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IFPRI Cohesion Workshop:

Surface Modification

Milling Induced Surface Property Changes in Crystalline Pharmaceutical Solids

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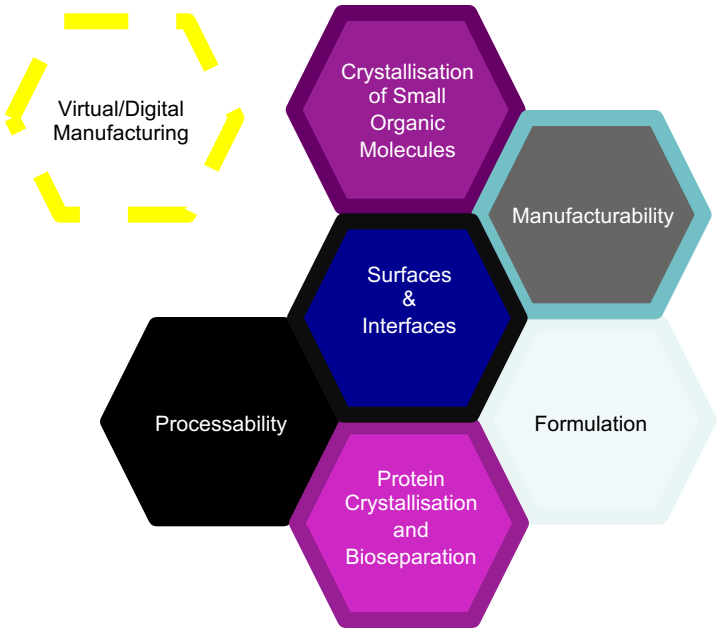

13-14 January 2020
Philadelphia, USA

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Outline

- Anisotropic Surface Energy
- Milling Induced Surface Property Change
  - Milling (Paracetamol + APIs)
  - FD-IGC – recent developments, formulation, mixing & structuring…
  - Case studies: Mannitol (milling), Mefanamic Acid (cohesion), Salbutamol sulphate (electrostatics)
  - Deconvolution
- Conclusion

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What is Surface Energy?

- Surface energy is defined thermodynamically as:

$$\gamma_{ij} = \left[\frac{\partial G}{\partial A}\right]_{T,P,N_i}$$

- We can determine γ_{ij} by measuring its contact angle, as described by Thomas Young:

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cdot \cos\theta$$

- Surface energy is a critical parameter to describe S-S, S-L, S-V interactions.

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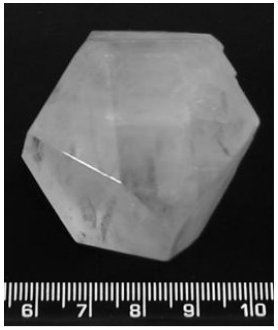
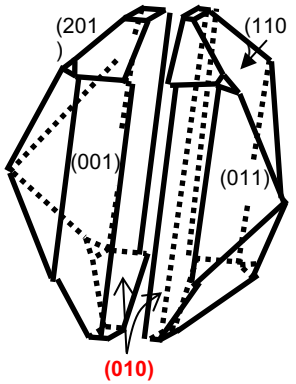
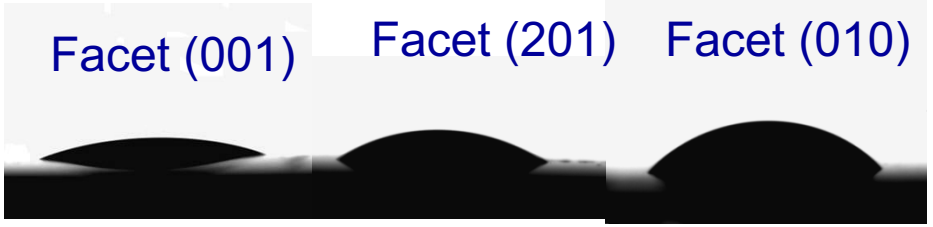
Wettability of Crystalline Solids

- Current assumption – particles are spherical and are isotropic.
- Particles are shaped/ facetted
- Water contact angle variation from 15.9° – 67.7°





Facet	θ_a on Form I Paracetamol Crystals	
	Diiodomethane	Water
(201)	48.8 ± 2.2	38.1 ± 4.6
(001)	49.8 ± 3.2	15.9 ± 3.1
(011)	50.7 ± 2.9	29.8 ± 5.7
(110)	50.2 ± 2.4	50.8 ± 4.9
(010)	27.8 ± 2.5	67.7 ± 2.5



Water on Facets of Form I Paracetamol Crystals

Heng et al., ***Langmuir*** (2006), 22 , p6905.

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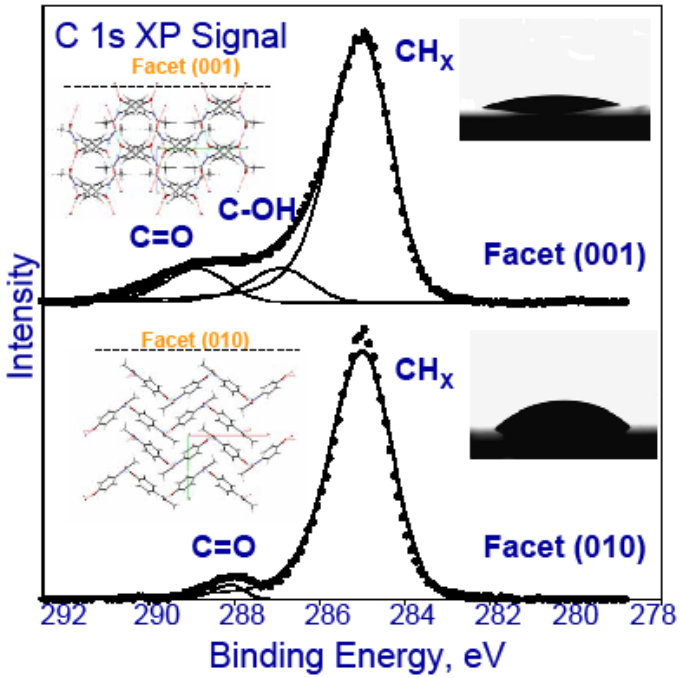
Anisotropic Surface Chemistry

- Variation in surface properties is due to surface chemistry
- Crystalline solids are ANISOTROPIC



Heng at al., ***Langmuir*** (2006), 22, p2760; Heng et al., ***J. Pharm. Sci.*** (2007), 96, p2134-2144

Particle engineering, handling, processing… can result in solids with different surface property.

Hadjittofis, Isbell, Karde, Varghese, Ghoroi, Heng, ***Pharm. Res.*** (2018), 35(5), 100

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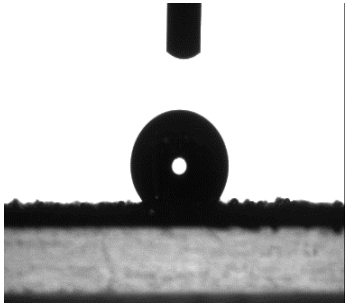
How to determine γ and W_{Adh}?

Experimental determination

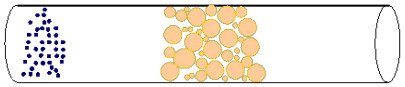
Solid-Liquid interaction

Contact angle → Adhesive bonds with liquid molecules → Reflected as change in contact angle



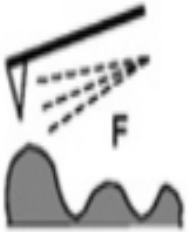
Solid-Vapour interaction

IGC → Adhesive bonds with vapour molecules → Reflected as change in retention time



Solid-Solid interaction

Atomic force microscopy (AFM) → Adhesive bonds with solid molecules → Reflected as pull-off force required



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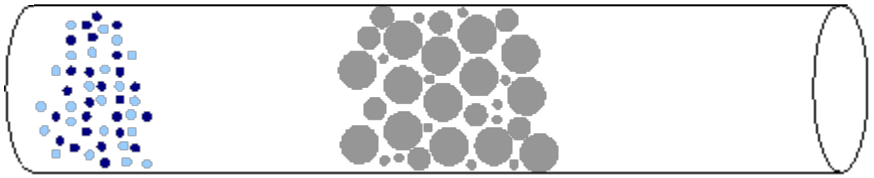
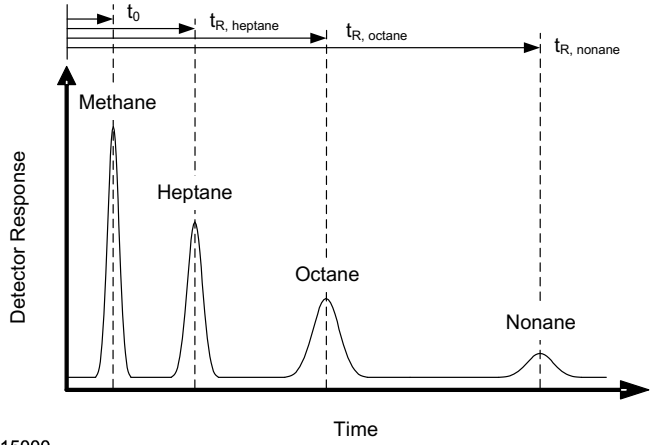
IGC – The Basics

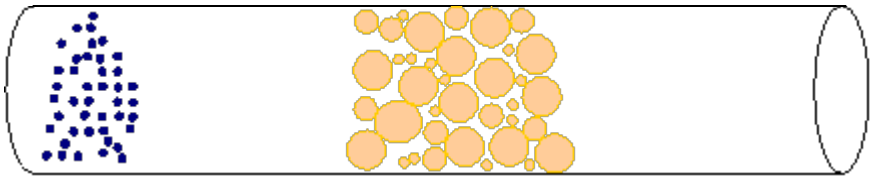
Analytical Gas Chromatography



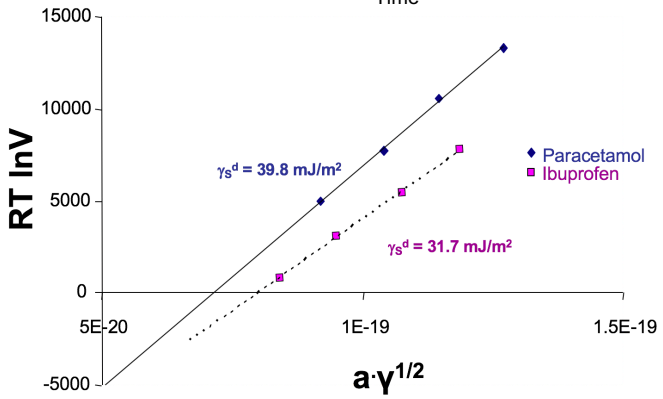
Sample Gas Pulse | Standard Analytical Packing | Separated Sample Peaks



INVERSE Gas Chromatography



Single Probe Gas Pulse | Packed Samples (Powder/Fibres) | Single Peak (Retention Time, t_r)



Heng and Williams. Solid State Characterisation of Pharmaceutical Solids, Wiley and Sons (2012).

