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Informatics approaches to particle properties

Andy Maloney, Mat Bryant, Ian Bruno. E-mail: maloney@ccdc.cam.ac.uk

INTRODUCTION

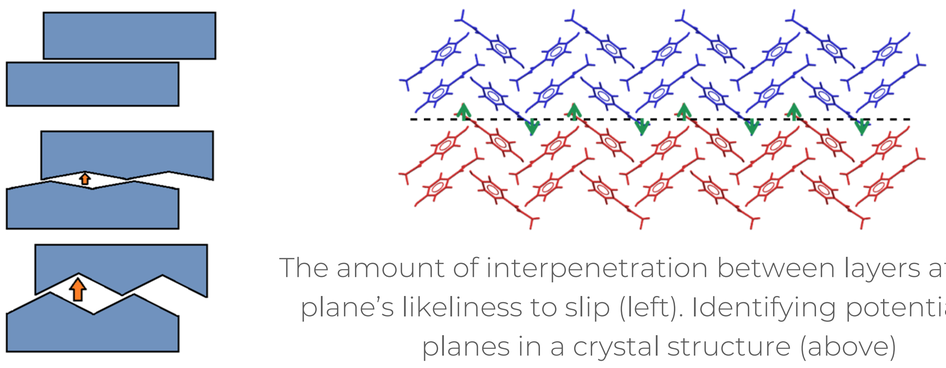
The attrition rate in pharmaceutical development is notoriously high, with as little as one in ten thousand candidate active pharmaceutical ingredients (APIs) realised as a marketed drug product. Many of these failures are associated with safety and efficacy problems, however issues including low solubility and poor performance of particulates in downstream manufacturing processes can render an API non-viable as a drug product.

Here we demonstrate a combination of existing and novel approaches to the assessment and prediction of particle properties intrinsic to the formulation and manufacture of pharmaceuticals. Digital design tools built around the CSD-System suite of software, including Synthonic Engineering methods, can be used to analyse and understand important particle properties and their effects on several key stages of pharmaceutical manufacturing. Ongoing development will produce a robust workflow that brings these approaches together to build on the knowledge gained from each step and explain how this knowledge can be combined to provide resolutions to decisions encountered during formulation and manufacturing processes.

UNDERSTANDING MORPHOLOGY

While the bulk product of an API will never be composed of perfectly formed single crystals of uniform morphology, having an understanding of the dominant faces and potential aspect ratio of the crystals can provide a great deal of information about potential downstream particle behaviour, particularly in terms of flow, sticking and tabletability.

Attachment energy calculations can be used to generate morphologies. Energies can be broken down into different components, meaning that interaction types and strengths can be projected onto the predicted faces, giving information of the reactivity of a face, or the potential for solvent effects on growth rates.

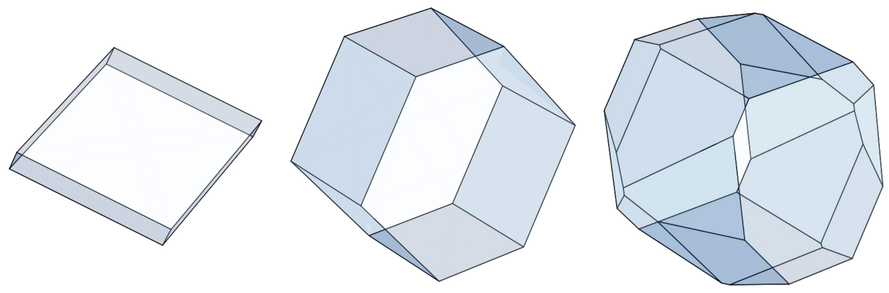


The amount of interpenetration between layers affects a plane's likeliness to slip (left). Identifying potential slip planes in a crystal structure (above)

UNDERSTANDING SURFACE PROPERTIES

The chemistry, energy and topology of a surface all contribute to the behaviour of an API during formulation. The aim of this analysis is to comprehensively describe the surfaces of a crystal in a standardised way. Surface features may correlate with specific properties, enabling risk assessment based on the dominant faces in the morphology.

By understanding the properties of dominant faces, an "average surface behaviour" can be generated for an API. This will change with differences in morphology, so if the surfaces are fully understood then the risks associated with batch variations, specific to an API, can be determined.



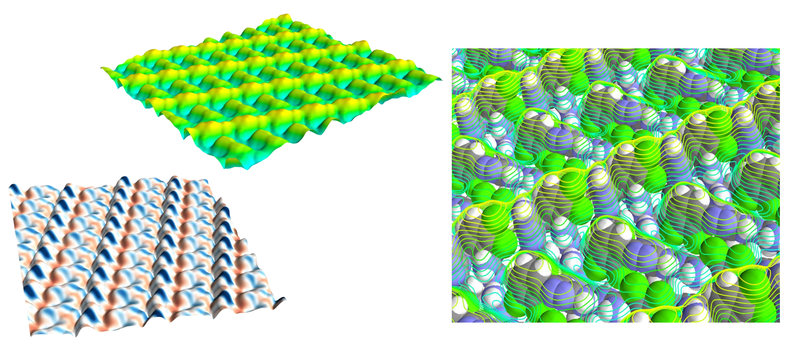
Variations in particle morphology can result from supersaturation effects

UNDERSTANDING MECHANICAL PROPERTIES

Various aspects of the crystal structure may affect the mechanical properties of a material, and result in unfavourable behaviour during manufacturing processes.

Detecting potential slip planes can been shown to correlate well with plasticity and tabletability. These can be identified through automatic scanning through a crystal structure.

Other descriptors, such as the nature of hydrogen bonding and the separating of any slip plane can be used to infer relative mechanical behaviour.



Surfaces coloured by topology (top left), charge distribution (bottom left) and a contour map of the surface topology (right)

Face	% area	Surface Energy (mJ mol^{-1} m^{-2})	Anisotropy Factor	Aromaticity	Donor density	Acceptor density	Roughness	Pi-stacking	Electrostatic %	van der Waals %	H-bonding %
{200}	27	125.1	0.60	13.6	1.74	3.48	2.91	No	3.9	64.3	31.7
{110}	22	132.0	0.53	10.3	1.90	2.50	5.88	No	4.0	54.2	41.8
{1-11}	24	118.1	0.53	9.6	1.10	2.90	3.15	No	5.2	63.6	31.2
{002}	18	104.2	0.53	15.6	1.20	3.09	1.77	Yes	4.7	59.0	36.3
{20-2}	9	111.2	0.50	16.4	1.20	3.50	2.34	Yes	4.1	64.3	31.5

CONCLUSION

By combining these digital design approaches with key experimental measurements, a material's industrially important characteristics such as solubility, tabletability, flow, and crystal growth behaviour can be better understood.

Knowledge gained from these approaches can be used to resolve key formulation and manufacturing decisions, and might anticipate bottlenecks in pharmaceutical processes.

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