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# Pharmaceutical Surface Science: Probing at the Nanometre Scale

Applications to drug-polymer interactions in inhalation systems

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## Synopsis

- Introduction
- AFM Studies
  - Drug-polymer interactions in DPI formulations.
  - Drug-polymer interactions in model suspension pMDI systems.
- Conclusions
- Acknowledgments


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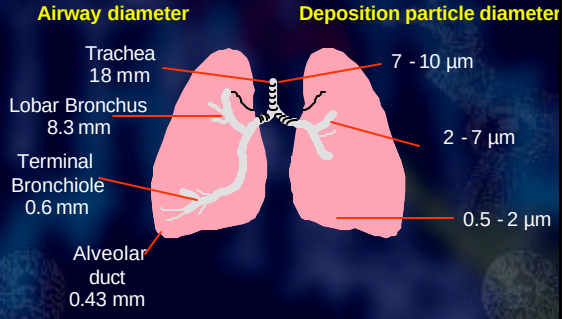
## Targeting by deposition





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## Dry Powder Inhalers (DPIs)

Key issues:

- Drug Particles must reach the deep lung.
- Particle size must be below 5µm.
- Powders must be micronised.
- Micronised powders are very cohesive

Currently less than 20% of the emitted dose reaches the deep lung!


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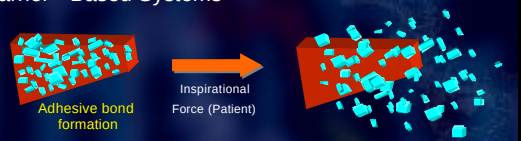
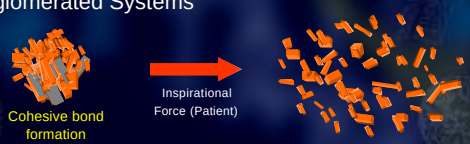
## Dry Powder Aerosols: Formulation Strategies

Carrier - Based Systems




Agglomerated Systems





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## Interactions to be controlled and modified

- Drug - Drug Interactions (Cohesion)
- Drug - Excipient Interactions (Adhesion)
- Drug - Device Interactions (Segregation)

Their properties govern overall stability and aerosol delivery performance of a formulation

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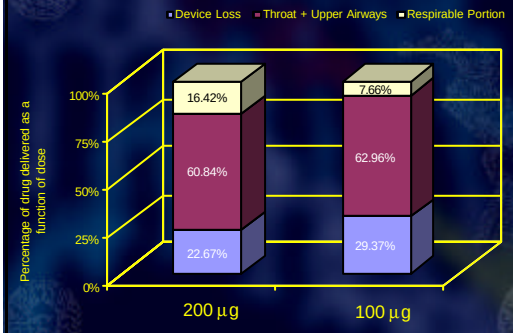
## Carrier-based DPI limitations




Increased % device loss concomitant with decrease in fine particle fraction !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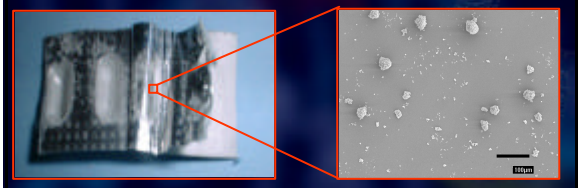

What governs these various interactions ?


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## A composite of Interparticulate Forces

Particle interactions are primarily dictated by:

- van der Waals Forces
- Electrostatic Forces
- Capillary Forces

The relative contribution of these components to the total adhesion/cohesion depends on the interacting materials and relative humidity.