Yla-maihaniemi, Thielmann, Heng, Williams. ***Langmuir*** (2008), 24 (17), p9551-9557.

Ho, Heng. ***KONA Powder and Particle Journal*** (2013), 30, p164-180 **--- (FD-IGC)***

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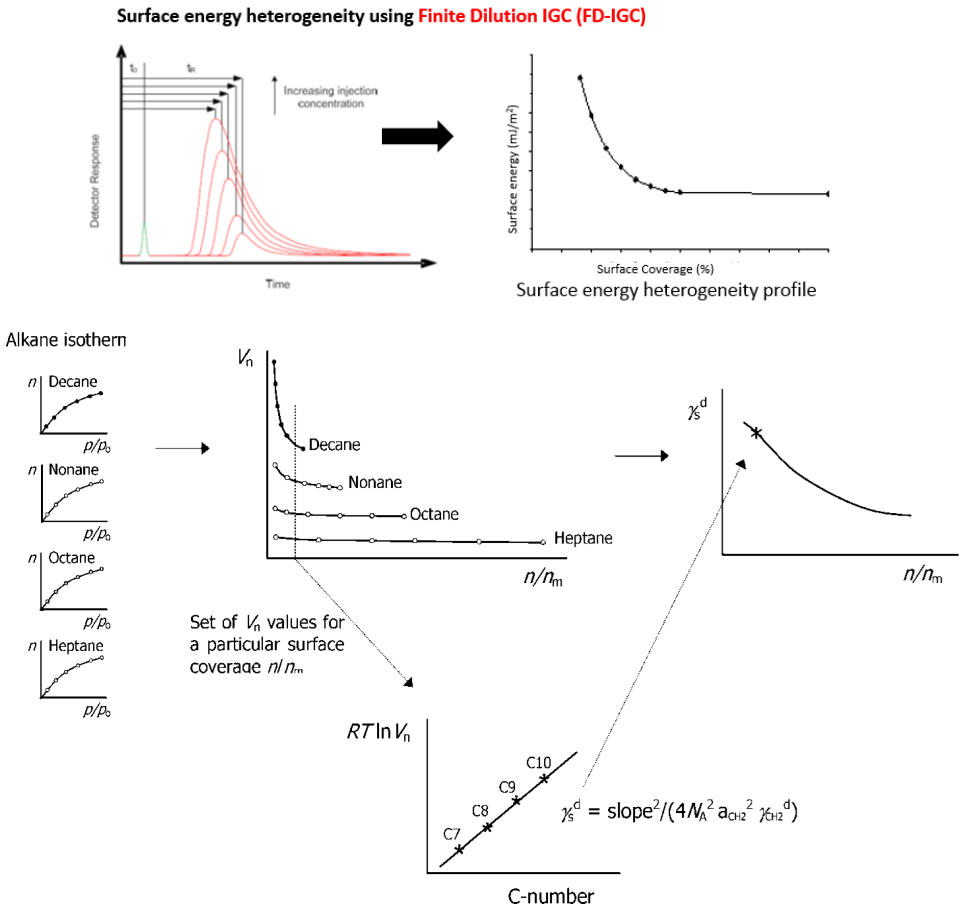
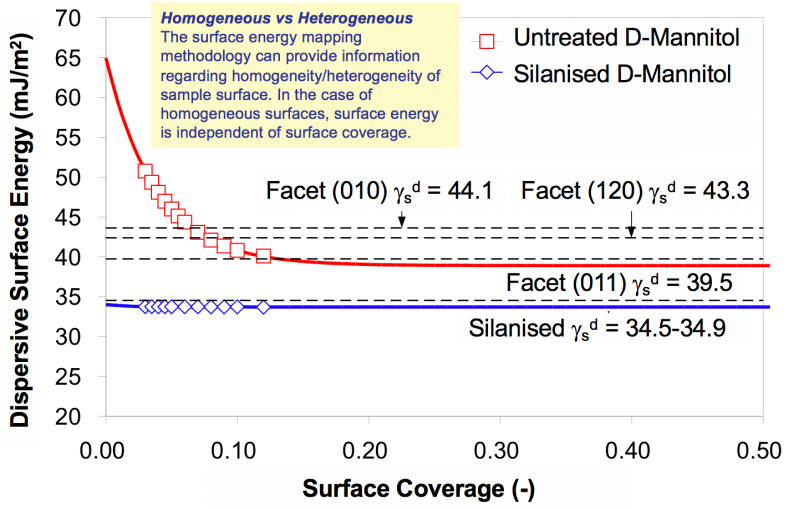
FD-IGC – Recent Advances



Allows determination of surface energy of materials at different probe surface coverage



Ho, Dilworth, Williams, Heng. **Int J Pharm.** (2010) 387(1-2) 79-86

Ho and Heng, ***KONA Powder Part. J.*** (2013), 30, p164-180.
Yla-maihaniemi, Thielmann, Heng, Williams. ***Langmuir*** (2008), 24 (17), p9551-9557.

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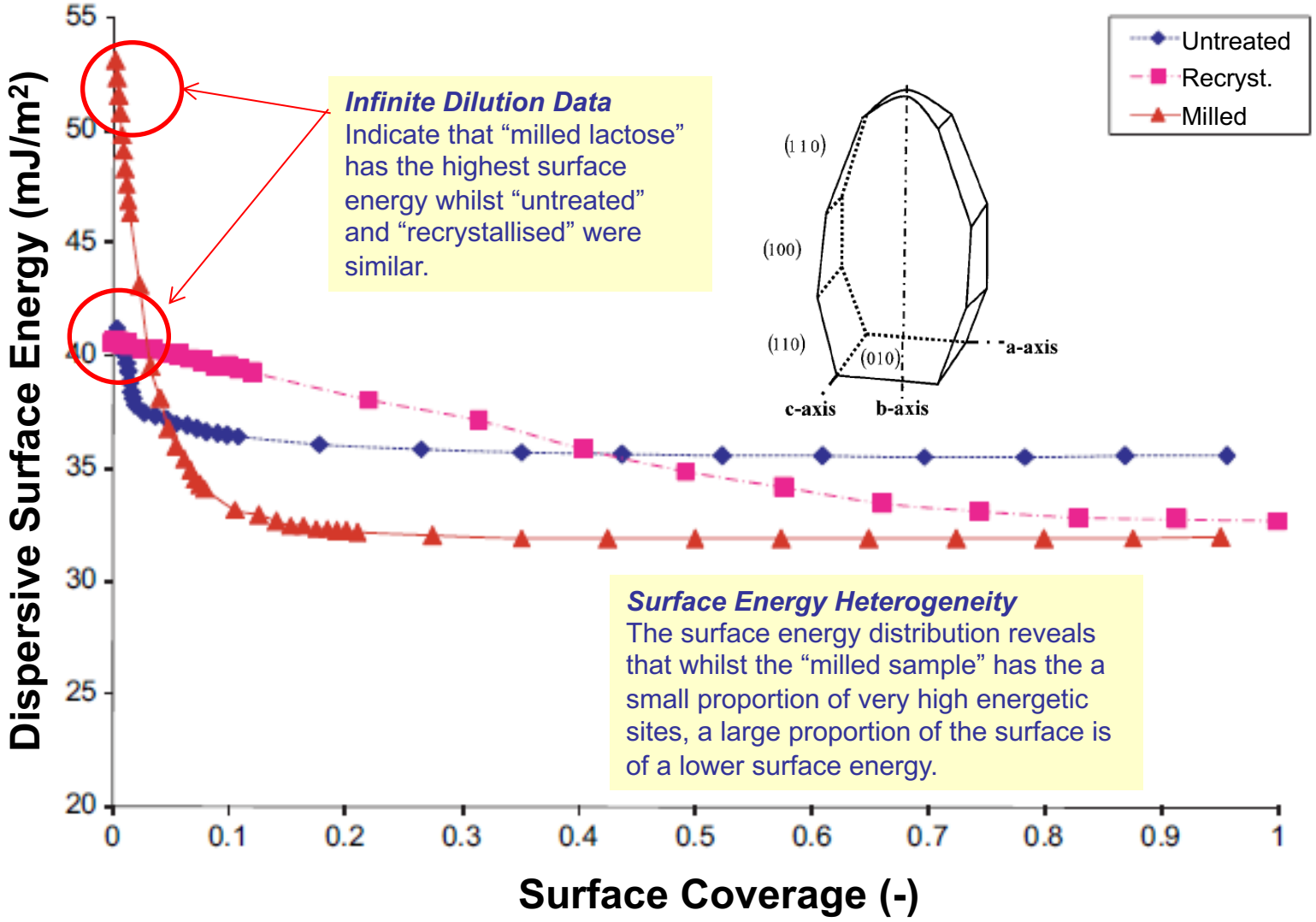
Heterogeneity: Case Studies



Thielmann, Burnett, Heng. ***Drug Dev Ind Pharm*** (2007), 33 (11), p1240-1253.

