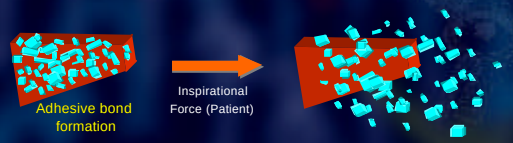
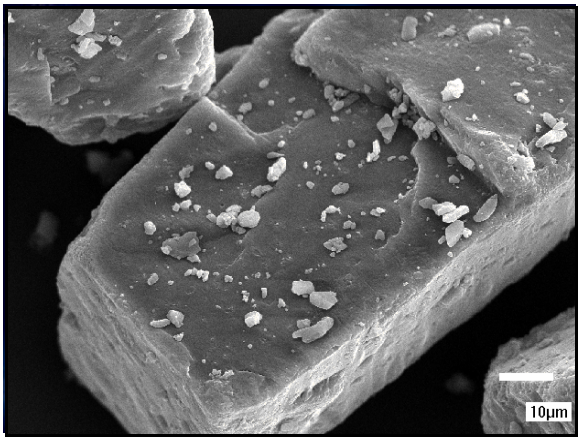
Variation in particle adhesion in carrier based dry powder inhaler (DPI) formulations

Dr Robert Price



University of Bath,
Pharmaceutical Technology Research Group.



A composite of Interparticulate Forces

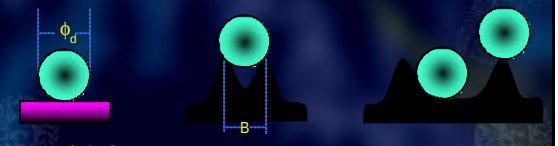
Particle interactions are primarily dictated by:

- 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.

Additional factors that influence particle adhesion

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

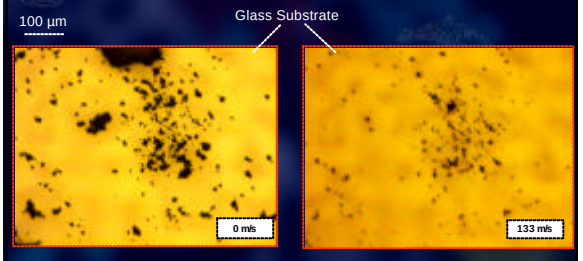


i. Smooth Surface

ii. ϕ_d > B

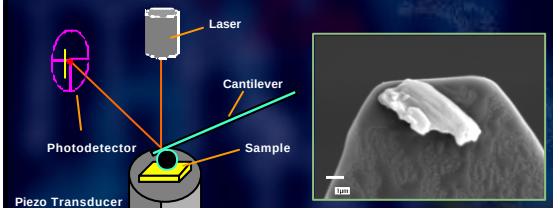
iii. ϕ_d < B

Entrainment Inefficiencies



Unable to elutriate respirable sized drug particles

Atomic Force Microscope (AFM)

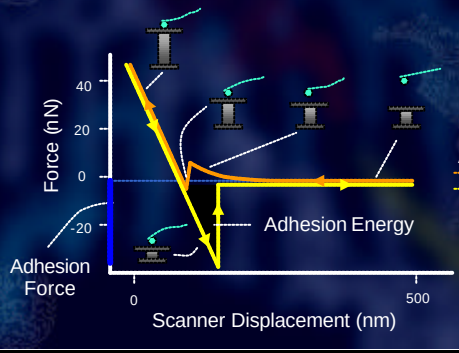


Model salbutamol sulphate drug probe

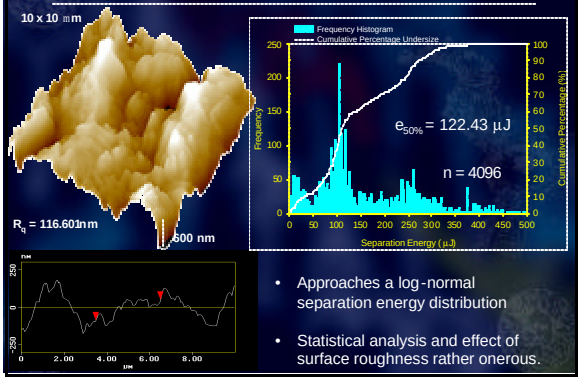
$F = kdx$

k = spring constant (N/m)
dx = cantilever deflection

Anatomy of a Force Curve

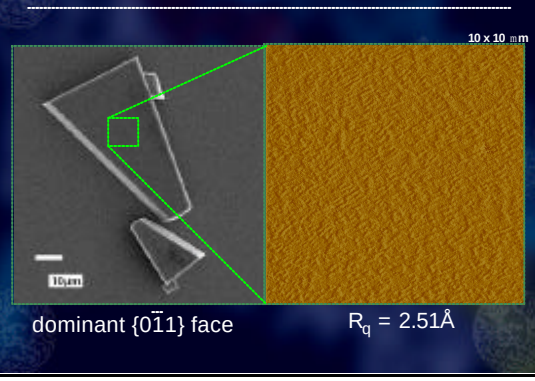


Commercial Grade Lactose



- Approaches a log-normal separation energy distribution
- Statistical analysis and effect of surface roughness rather onerous.