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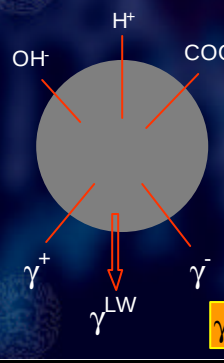
## Physico-chemical Link




- Lifshitz (1955) grouped the electrodynamic interactions:
  - London- van der Waals
  - Keesom-van der Waals
  - Debye- van der Waals

  Collectively known as Lifshitz- van der Waals (LW) interactions
- Electron-donor and electron acceptor interactions are AB interactions, for Lewis acid-base.

$$\gamma_s^T = \gamma_s^{LW} + 2\sqrt{\gamma_s^+\gamma_s^-}$$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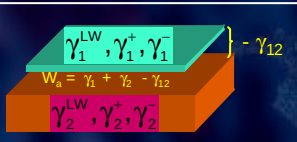
## Work of adhesion ($W_a$)




$$W_a = 2\left(\sqrt{\gamma_1^{LW}\gamma_2^{LW}} + \sqrt{\gamma_1^+\gamma_2^-} + \sqrt{\gamma_1^-\gamma_2^+}\right)$$

LW attraction between solid 1 and 2 | Polar adhesion between solid 1 and 2

How is the $W_{ad}$ related to a measured interfacial force ?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## Pull-off Forces

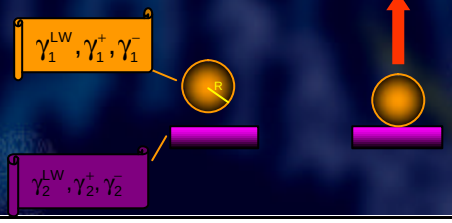
$F_{Pull\text{-}off} = 2\pi R W_{ad}$ (DMT)

$$F_{pull-off} = 4\pi R\left(\sqrt{\gamma_1^{LW}\gamma_2^{LW}} + \sqrt{\gamma_1^+\gamma_2^-} + \sqrt{\gamma_1^-\gamma_2^+}\right)$$

$F_{Pull\text{-}off} = 3/2\pi R W_{ad}$ (JKR)

$$F_{pull-off} = 3\pi R\left(\sqrt{\gamma_1^{LW}\gamma_2^{LW}} + \sqrt{\gamma_1^+\gamma_2^-} + \sqrt{\gamma_1^-\gamma_2^+}\right)$$

$F_{ad}$ µ $W_{ad}$



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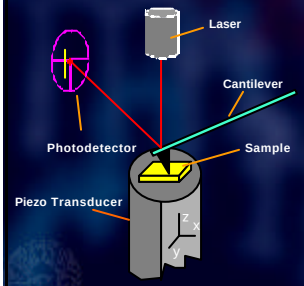
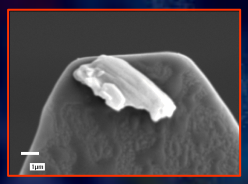
## Atomic Force Microscope (AFM)




Model salbutamol sulphate drug probe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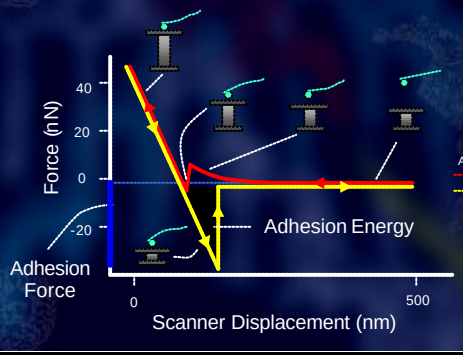
## Anatomy of a Force Curve





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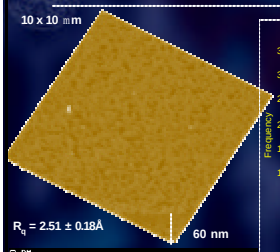
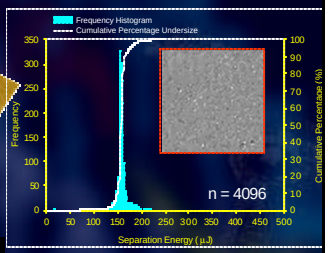
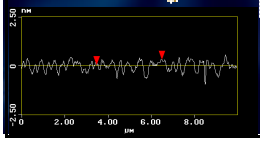
## Atomically Smooth Lactose