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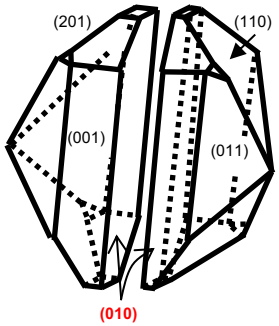
Milling

- Infinite concentration approach.
- "Preferentially" probe highest sites only.
- Not able to probe heterogeneity.



Facets	γ^d
(001)	34.9
(201)	34.4
(011)	33.9
(110)	34.2
(010)	45.1

Heng, Thielmann, Williams. **Pharmaceutical *Research*** (2006), 23 (8), p1917-1927.

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Milling

Facet	Advancing Contact Angle, θ_a (Deg)				
	Paracetamol Form I	Paracetamol Form II	Aspirin	Racemic Ibuprofen	S-(+)-Ibuprofen
(201)	38.1 ± 4.6	-	-	-	-
(001)	15.9 ± 3.1	**64.5 ± 3.5**	60.7 ± 3.5	68.5 ± 4.8	64.5 ± 3.9
(011)	29.8 ± 5.7	-	42.9 ± 4.8	46.9 ± 5.5	-
(110)	50.8 ± 4.9	16.6 ± 1.4	-	-	48.4 ± 4.0
(010)	**67.7 ± 2.5**	17.9 ± 2.5	-	-	-
(100)	-	-	***52.9 ± 2.5***	**77.2 ± 4.0**	**70.7 ± 3.1**

Milling exposes the weakest attachment energy plane which is found to be the most hydrophobic facet.

Heng et al., ***Journal of Pharmaceutical Sciences*** (2007), 96 (8), p2134-2144; Ho et al. ***The Journal of Adhesion*** (2008), 84 (6), p483-501.

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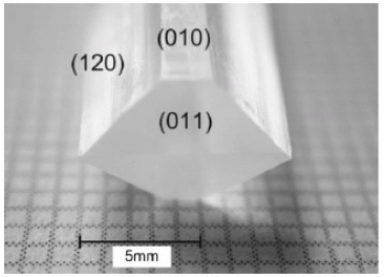
Milling of Mannitol



γ^d= 44.1 mJ/m^2
γ^p= 12.8 mJ/m^2
γ^T= 56.9 mJ/m^2

(010)

(120)

γ^d= 43.3 mJ/m^2
γ^p= 18.6 mJ/m^2
γ^T= 61.9 mJ/m^2

(011)

γ^d= 39.5 mJ/m^2
γ^p= 35.4 mJ/m^2
γ^T= 75.9 mJ/m^2

b
c
a
crystal lattice axes

a)

Direction of fracture due to geometry

(010)

(120)

(011)

Crystal Shape:
- Increase in particle aspect ratio

Crystal Surface Chemistry:
- Decrease in γ^d
- Increase in γ^p
- Increase in γ^T

b)

Direction of fracture based on thermodynamics

(010)

(120)

(011)

Crystal Shape:
- No change or small decrease in particle aspect ratio

Crystal Surface Chemistry:
- Increase in γ^d
- Decrease in γ^p
- Decrease in γ^T

Ho, Wilson, Heng. ***Crystal Growth & Design*** (2009), 9 (11), 4907-4911; Ho et al., ***International Journal of Pharmaceutics*** (2010), 387(1-2), p79-86. Ho et al., ***Pharmaceutical Research*** (2012), 29 , p2806-2816.

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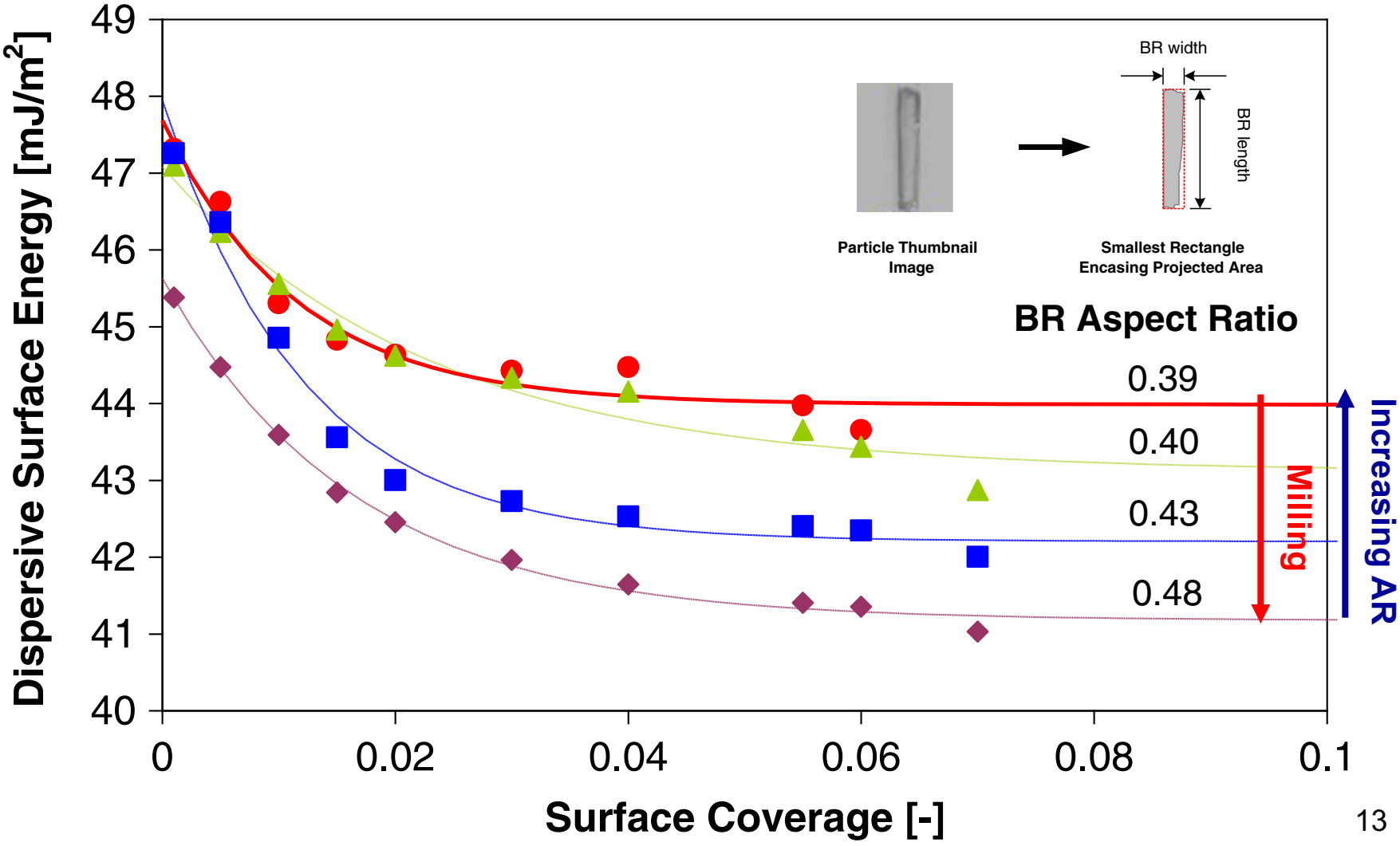
Milling of Mannitol



Ho et al., ***Pharmaceutical Research*** (2012), 29 , p2806-2816.

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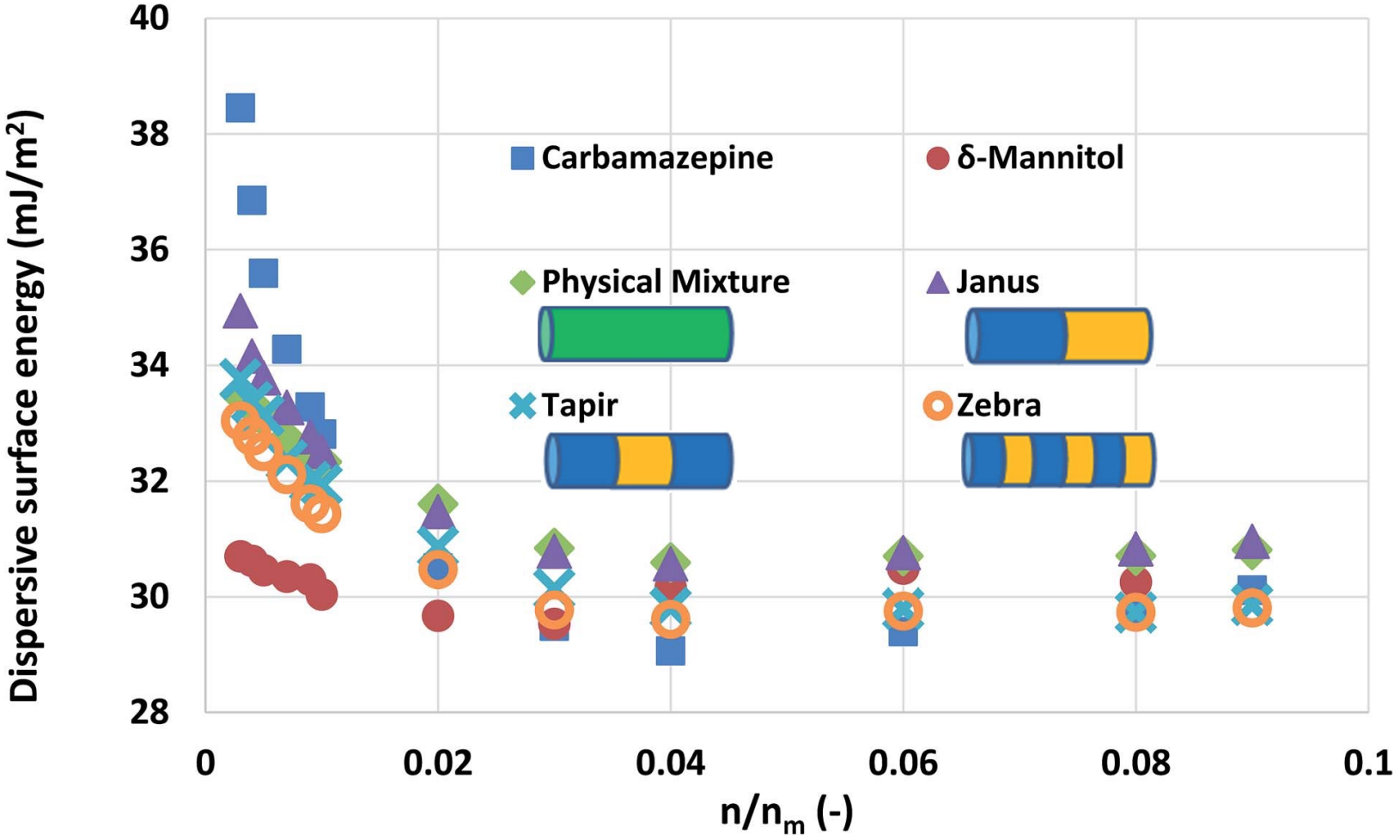
Mixing

