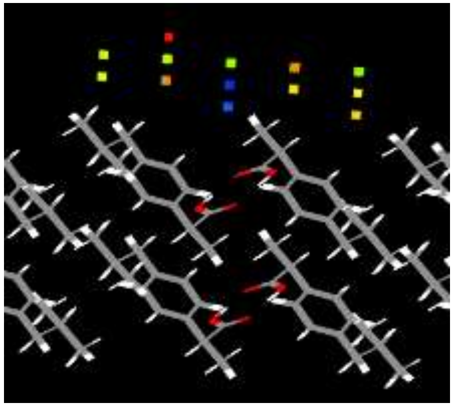


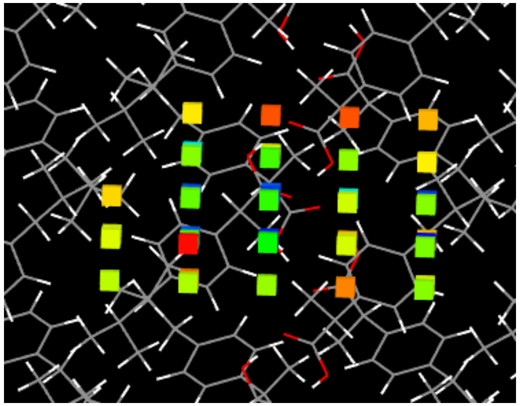


- Cubes represent grid points that pass the -2kcal/mol threshold
- Blue strongest interactions, red weakest
- Ethanol seems to more strongly interact with the capping (011) surface in comparison to side (002) surface

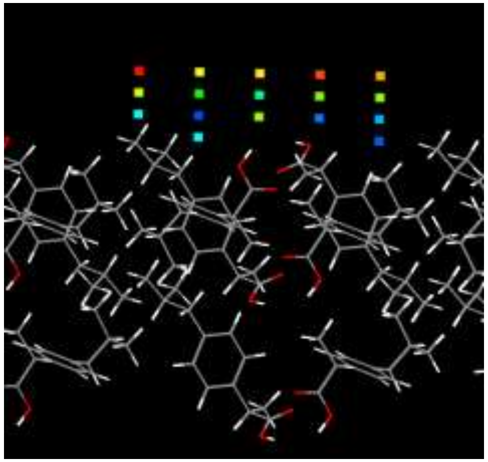
SystSearch of Capping and Side Faces of Ibuprofen

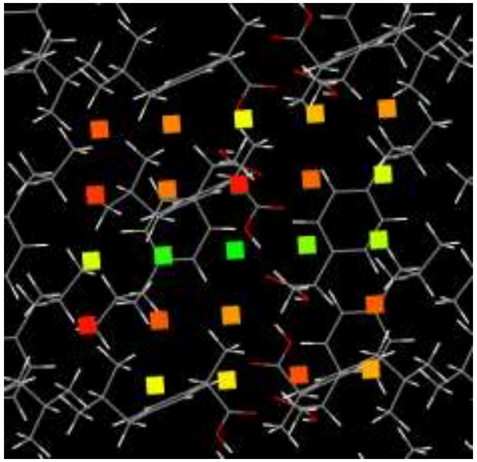
Toluene (002)





(011)





- Toluene found to interact well with both faces
- Suggests that it solvates both faces relatively equally

Interaction Energies of EtOH and Toluene

The interactions found at each surface were binned per 1kcal and the average energies of each bin calculated for EtOH and Toluene

Energy cut-off (kCal/mol)	Ethanol			Toluene		
	{011}	{100}	{002}	{011}	{100}	{002}
-2	-2.61	-2.13	-2.10	-2.45	-2.52	-2.47
-3	-3.91			-3.39	-3.16	-3.44
-4	-4.86			-4.15	-4.24	-4.04
-5	-5.40					
-6	-6.26					

- No interactions of EtOH with (002) or (100) surfaces stronger than -3kcal/mol
- Interactions of EtOH with (011) surface go up to > 6kcal/mol
- Toluene interactions with the three faces relatively equal

These results suggest that the strong solvation of the (011) face and poor solvation of the (002) face from EtOH results in the more equant morphology in EtOH, in comparison to toluene

EtOH

Toluene

Conclusions

- Majority of the lattice energy of ibuprofen consistent with the energy being released from the nearest neighbour interactions
- Strongest interaction within the crystal structure are the OH…O H-bonding dimers
- These OH…O H-bonds also dominated the growth of the (011) surface along the long axis of the needle
- Side (002) and top (100) surfaces dominated by weaker vdW interactions
- α-factor predicted growth mechanisms in good agreement with experimental data
- Capping faces predicted to have the greater interfacial roughening at the molecular level
- Rare observation of re-entrant face at enhanced supersaturations, probably influenced by the interfacial roughening at this surface
- H-bonding solvent EtOH calculated to strongly interact with the (011) capping surface and weakly interact with the side (002) surface
- Non H-bonding solvent toluene calculated to interact relatively equally with all surfaces
- Suggests that EtOH inhibits the growth of the capping face of ibuprofen and results in more equant morphology