- Normally distributed data
- Statistical analysis (mean and standard deviation).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## Energetic analysis of experimental measurements

| Material | $\gamma_s^{LW}$ (mJ/m²) | $\gamma_s^-$ (mJ/m²) | $\gamma_s$ (mJ/m²) | $W_a$ (mJ/m²) |
|---|---|---|---|---|
| Salbutamol* | 41.5 | 19.3 | 5.8 | 126.52 |
| Lactose* | 47.90 | 28.00 | 5.70 | 135.64 |
| | | | | |
| PTFE | 18.5 | 0 | 0 | 54.41 |
| PP | 25.7 | 0 | 0 | 64.12 |
| PE | 33.0 | 0 | 0 | 72.66 |
| PVC | 43.0 | 0.04 | 3.5 | 85.32 |

*D. Cline and R. Dalby, Pharm Res. 19 (2002) 1274-1277

$$W_a = 2\left(\sqrt{\gamma_1^{LW}\gamma_2^{LW}} + \sqrt{\gamma_1^+\gamma_2^-} + \sqrt{\gamma_1^-\gamma_2^+}\right)$$


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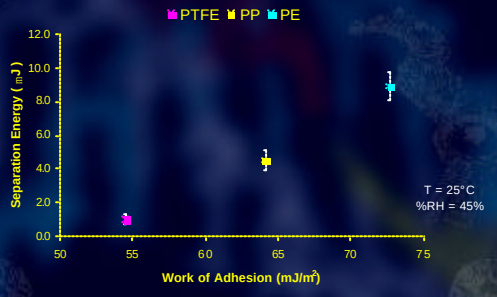
## Relationship between separation energy and work of adhesion




$E_{sep} \mu W_{ad}$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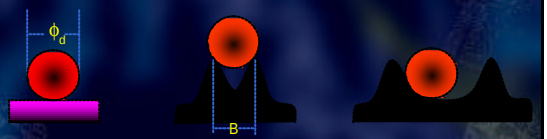
## Additional factors that influence particle adhesion

| | | |
|---|---|---|
| Surface Energy | - | Intrinsic "free" energy |
| Surface Roughness | - | Contact Area |
| Mechanical Properties | - | Hardness |
| Environmental Conditions | - | Temp. & %RH |




i. Smooth Surface

ii. $\phi_d$ > B

iii. $\phi_d$ < B

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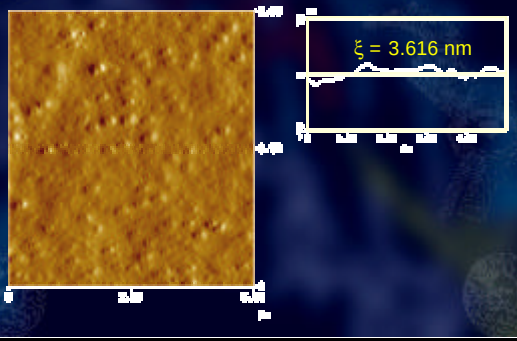
## Polymer blister film





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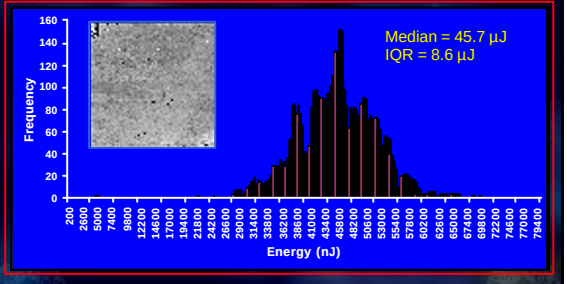
## Drug-Polymer interaction




Dispersions due to variations in surface roughness at the nm scale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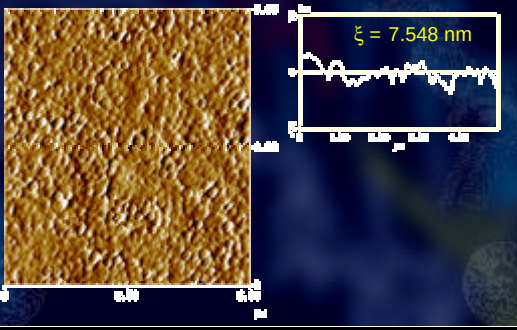
## Increase in roughness upon blister formation