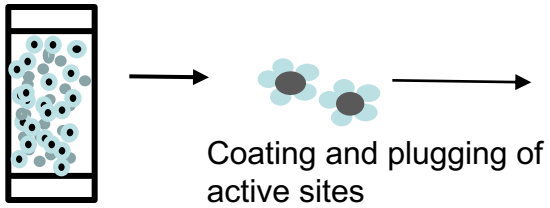


Hadjittofis, Zhang, Heng, ***RSC Advances*** (2017), 7 (20), 12194-12200

Mixing & Structuring

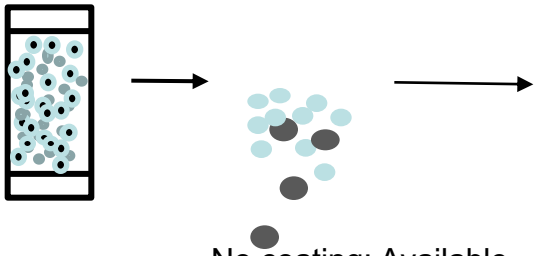
Scenarios for interparticle interactions in binary powder systems

Ordered Mixing



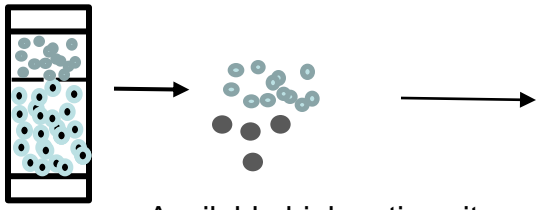
Coating and plugging of active sites

Random Mixing

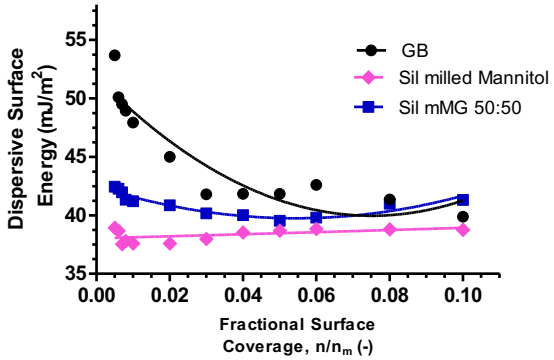


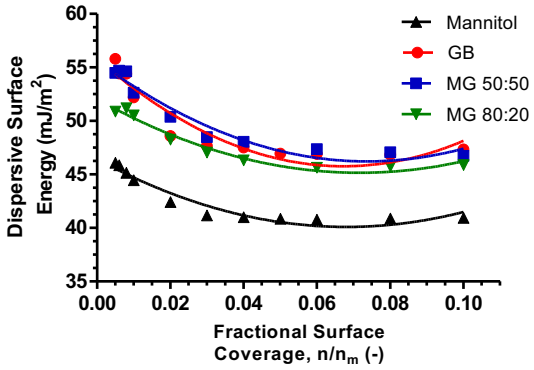
No coating: Available active sites

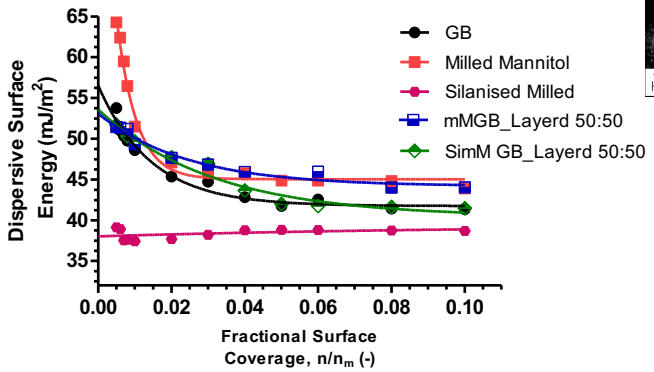
Layered

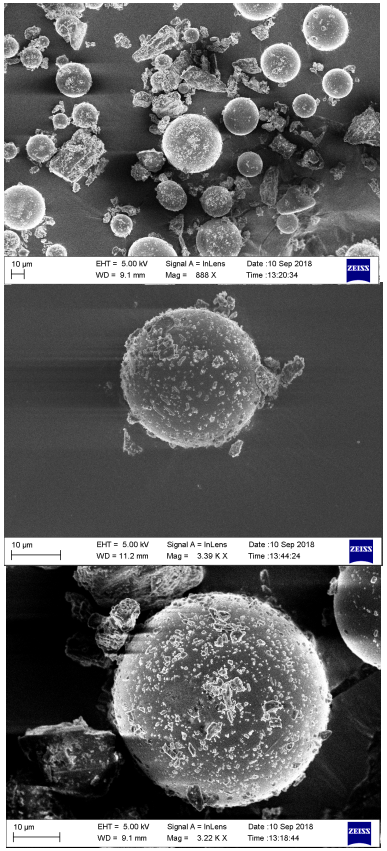


Available high active sites









Interparticle structuring is important!

Lactose (Coase+fines): Ho, Muresan, Hebbink, Heng. ***Int. J. Pharm.*** (2010), 388(1-2), p88-94.

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What affects "γ_{ij}"?

Size: May not change the γ, if density of atoms/molecules per unit area remains same.

Shape: Changes orientation or arrangement of atoms/molecules on the surface. Anisotropy of material.

Surface roughness: Topographical heterogeneity, edges, surface flaws may cause variation in density of molecules, broken molecular bonds etc.

Surface Chemistry: surface functional groups and adsorbed impurities

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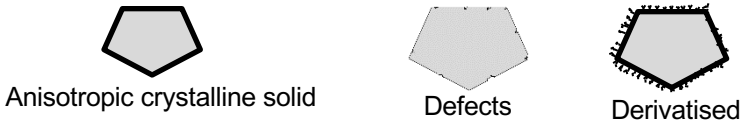
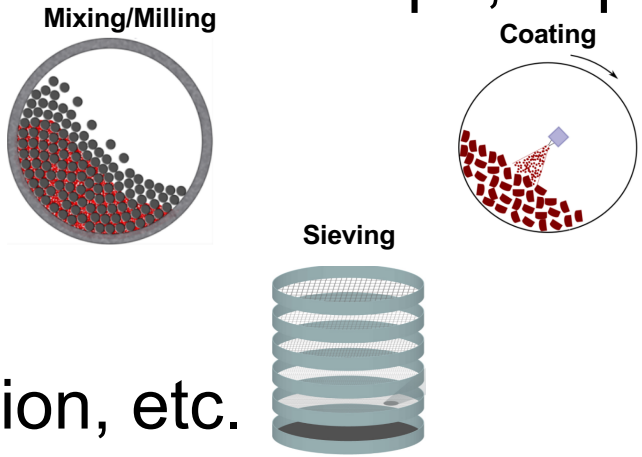
Variation in Surface Properties



- Preparation
  - Crystallisation – different habits/shape, aspect ratio
- Size Reduction
  - Milling/micronisation
- Powder Handling
  - Segregation, aggregation, etc.



Key message:
Need to fully understand characteristics of particles (size, chemistry, stability).

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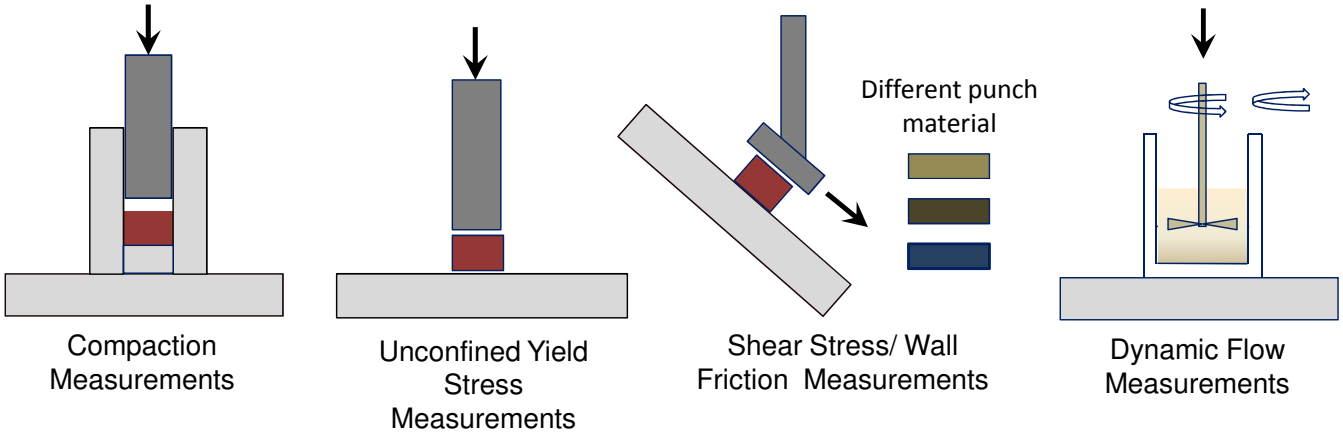
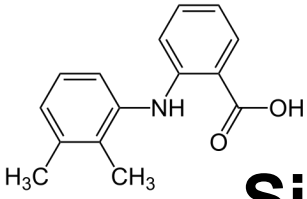
Unconfined Yield Strength



