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Physico-chemical interactions in inhaled products

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Synopsis

- Introduction
- Theoretical and experimental studies
  - Interfacial interactions in dry powder formulations
  - Interfacial interactions in pressurised driven formulations
- Conclusions

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Interfacial Interactions

- Govern inter-particulate adhesion
- They are governed by surface thermodynamics (particularly for sols).
- "Fundamental adhesion" is related to the thermodynamic work of adhesion (W_{ad})

$$W_{ad} = -\Delta G_{12} = \gamma_1 + \gamma_2 - \gamma_{12}$$

Dupré (1869)

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Interactions to be controlled and modified

- Drug - Drug Interactions (Cohesion)
- Drug (1) – Drug (2) Interactions (Adhesion)
- Drug - Excipient Interactions (Adhesion)
- Drug - Device Interactions (Segregation)

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

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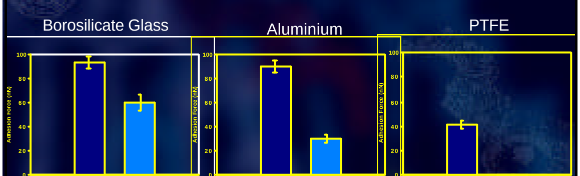
Start with a result!



Adhesion studies under ambient environmental conditions

In situ adhesion studies in a model propellant (2H, 3H perfluoropentane (HPFP))

What controls these interactions and can we modify them ?

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Colloidal Interactions in solution

Extended DLVO Theory:

- Lifshitz-van der Waals Interaction
- Electrostatic double layer forces

(DLVO Theory)

- Lewis acid/base interaction
  - Hydrogen bonding
  - Hydrophobic interaction
- Steric interaction
  - Entropic contribution
  - Osmotic contribution

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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.

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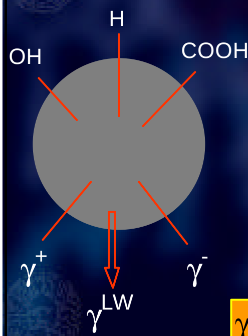
Physico-chemical Link



- 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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Polar interactions

- Electron acceptor – electron donor interactions are asymmetrical:
  - The electron acceptor (γ^+) parameter is usually quite different to the electron-donor (γ^-) parameter
  - Interfacial interactions are 'reciprocal' (not additive).
  - Thus, electron acceptors of substance i will interact with electron donors of substance j, and vice versa:

$$\Delta G_{ij}^{AB} = -2\sqrt{\gamma_i^+ \gamma_j^-} - 2\sqrt{\gamma_i^- \gamma_j^+}$$

We need to measure γ^{LW}, γ^+ and γ^-!

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Surface and Interfacial Energies

- At present, there is no direct method available for determination of the surface energetic properties of a solid.
- May be regarded as the sum of the free energy of all adsorption sites per unit area (mJ/m^2).
- Related techniques
  - Contact angle
  - Inverse gas chromatography (IGC)
  - Capillary intrusion
  - Immersion calorimetry
  - Vapour sorption?

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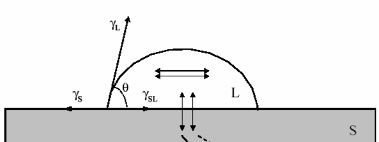

$$(1 + \cos\theta)\gamma_L = -\Delta G_{SL}^{TOT} = -\Delta G_{SL}^{LW} - \Delta G_{SL}^{AB}$$

$$(1 + \cos\theta)\gamma_L = 2\left(\sqrt{\gamma_S^{LW}\gamma_L^{LW}} + \sqrt{\gamma_S^+\gamma_L^-} + \sqrt{\gamma_S^-\gamma_L^+}\right)$$

Young-Dupré equation

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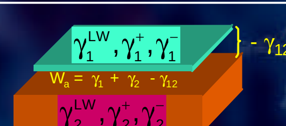
Work of adhesion (W_a)



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

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

- In vacuo, always attractive and cannot be zero
- γ^{LW} of all materials in the condensed state has a finite, positive value

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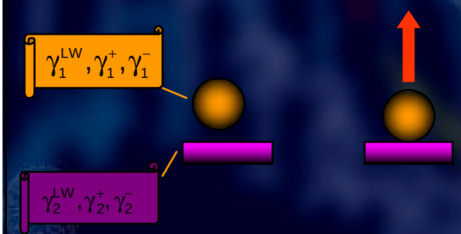
Pull-off Forces

$F_{Pull\text{-}off} = 2\pi RW_{ad}$ (DMT) $F_{pull-off} = 4\pi R\left(\sqrt{\gamma_1^{LW}\gamma_2^{LW}} + \sqrt{\gamma_1^{+}\gamma_2^{-}} + \sqrt{\gamma_1^{-}\gamma_2^{+}}\right)$