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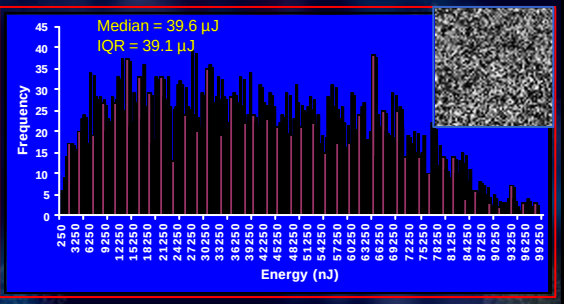
## Drug-Polymer interaction





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## Summary

- Surface energy properties of substrate surface play a dominant role in the adhesion of individual drug particles.
- Adhesion of micron sized particles is highly dependant on the surface roughness at the nanometre scale.
- The presence of additives may lead to instability and a source of segregation of drug particulates in a dry powder formulation.


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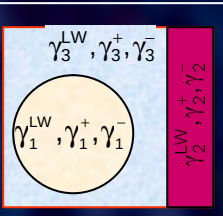
## pMDI Model Interactions




$\gamma^+_3, \gamma_3 = 0$

$$W_{132} = 2\left(\left(\sqrt{\gamma_1^{LW}\gamma_3^{LW}} + \sqrt{\gamma_2^{LW}\gamma_3^{LW}} - \sqrt{\gamma_1^{LW}\gamma_2^{LW}} - \gamma_3^{LW}\right) - \sqrt{\gamma_1^+\gamma_2^-} - \sqrt{\gamma_1^-\gamma_2^+}\right)$$

LW repulsion between solid 1 and solid 2 with solution

LW attraction between solid 1 and solid 2 LW attraction of solution

Polar adhesion between solid 1 and 2

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## Drug-Canister model interactions

| Material (2) | Solvent (3) | Repulsive LW interaction ($mJ/m^2$) | Attractive LW interaction ($mJ/m^2$) | Attractive AB interaction ($mJ/m^2$) | $W_{132}$ Total interaction ($mJ/m^2$) |
|---|---|---|---|---|---|
| Borosilicate Glass | HPFP | 104.22 | -126.41 | -9.21 | **31.40** |
| Anodised Aluminium | HPFP | 96.81 | -111.02 | -4.36 | **17.67** |
| PTFE | HPFP | 89.32 | -95.46 | -1.65 | **7.80** |

Drug particle (1): Salbutamol sulphate (micronised)

Model Propellant: 2H, 3H perfluorpentane (HPFP)


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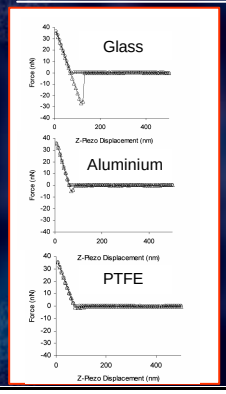
## Direct Force Measurements




$F_{ad}$ = 28.63 nN ($W_{132}$ = 31.40 $mJ/m^2$)

$F_{ad}$ = 6.24 nN ($W_{132}$ = 17.67 $mJ/m^2$)

$F_{ad}$ = 0.85 nN ($W_{132}$ = 7.80 $mJ/m^2$)

P. Young and R. Price, J. Coll. Int. Sci (2003) In Press.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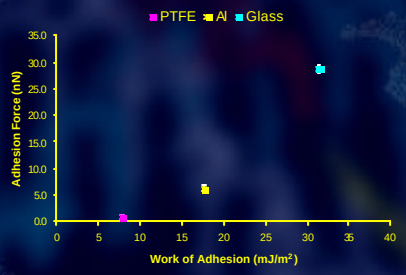
## pMDI drug-wall interactions




$F_{ad} \mu W_{ad}$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## Conclusions

- AFM can be used to determine the adhesive characteristics of particulate materials to polymer surfaces.
- In combination with bulk techniques, AFM may potentially play a pivotal role in the design and modifications of DPI and suspension based systems.
- There is a further need to correlate:
  - Relationship between surface thermodynamics (contact angles, IGC), force measurements (AFM, CPD) and *in vitro* performance.
  - Macroscopic properties of surfaces and meso scale properties of interfacial interactions and related adhesion.

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100µm