A Digital Approach from Crystallographic Structure to Particle Attributes for Predicting the Formulation Properties of Inhalation Pharmaceuticals

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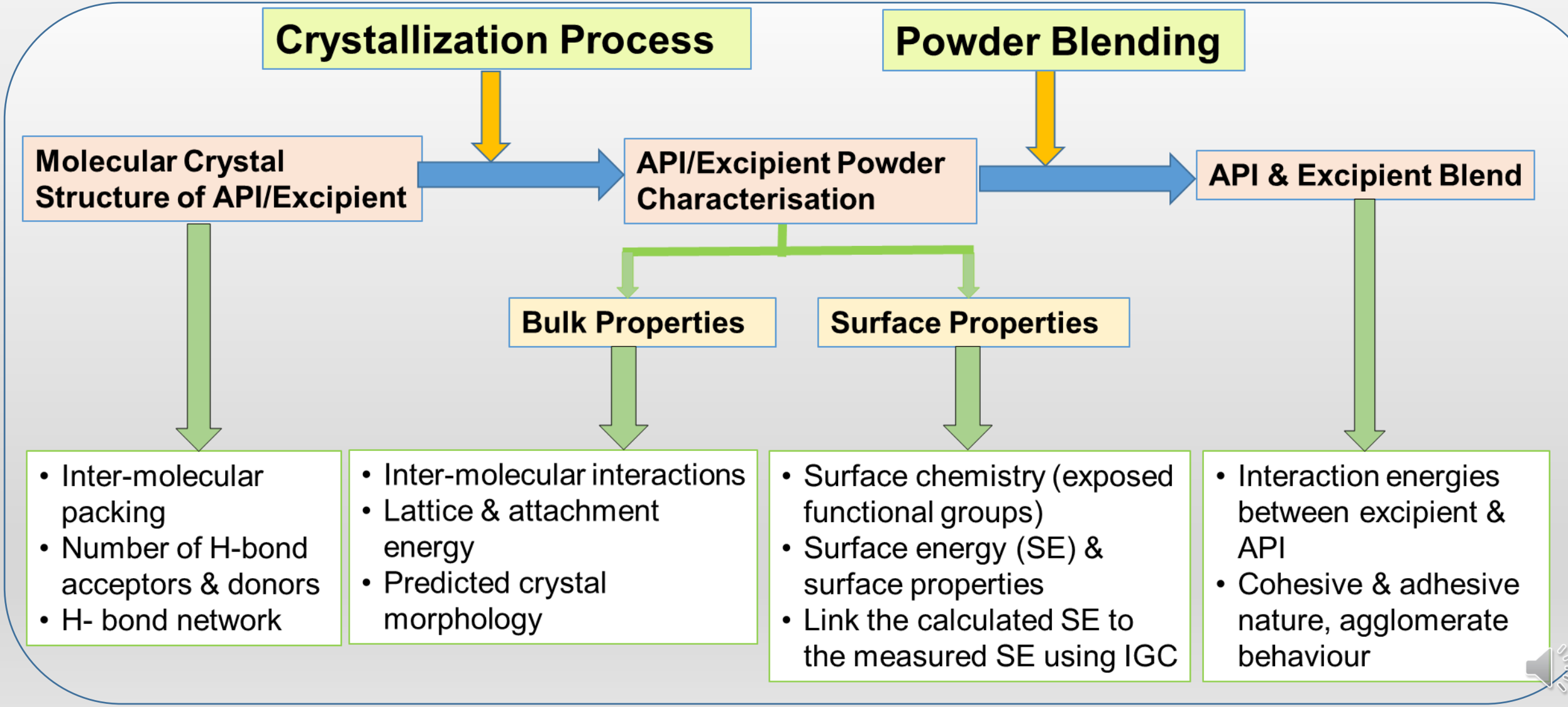
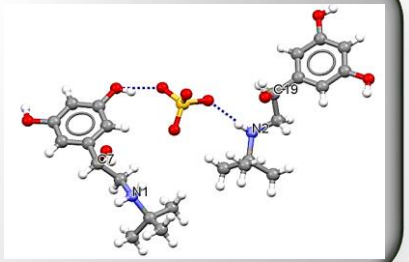
A Digital Workflow from Crystallographic Structure to Particle Properties for the Prediction of the Formulation Properties



Material and Methodology

Material

- Molecular formula: $2[C_{12}H_{20}NO_3]^+.SO_4^{2-}$
- Crystal structure obtained from CCDC (refcode: ZIVKAQ)



Computational method

- Partial atomic-charges calculated using semi-empirical quantum mechanics MOPAC.
- Lattice energy, slice (E_{sl}^{hkl}) & attachment energies (E_{att}^{hkl}) calculated with HABIT98
- Crystallisation energy : $E_{cr} = E_{att}^{hkl} + E_{sl}^{hkl}$
- The relative growth rate (R_{hkl}) is proportional to E_{att}^{hkl}
- Surface energy of crystal surfaces was calculated by

$$\gamma_{hkl} = \frac{Z * d_{hkl} * |E_{att}^{hkl}|}{2 * N_A * V}$$

where Z: the number of molecules in unit cell, d_{hkl}: thickness of growth step layer, N_A: Avogadro's constant & V: unit cell volume.