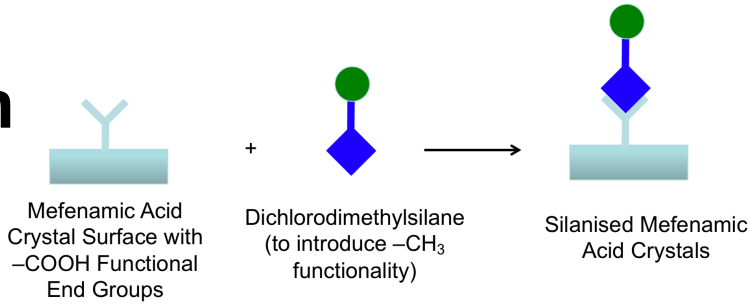
Bulk Property Measurements

Shear Properties Measurements

Dynamic Flow Properties Measurements



Silanisation



Milling: Shah, Wang, Olusanmi, Narang, Hussain, Tobyn, Heng, ***Int J Pharm*** (2015), 495 (1), 234-240
Roughness:Wang, Shah, Olusanmi, Narang, Hussain, Gamble, Tobyn, Heng, ***Int J Pharm*** (2016) 496 (2), 407-413

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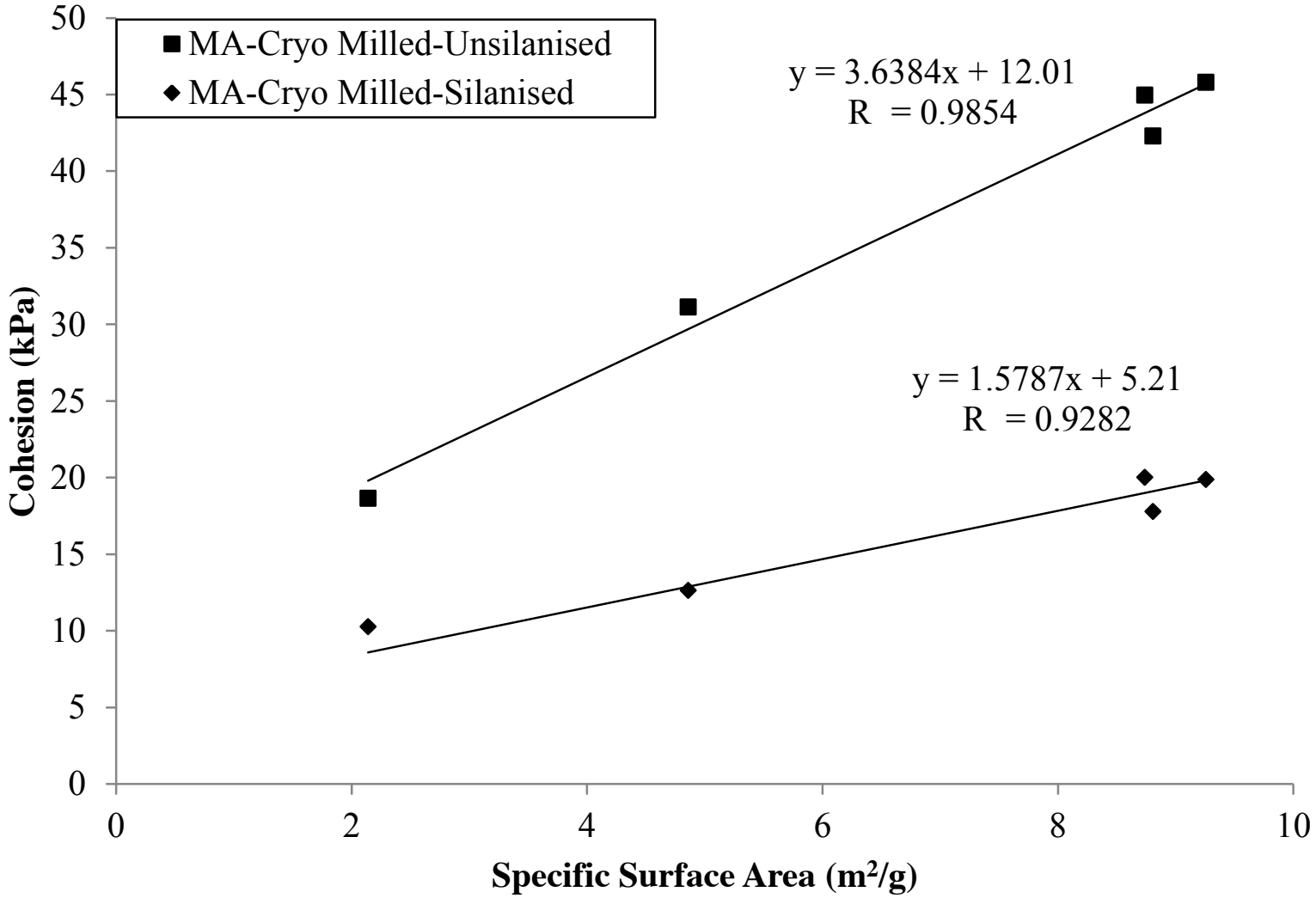
Decouple γ_s from σ



Shah, Olusanmi, Narang, Hussain, Tobyn, Hinder, Heng. ***Pharmaceutical Research*** (2015), 32, 248-259.

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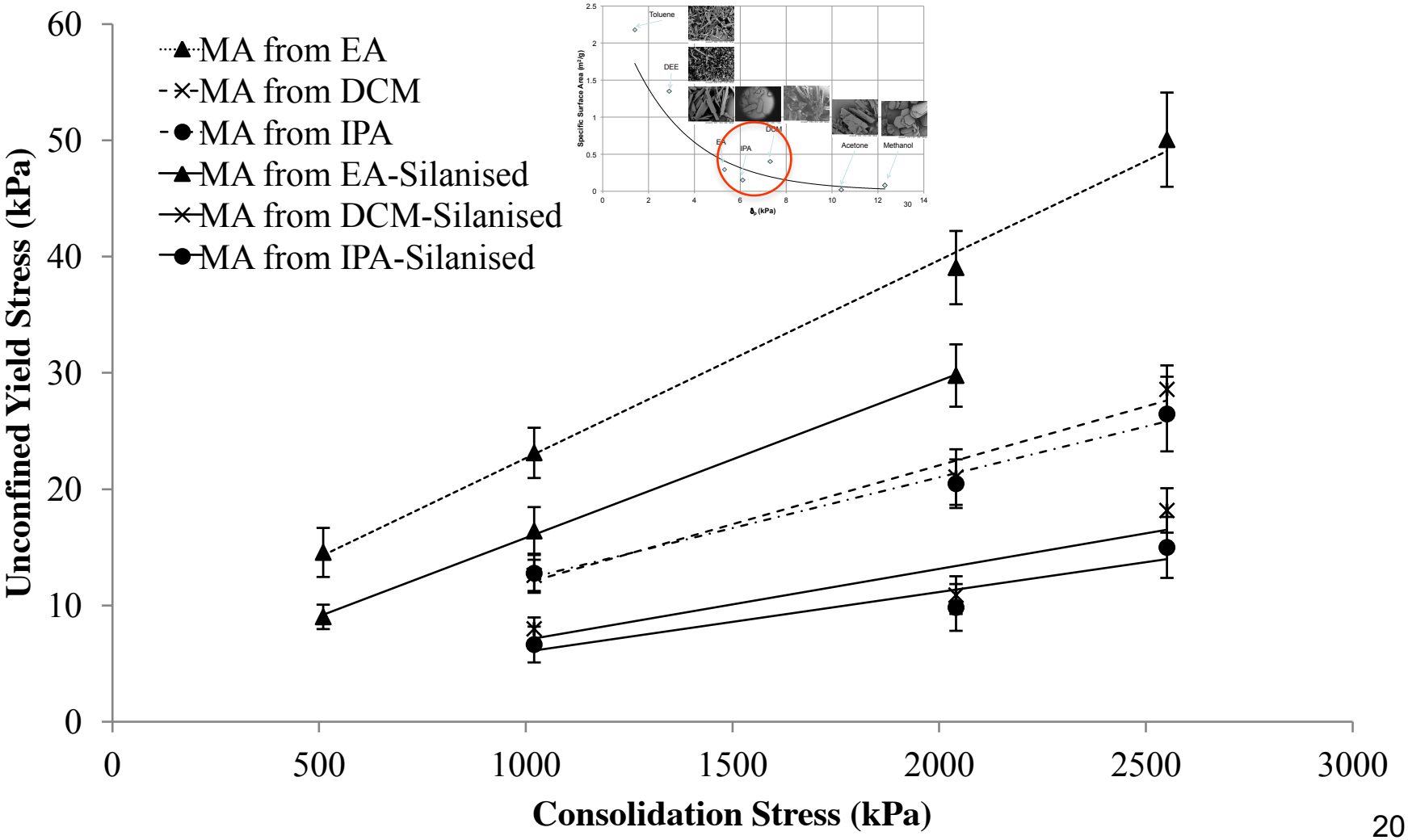
Impact of Shape/Habits



Shah, Olusanmi, Narang, Hussain, Tobyn, Gamble, Heng. ***Int. J. Pharm.*** (2014), 472, 140-147

