Pharmaceutical Surface Science: A potential way forward!

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Synopsis

• Introduction
• AFM Studies
  – Adhesion Force Measurements
  – Characterisation of Amorphous domains
  – Surface Stability of Amorphous domains
• Conclusions
• Acknowledgments

Why is surface characterisation important?

- Pharmaceutical processes involve interfacial contact.
- A change in surface nature will affect interfacial interactions.
- The success or failure of a formulation is dependant on the nature of the surfaces.

What influences the surface properties of powders?

- Presence of different crystal habits
- A change in polymorphic form
- Presence of amorphous material
Colloid interactions in air

Particle interactions are primarily dictated by:

I. van der Waals Forces (LW and AB)
II. Electrostatic Forces
III. Capillary Forces

The relative contribution of forces (II.) and (III.) to the total adhesion/cohesion depends on the interacting materials and relative humidity.

Colloidal Interactions in solution

Extended DLVO Theory

- Lifshitz-van der Waals Interaction
- Electrostatic double layer forces
- Lewis acid/base interaction
  - Hydrogen bonding
  - Hydrophobic interaction
- Steric interaction
  - Entropic contribution
  - Osmotic contribution

Additional factors that influence particle adhesion

- Intrinsic "free" energy
- Contact Area
- Hardness
- Temp. & %RH

Atomic Force Microscope (AFM)

\[ F = k \Delta x \]

\( k \) = spring constant (N/m)
\( \Delta x \) = cantilever deflection

In-situ AFM set-up

- Hermetically sealed system.
- Potential for high vapour pressure propellant studies.
- Forces and surface stability measurements.
Adhesion Energy

Approach
Retract

Anatomy of a Force Curve

<table>
<thead>
<tr>
<th>Force (nN)</th>
<th>Scanner Displacement (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>500</td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Commercial Grade Lactose

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

Atomically Smooth Lactose

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

Modified \(\alpha\)-lactose surfaces

- Dominant \(\{011\}\) face
- \(R_q = 2.51\AA\)

Nanometre smooth Lactose

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

The role of surface roughness on particle adhesion

- Separation energy
- Statistical analysis
- Effect of surface roughness.
Conclusion (1)

- AFM provides a fundamental insight into the microscopic interactions which govern bulk properties of a DPI formulation.
- Variation in excipient surface roughness at the nanometre-Ångstrom scale dramatically influences drug-lactose interactions.
- Controlling surface roughness of excipient surfaces may lead to increased fine particle delivery.

Can the surface roughness of commercial grade lactose be controllably modified?

UoB surface engineered Lactose

![Graph showing the effect of etching conditions on %FPF](Image)

- Saalbutamol Sulphate:Lactose (1 : 67.5 %w/w) blend
- In vitro apparatus: TSI @ 60 L/min (cut-off dₜₐₐ = 6.4µm).
- Cyclohaler device (n = 10)

Crystalline vs. Processed

- Generation of Amorphous regions
  - Thermodynamically metastable
  - Physico-chemical instability
  - Irreversible changes to a formulation

Is a few % amorphous content important?

If all at the surface!
- Altered interfacial interactions
- Change in product properties
- Batch-to-batch variation

How do we measure the nature of processed powder surfaces?
Phase Imaging

Weak Adhesion
Small shift

Strong Adhesion
Large shift

Drive Oscillation
Cantilever Response

Oscillating Cantilever

Cross section of a Starch particle

Amplitude
Phase

Salbutamol Sulphate Crystal

Topography

Phase

Processed material

A. 6 minutes mill
B. 12 minutes mill
C. 18 minutes mill
C. 24 minutes mill

Processed salbutamol sulphate crystal

Topography

Phase

6 minutes milling

12 minutes milling
Processed salbutamol sulphate crystal

1µm x 1µm

Topography
18 minutes milling

Phase

Processed salbutamol sulphate crystal

1µm x 1µm

Topography
24 minutes milling

Phase

Amorphous mobility

Micronised particle surface

45% RH

Ostwald ripening?

Metastable Surface

Micronised particle (30%RH)

Surface Reconstruction

Micronised particle (65%RH)
Conclusion

- The presence and molecular mobility of amorphous regions will adversely affect the stability and characteristics of a DPI formulation.
- Development of new methodologies are required in the conditioning and processing of inhalation drug products

SEDS: A potential long term solution?

Interfacial interactions and stability may remain an issue?

Constructive particle production wish-list

- High purity micron sized particles
- Defined morphological structures (spherical preferred)
- Defined surface structure (nanometre asperities)
- Single step operation with a dial-up particle size input
- Physico-chemical stable particles
- Controlled physico-chemical properties (surface energy)

Solution atomisation and stabilisation by sonication (SAXS)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>Vapour pressure</td>
</tr>
<tr>
<td>Spray Temp.</td>
<td>Vapour pressure</td>
</tr>
<tr>
<td>Solvent Concentration</td>
<td>Particle size, viscosity</td>
</tr>
<tr>
<td>Flow rate</td>
<td>Degree of solvent evaporation</td>
</tr>
<tr>
<td>Separation distance</td>
<td>Supersaturation, viscosity, particle size</td>
</tr>
</tbody>
</table>

Resulting morphology dependent on surface tension and viscosity of supersaturated droplet?
Conventionally processed material

As supplied Paracetemol

Micronised Paracetemol

SAXS produced paracetemol particles

1% w/w

5% w/w

10% w/w

Ethanol

5.8 kPa

Methanol

12.3 kPa

Acetone

24.0 kPa

Stability of micronised and SAXS produced budesonide particles in a HFA pMDI

Micronised Budesonide

SAXS produced Budesonide

Extended dispersion testing

in-vitro ACI deposition behaviour

• Model budesonide formulations in HFA-227 (100µg dose)
• In vitro apparatus: ACI @ 28.3 L/min
• No significant difference in %FFP and Delivered Dose
The AFM can be used, in real time, to characterise:

- Adhesive characteristics of particulate materials.
- Physical transformations on particle surfaces.
- Thermodynamically metastable amorphous domains, at a nanometre level.
- Long term stability of the powdered systems.

General Conclusions

- In combination with bulk techniques, AFM may potentially play a pivotal role in the design and modifications of DPI and suspension based formulations.
- 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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108 µm