International Fine Particle Research Institute

Adhesion of powders to metal surfaces during compaction

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Renewal proposal

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Sticking 1 – Experimental characterisation (overview of years 1-3)

Undesired adhesion of powders to metal punch surfaces during compaction, "sticking", typically occurs at full production scale and is difficult to predict during formulation and process development. The main objective of the project was to predict potential sticking behaviour of a new chemical substance. A range of carefully selected pharmaceutical active ingredients and excipients were tested: Ibuprofen, Aspirin, Paracetamol, Mannitol, Maize starch, Microcrystalline cellulose and Sorbitol. A **database of sticking behaviour** was constructed by characterising sticking under different levels of compaction stress (20, 50, 75, 100, 150, 250 MPa), loading rate (10 mm/min and drop test frame), temperature (room and 50 ˚C) and relative humidity (33% RH and 75% RH). Three repeat tablets were compressed at each testing condition for repeatability. To observe progressive deposition of material on the punch surface, 20 successive compaction experiments were carried out. Sticking was quantified by the amount of powder present on the punch surface after compaction. An image processing routine was developed to determine the percentage area covered together with pixel intensity which is related to the thickness of the deposited layer.

The empirical sticking database allowed us:

1. to formulate **sticking hypotheses** based on temperature, humidity and breakage effects, supported by additional characterisation methods including: AFM for topology, AFM Kelvin probe, SEM/EDX, particle size measurement, and contact angle measurement
2. to construct a **database of powder properties** including chemical formula, physical characteristics, mechanical properties of particles, interaction properties between particles, thermal properties and humidity related properties
3. to relate powder properties to sticking using **Principal Component Analysis (PCA)** for materials with known properties
4. to predict sticking behaviour of new chemical entities, we identified suitable chemical descriptors for the powders (**Mordred descriptors**) which were derived from chemical formula only
5. to perform **Principal Component Analysis** (PCA) to relate chemical formula (Mordred descriptors) to sticking behaviour to powder properties (experimentally determined sticking database) and determine a parameter space for sticking. We included a further 30 materials routinely used in solid dosage form formulation from the

Handbook of Pharmaceutical Excipients for which we did not have sticking information and a further 5 more materials known for their sticking behaviour. A PCA based prediction map for sticking (Figure 1) was generated.

6. to identify a **sticking diagnosis test** and characterise ascorbic acid (predicted to be sticking) and polyethylene Glycol PEG 3350 (predicted to be non-sticking) to **validate** the prediction of the model.

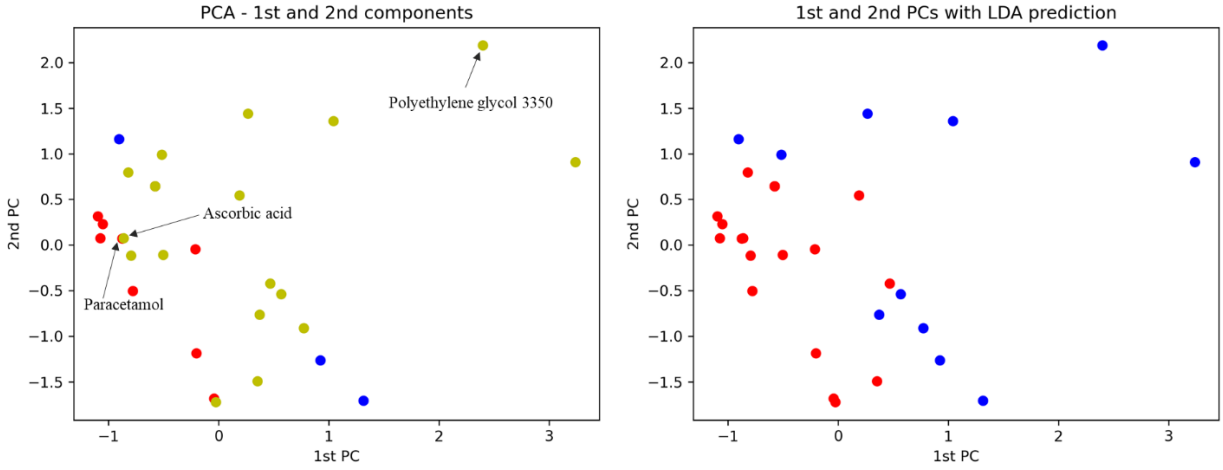


Figure 1 Sticking map obtained by performing PCA using Mordred descriptors. Red: sticking material. Blue: non-sticking materials. Green: uncharacterised material (left) and predicted sticking (right). Ascorbic acid and PEG3350 were selected for validation. Note: validation results and the maps will be finalised for IFPRI AGM.