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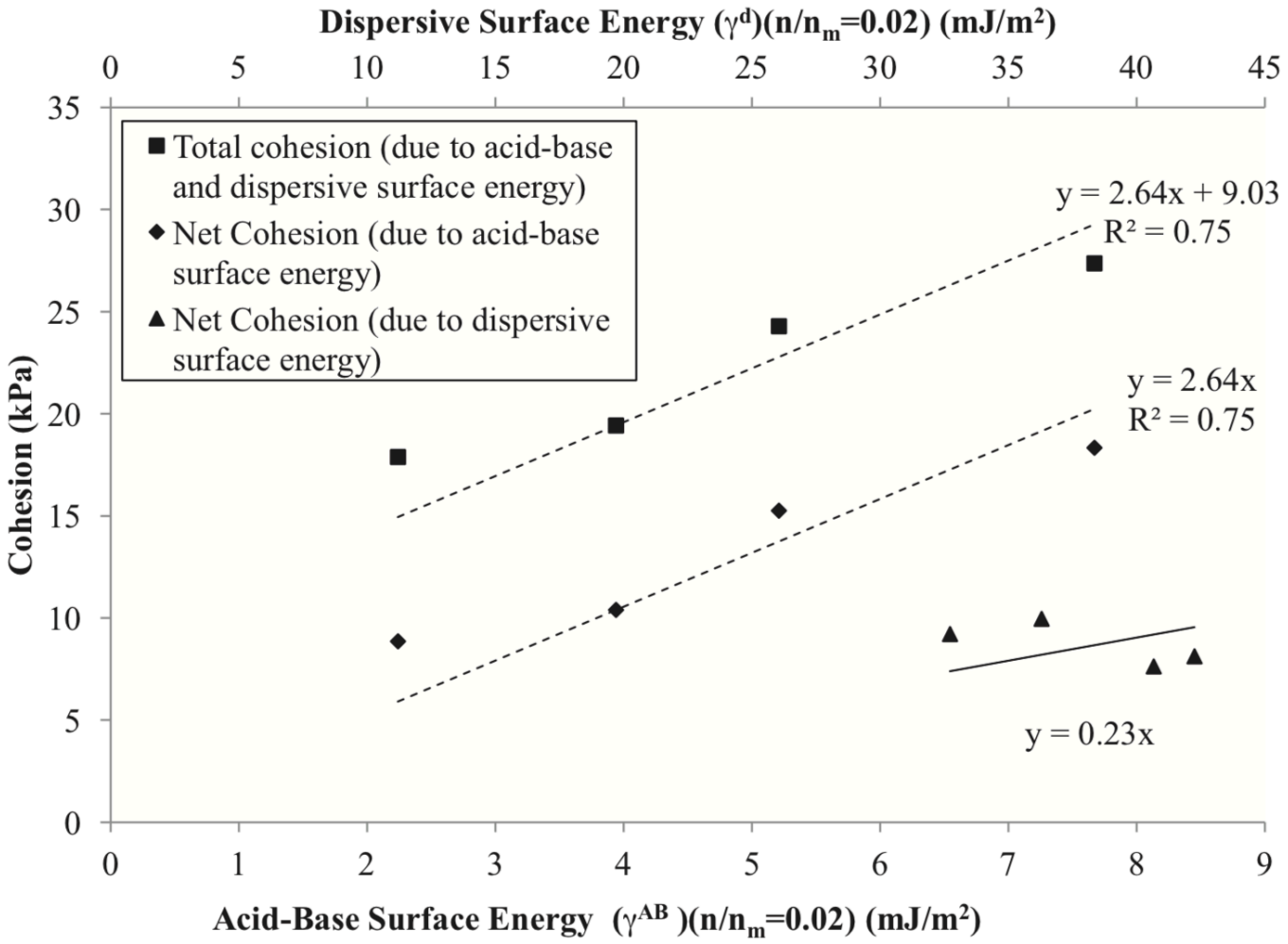
Contribution of γ_s^d and γ_s^{AB}



Shah, Olusanmi, Narang, Hussain, Tobyn, Gamble, Heng. ***Int J Pharm*** (2014), 475, 592-596.

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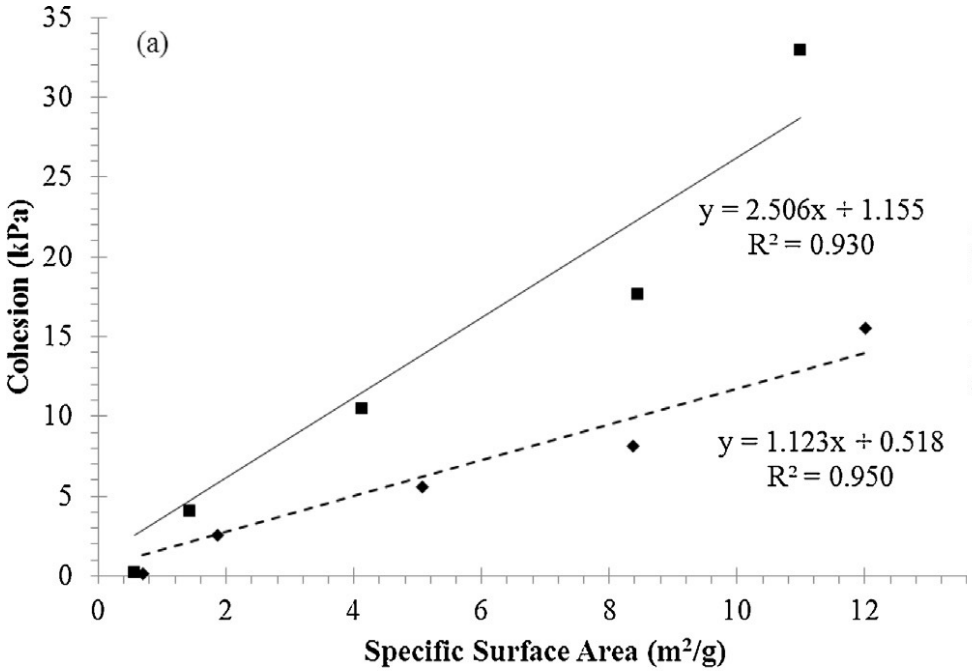
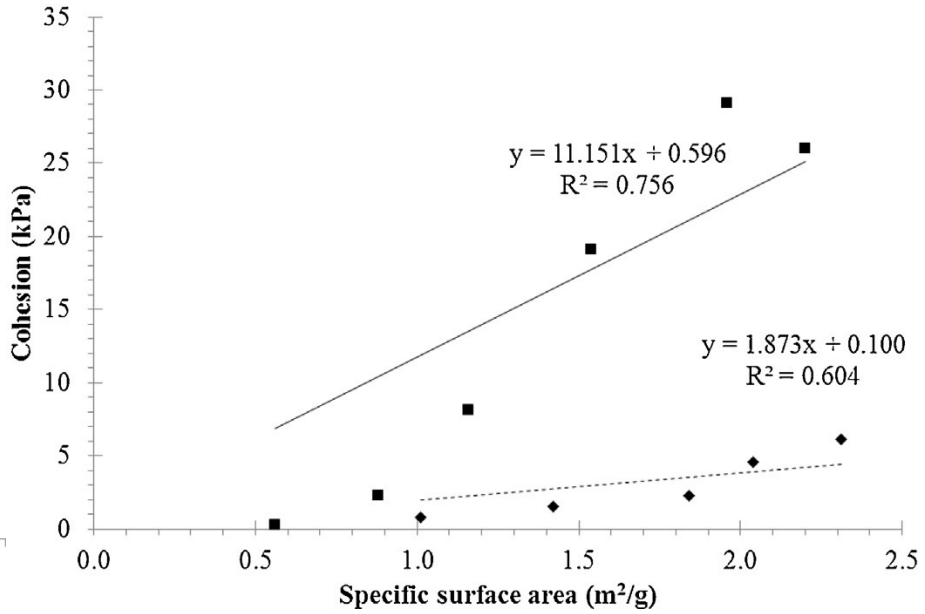
Influence of Milling





Ccontributions from surface area and surface energy on cohesion for brivanib milled at (a) cryogenic temperature and (b) room temperature (squares for un-silanised and diamonds for silanised powders)

Shah, Wang, Olusanmi, Narang, Hussain, Tobyn, Heng ***Int J Pharm*** (2015), 495 (1), 234-240
Wang, Shah, Olusanmi, Narang, Hussain, Gamble, Tobyn, Heng ***Int J Pharm*** (2016) 496 (2), 407-413