$F_{Pull\text{-}off} = 3/2\pi RW_{ad}$ (JKR) $F_{pull-off} = 3\pi R\left(\sqrt{\gamma_1^{LW}\gamma_2^{LW}} + \sqrt{\gamma_1^{+}\gamma_2^{-}} + \sqrt{\gamma_1^{-}\gamma_2^{+}}\right)$



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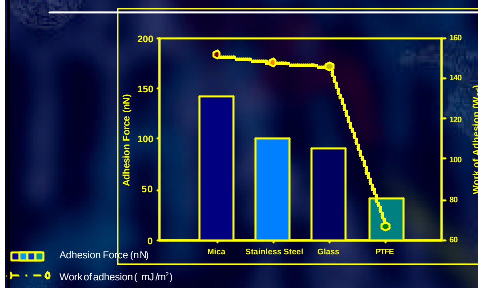
Force measurements at low %RH



$F_{ad} \propto W_{ad}$

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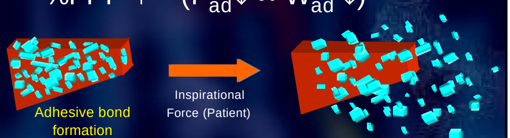
Relationship between %FPF and adhesion in a carrier based formualtion

%FPF ↑ $(F_{ad}\downarrow \propto W_{ad}\downarrow)$



$F_{adhesion}$ (drug-excipient) ∝ contact area ∝ work of adhesion

$F_{cohesion}$ (drug-drug) ∝ contact area ∝ work of cohesion

Need to balance adhesion/cohesion to maintain stability

$W_{ad} >>> W_{coh}$

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Energetic analysis of experimental measurements

Material	γ^{LW} (mJ/m²)	γ^{+} (mJ/m²)	γ^{-} (mJ/m²)
Salbutamol	41.5	19.3	5.8
Ipratropium bromide	44.9	8.7	26
Trehalose A	42.9	26.1	5.9
Mannitol A	57.7	19.9	0.0
Mannitol B	68.6	21.3	0.0

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

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

$$SEI = 2\left(\sqrt{\gamma_1^{LW} SA_1\, \gamma_2^{LW} SA_2} + \sqrt{\gamma_1^{+} SA_1\, \gamma_2^{-} SA_2} + \sqrt{\gamma_1^{-} SA_1\, \gamma_2^{+} SA_2}\right)$$

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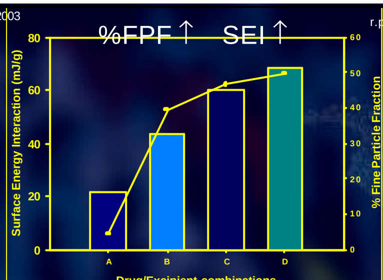
%FPF ↑ SEI ↑



Ref	Excipient	Drug	SEI (mJ/g)	% FPF
A	Mannitol A	Salbutamol	21.3	4.2
B	Mannitol B	Ipratropium	43.7 ↑	39.3 ↑
C	Trehalose A	Salbutamol	60.4 ↑	46.6 ↑
D	Trehalose A	Ipratropium	68.1 ↑	49.7 ↑

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

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Surface Thermodynamics and FPF

- The foundations of physico-chemical interactions, particularly for carrier based DPI formulations, are governed by work of adhesion.
- Theoretical analysis of experimental measurements suggests that:
  - Understanding and controlling non polar and polar surface energies of drug and excipient may affect stability and fine particle delivery.
  - Judicious selection of drug and excipient combination may be possible
  - Fine particle delivery performance is dependant on the work of adhesion being greater than work of cohesion

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Drug-Canister model interactions

Material (2)	Solvent (3)	Repulsive LW interaction (mJ/m²)	Attractive LW interaction (mJ/m²)	Attractive AB interaction (mJ/m²)	ΔG_{132} Total interaction (mJ/m²)
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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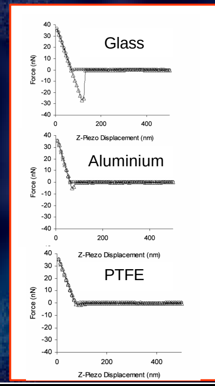
Direct Force Measurements



F_{ad} = 28.63 nN (ΔG_{132} = -31.40 mJ/m²)

F_{ad} = 6.24 nN (ΔG_{132} = -17.67 mJ/m²)

F_{ad} = 0.85 nN (ΔG_{132} = -7.80 mJ/m²)

P. Young and R. Price, J. Coll. Int. Sci (2003) In Press.

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Conclusions

- Varying acid-base properties of surfaces and solutions may be the basis for target oriented design of interfaces.
- “Practical adhesion” depends not only thermodynamic surface characterisation.
- 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.