Sticking 2 – Science: hypothesis verification (renewal proposal)

The materials in Sticking 1 were purposefully selected to test the predictive limits of the material space determined (Figure 1) and the validity of the sticking hypotheses (temperature, humidity and breakage) drawn on empirical considerations. There is scope to improve the predictive capability of Sticking 1 by developing the underlying science in Sticking 2. The two stages of the project are compared in Figure 2.

In Sticking 1 we linked chemical formula directly to sticking (e.g. linked molecule to bulk powder behaviour). This approach disregarded the intervening steps, including molecule-crystal, crystal-particle, particle-bulk and bulk-manufacturability relationships. In Sticking 2, we propose:

1. to link molecule to sticking in two steps: molecule to crystal and crystal to sticking behaviour in compaction, using the PCA based methodology developed in Sticking 1
2. to understand the mechanisms responsible for sticking and verify the three hypotheses drawn in Sticking 1 (temperature, humidity, and breakage) and unpick the complexity of the relationships between material properties (chemical and crystallographic information, physical characteristics of the particles and bulk powders, mechanical properties of particles, interaction properties between particles, thermal properties and humidity related properties) and the process and environment conditions during compaction.

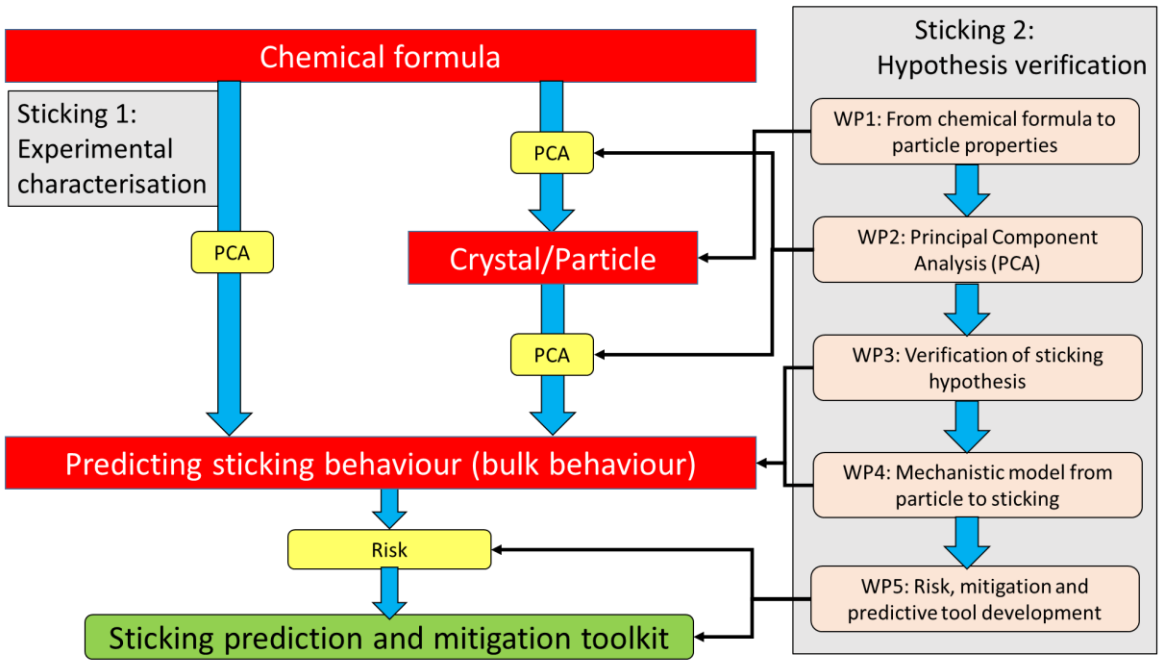


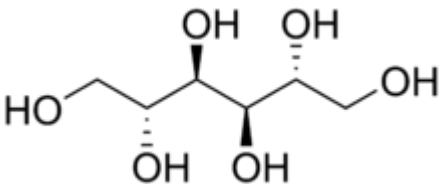
Figure 2 High level comparison of Sticking 1 and Sticking 2

The Mannitol – Sorbitol anomaly

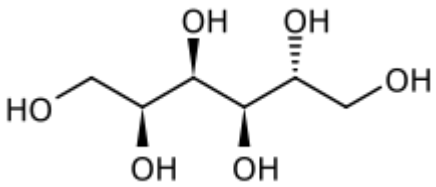
To justify the necessity of the science-based approach and the work packages proposed below, we tested the limits of the predictive capability of Sticking 1. The most striking anomaly discovered in Sticking 1 is summarised below using simplified statements.