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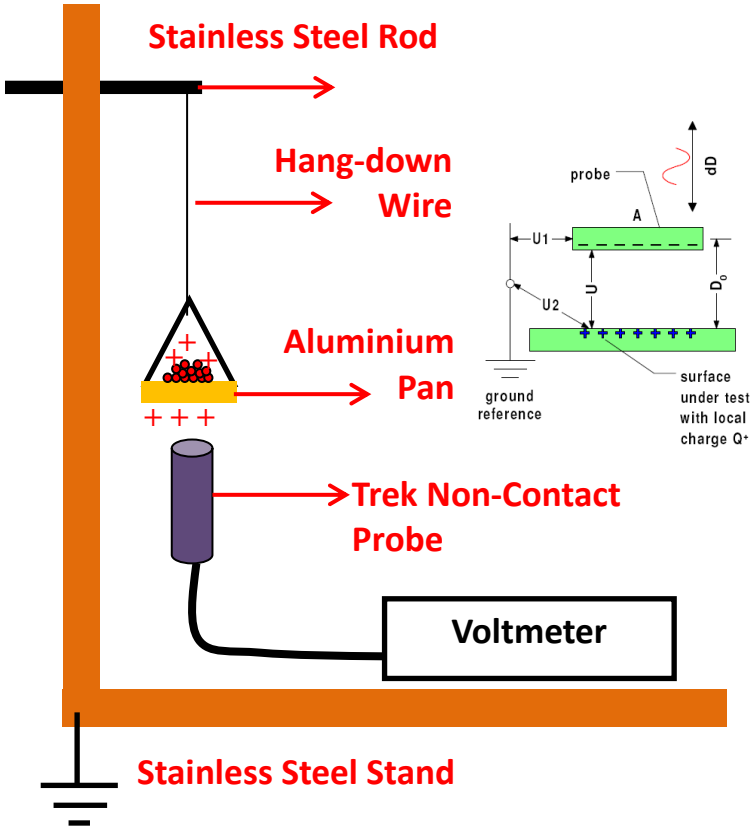
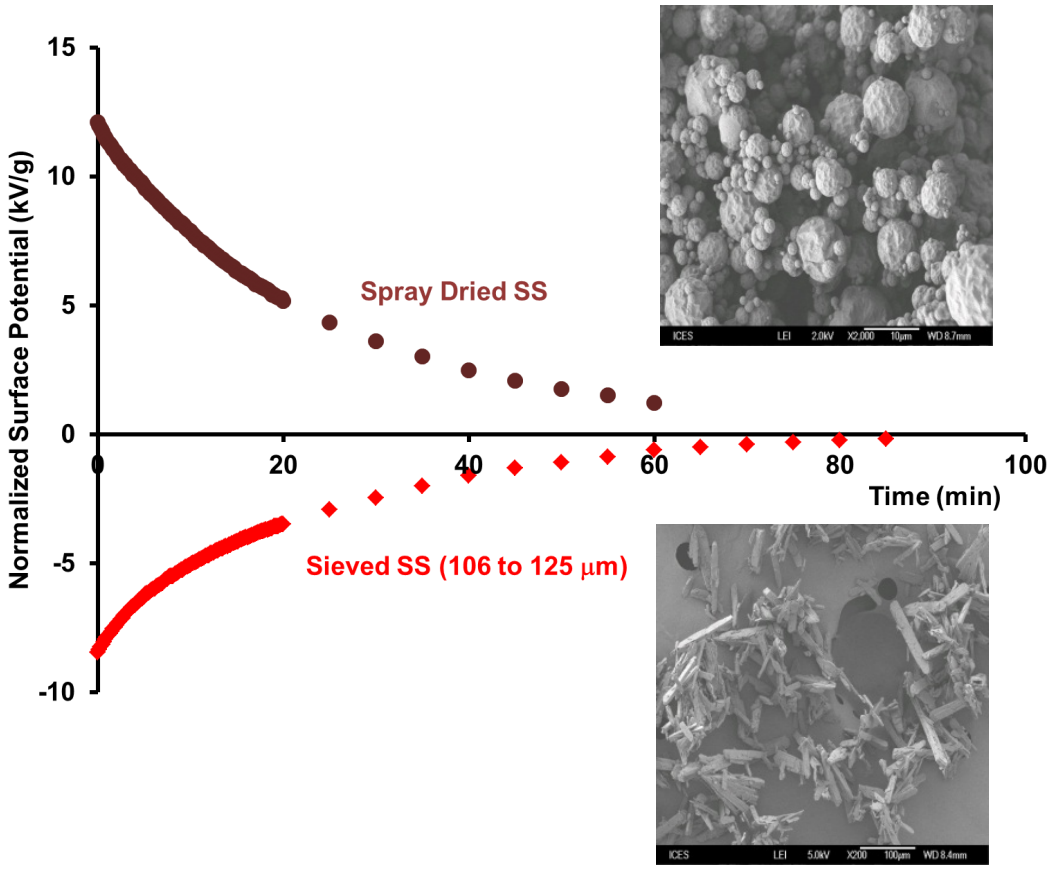
Surface Potential Measurement*





* Collaboration with ICES, Singapore

Kwek, Vakarelski, Ng, Heng, Tan ***Colloids Surf A***, (2011), 385, 206-212
Kwek, Jeyabalasingam, Ng, Heng, Tan, ***Ind Eng Chem Res*** (2012) 51 (50), 16488-16494
Biegaj, Rowland, Lukas, Heng, ***Ind. Eng. Chem. Res.*** (2016), 55 (19), 5585-5589

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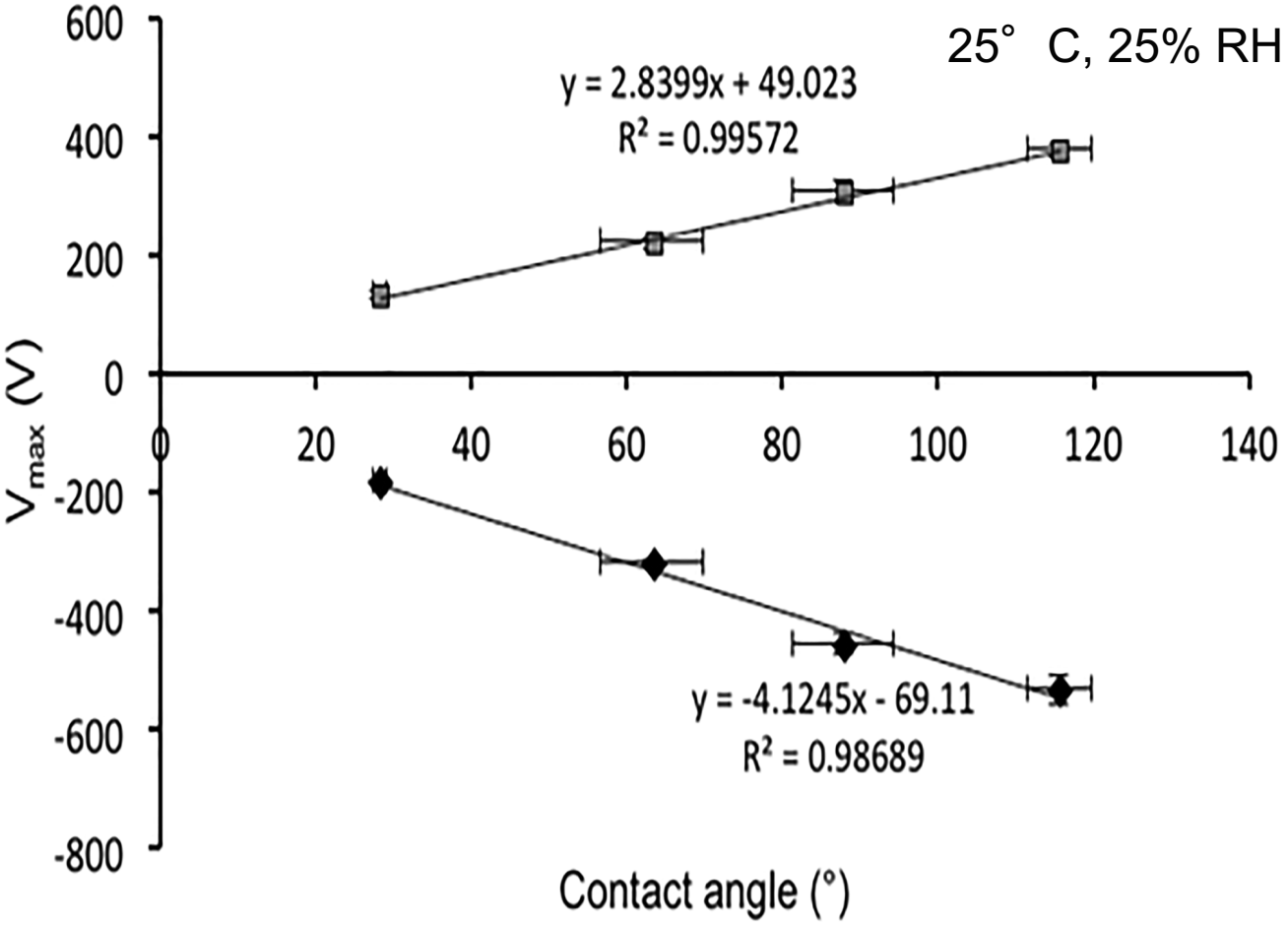
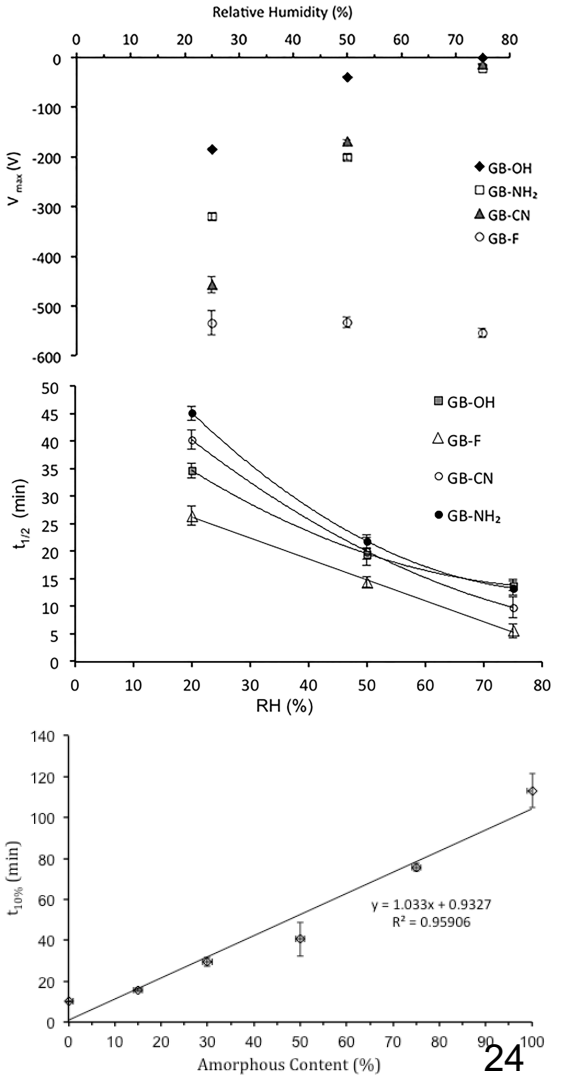
Surface Chemistry





Biegaj, Rowland, Lukas, Heng, ***ACS Omega*** (2017), *2* (4), pp 1576–1582

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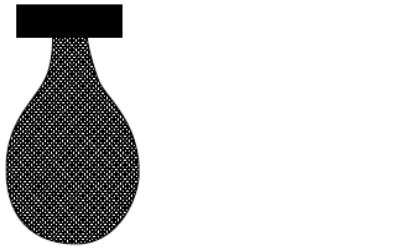
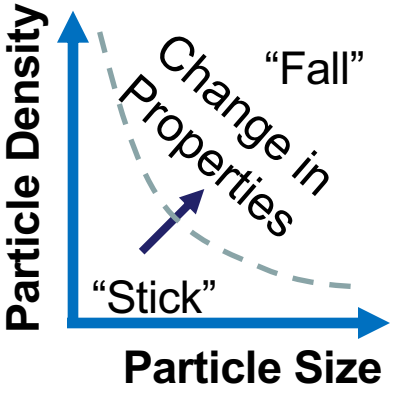
Sticking/Cohesion



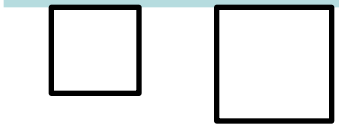
$W_{Adh} = \gamma \times (1 + \cos \theta)$

$W_g = mg$

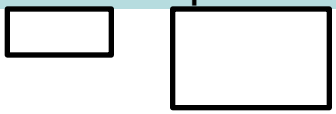


Effect of surface energy

Effect of particle size

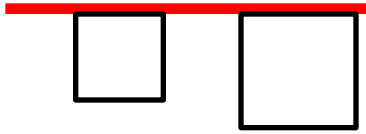


Effect of particle shape



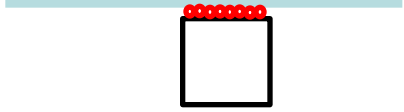
Effect of particle density

Effect of substrate properties

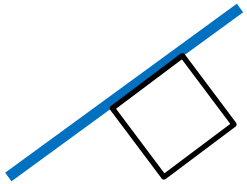


Effect of roughness

Effect of "glidants"



Effect of "lubricants"



Influence of shear?