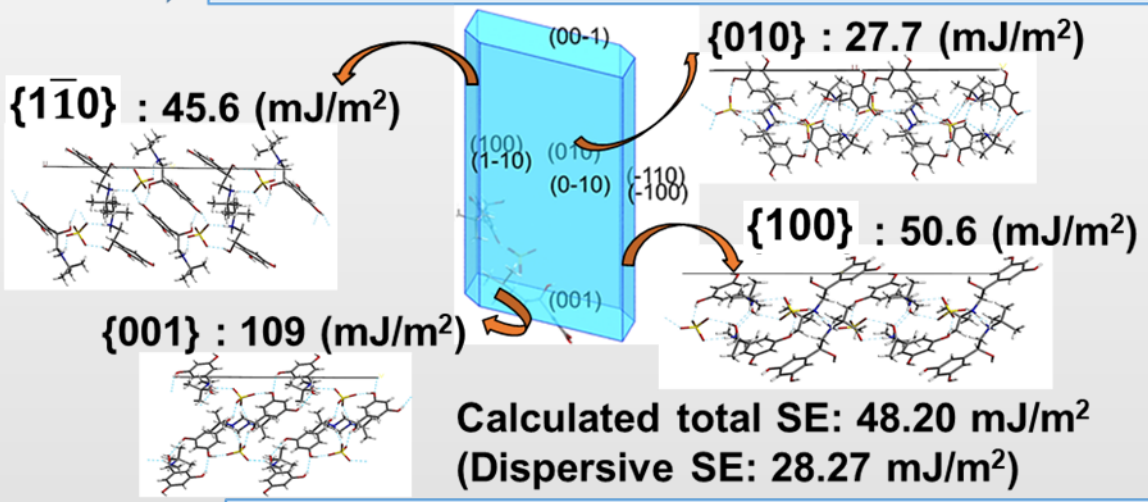
Experimental method

- TBS crystals prepared by cooling crystallisation for comparison to the *in-silico* predicted crystal morphology.
- Surface energy (SE) analysis conducted using a Surface Energy Analyser (iGC-SEA, SMS).
- Non-polar & polar probes injected into column with 0.5% to 13% surface coverage for all probes, except n-decane.
- The dispersive (γ_d) & acid-base (γ_{ab}) components of SE calculated using Dorris-Gray method & Peak Centre of Mass Parameter.
- All measurements performed triplicate for TBS supplied by AZ.

Important Findings & Discussions

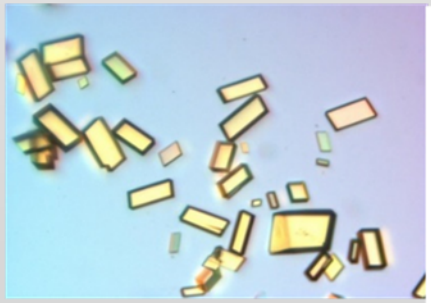
Terbutaline Sulfate (TBS)

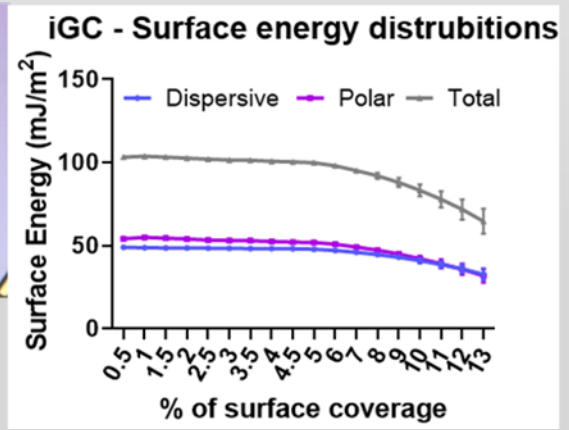
In-silico Characterisation (Morphology, Surface Chemistry & Surface Energy (SE))



Calculated total SE: 48.20 mJ/m²
(Dispersive SE: 28.27 mJ/m²)

Experimental Crystal Morphology & SE Measurements





- Predicted morphology agrees well with the observed experimental morphology, with the {010}, {100}, {001} and {1 $\bar{1}$ 0} surfaces.
- IGC data showed surface energy decreased with increasing surface coverage.
- SE of the {1$\bar{1}$0} and {001} surfaces were greatest whilst the SE of the {010} is the lowest.
- Measured SE correlates well with calculated SE of the most energetic surface {001}, suggesting that experimental technique probes higher SE sites.

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Conclusions & Acknowledgements

- IGC measures highest-energy surface sites, corresponding to highest SE face with calculated dispersive and total SE correlating better at a higher surface coverage.
- The calculated SE is helpful for assessing and interpreting the measured IGC data, through its ability to both partition SE between the different morphological forms.
- This study demonstrates the utility of synthonic modelling in understanding the surface properties of pharmaceutical materials at the molecular scale through a workflow-based pathway encompassing molecule structure, intermolecular packing, crystal morphology, surface energy and formulation properties.
- The analysis has shown the potential for a molecular modelling approach to study surface-surface contact forces when designing inhalation formulations.

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