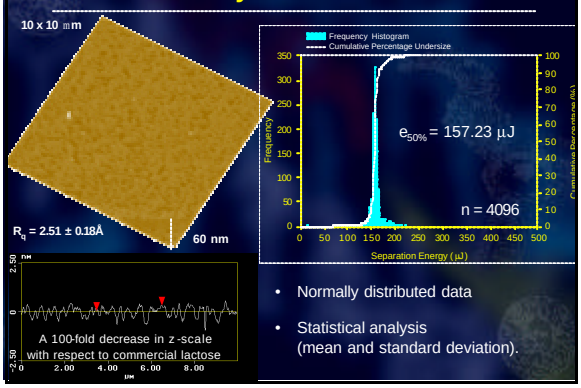
Modified α-lactose surfaces



dominant $\{0\bar{1}1\}$ face

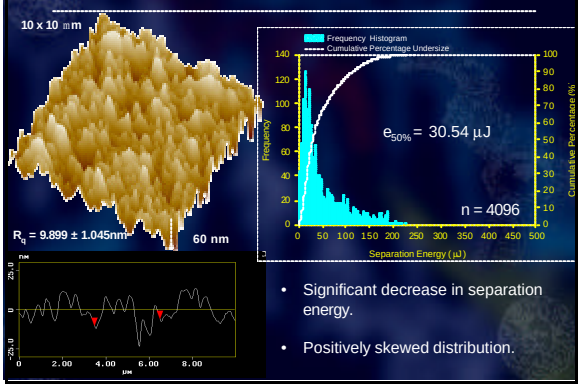
R_q = 2.51Å

Atomically Smooth Lactose



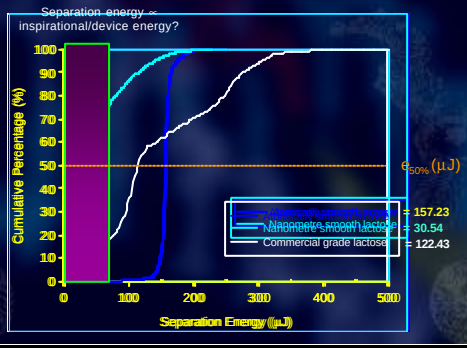
- Normally distributed data
- Statistical analysis (mean and standard deviation).

Nanometre smooth Lactose

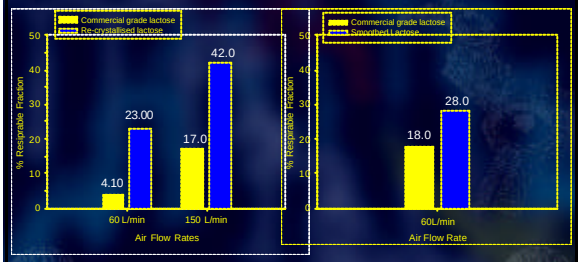


- Significant decrease in separation energy.
- Positively skewed distribution.

The role of surface roughness on particle adhesion



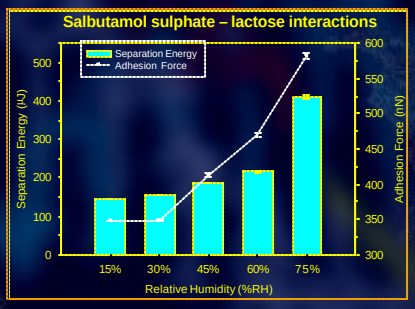
The effect of surface rugosity on %FPF

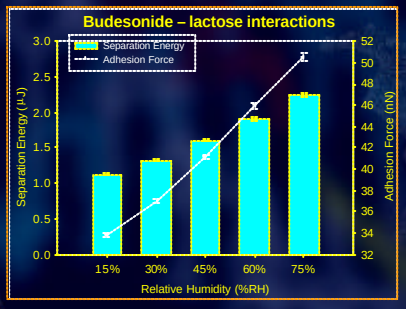


Dose: 400μg Salbutamol sulphate Device: Rotohaler®
D. Ganderton, (1992) J.Biopharm. Sci., 3 101-105.
Patent: US 5,376,386

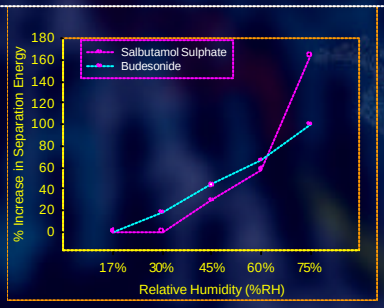
Dose: 200μg BDP Device: Pulvinal®
P. Colombo et al. (2000) RDD VII, 629 – 631.
Patent: WO 01/05429

The Role of RH on drug-lactose interactions





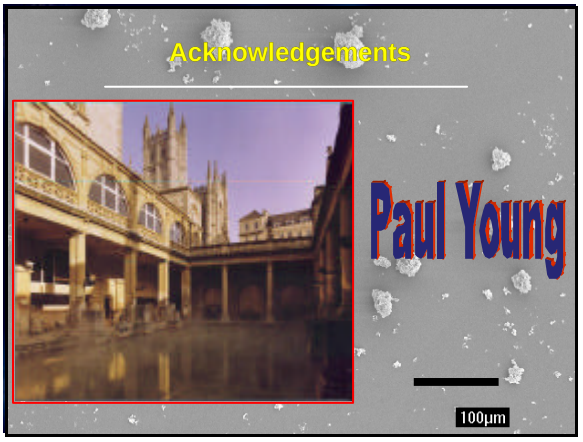
Normalised Separation Energy



Hydrophobic, water insoluble budesonide more susceptible to capillary interactions at low RH

General conclusions

- AFM provides a fundamental insight into the microscopic interactions which govern bulk properties of a DPI formulation.
- Variation in exipient surface roughness at the nanometre-Ångstrom scale dramatically influences drug-lactose interactions.
- Environmental conditions may play a critical role in the aerolisation efficiency and therapeutic efficacy of respirable particles.
- In combination with bulk techniques, AFM may potentially play a pivotal role in the design and modifications of DPI formulations.


Acknowledgements
Paul Young
100µm