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Spreading

Consider a liquid i spreading over a solid surface j, a new interface ij is created during the wetting process.

$$\partial G = \left(\frac{\partial G}{\partial A_{\mathrm{i}}}\right)_{\mathrm{T,P}} dA_{\mathrm{i}} + \left(\frac{\partial G}{\partial A_{\mathrm{j}}}\right)_{\mathrm{T,P}} dA_{\mathrm{j}} + \left(\frac{\partial G}{\partial A_{\mathrm{ij}}}\right)_{\mathrm{T,P}} dA_{\mathrm{ij}}$$

The change in the surface area of the individual components:

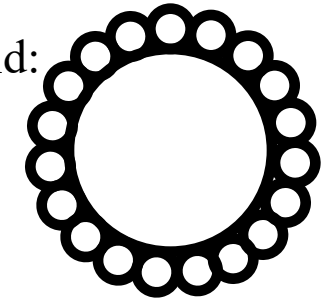
$$dA_i = dA_{ij} = -dA_j$$

The spreading coefficient, therefore:

$$-\left(\frac{\partial G}{\partial A_{\mathrm{i}}}\right)_{\mathrm{T,P}} = S_{\mathrm{ij}} = \gamma_{\mathrm{j}} - \gamma_{\mathrm{i}} - \gamma_{\mathrm{ij}}$$

Analogously, for a solid:

$$S_{\mathrm{ij}} = W_{ij} - W_{\mathrm{C}}$$

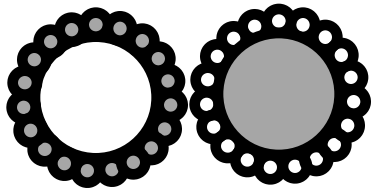


Effect of surface energy

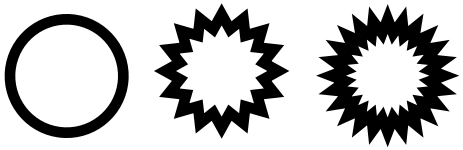
Effect of particle density

Effect of particle size

Effect of A/B or B/A



Effect of roughness



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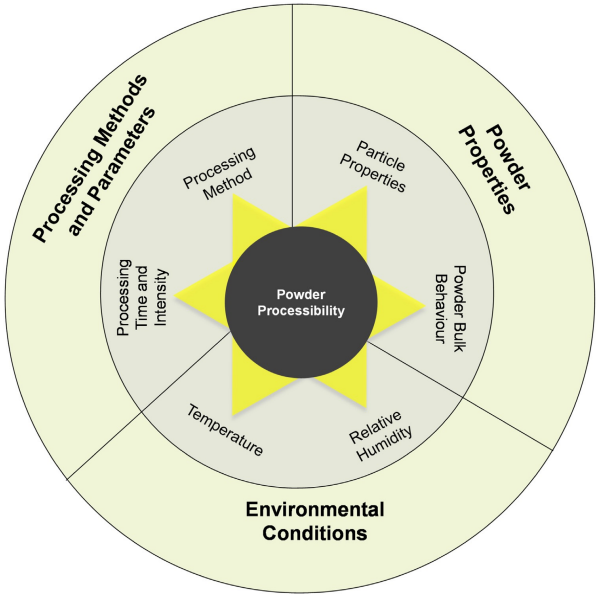
Conclusion

The interfacial properties of a crystalline solid is anisotropic.

Powder processing may result in a change in powder surface property and hence affect powder handling and resulting performance.



Shah, Karde, Ghoroi, Heng, ***Int J Pharm.*** (2017) 518 (1-2), 138-154

Key message:
Need to better understand characteristics of particles (size, shape, roughness, chemistry).

EP/N025261/1

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Vikram Karde (EPSRC VFL)

Thank You!

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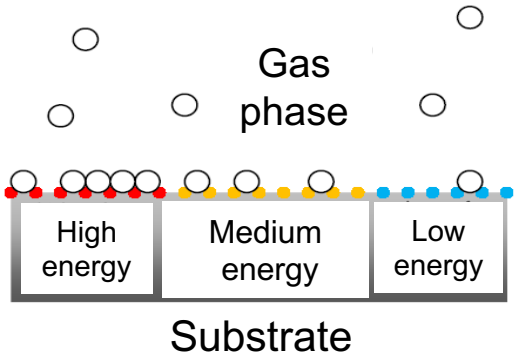
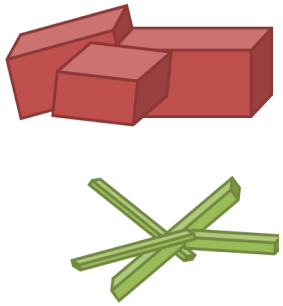
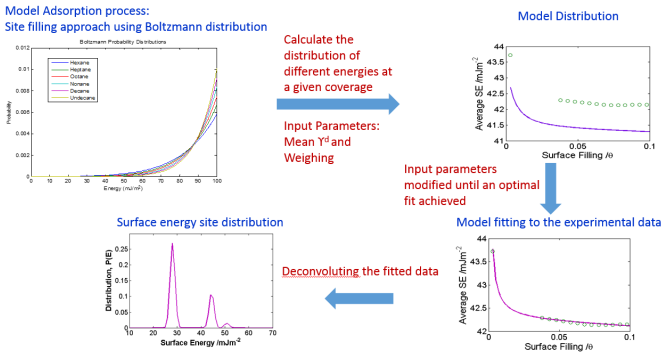
Deconvolution

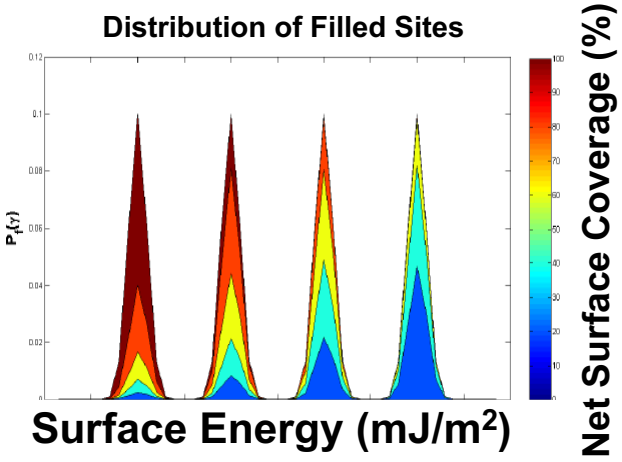
Adsorption to heterogeneous surfaces
The physical picture

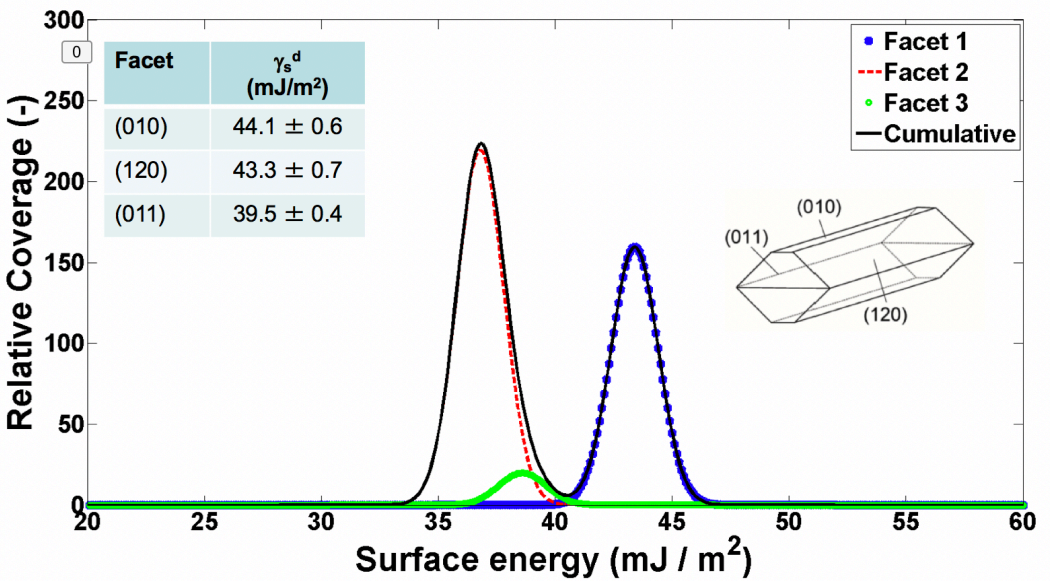




FD-IGC







Methodology: Jefferson, Williams, Heng. ***J Adh Sci Technol*** (2012), 25, p339-355.
Polymorph: Smith, Shah, Parambil, Burnett, Thielmann, Heng, ***AAPS J.*** (2017) 19 (1), 103-109

Deconvolution:Binary Mixture