- Mannitol and Sorbitol have the same chemical formula $C_6H_{14}O_6$
- Sticking behaviour: Mannitol is sticking while Sorbitol is not sticking
- Chemical structure: Mannitol and Sorbitol are isomers: differ only in the orientation of the hydroxyl group on carbon 2.

Mannitol:



Sorbitol:



- Crystallinity: Mannitol is a crystalline material, while Sorbitol is amorphous (typically sticking is more severe as the amorphous content increases, yet Sorbitol is not sticking)
- Meting point Mannitol 170 ˚C, Sorbitol 100 ˚C (typically sticking is more severe as the melting point decreases, yet Sorbitol is not sticking)
- Solubility: Mannitol is slightly soluble in water, while sorbitol is highly soluble in water (typically sticking is more severe as RH increases)
- Hygroscopicity: Mannitol is less hygroscopic than sorbitol (see RH effect above). This can explain plasticity of sorbitol (please see AGM material evidencing brittle behaviour of Mannitol and plastic behaviour of Sorbitol conditioned at high RH
- Stability: Mannitol is more stable than sorbitol (see RH and T effect above)

Note: for most materials we can find conditions where severe sticking occurs and conditions where sticking is negligible. For any of the broad statements in the bullet points above we can find materials that present exceptions, please see our reports.

WP1: From chemical formula to particle properties

The concept, illustrated in Figure 3 links molecular structure and unit cell packing to crystal habit which exhibiting heterogeneous surface properties affecting sticking behaviour.

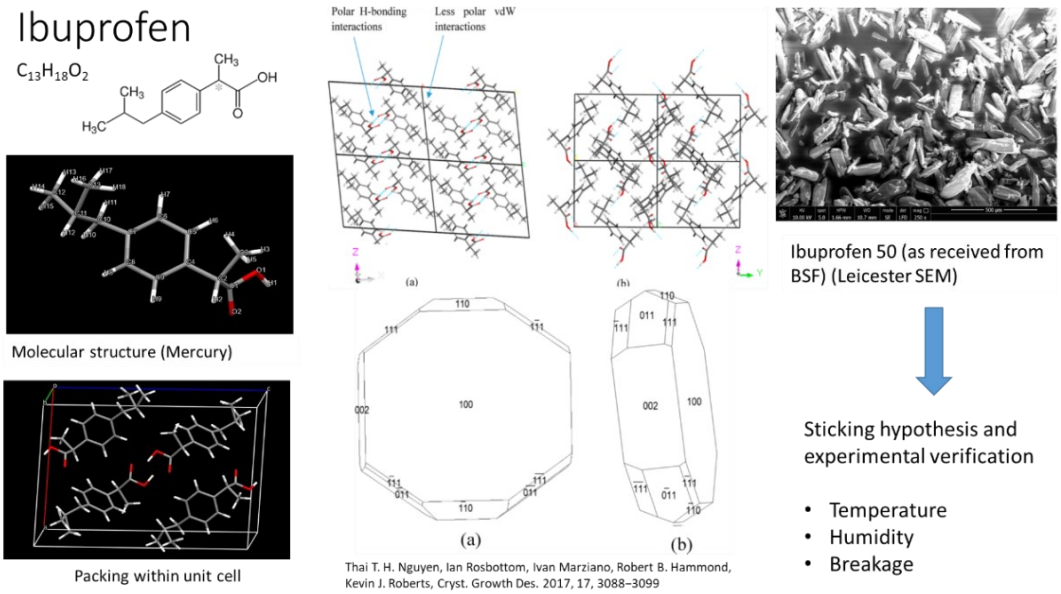


Figure 3: Linking chemical information – crystal information – sticking behaviour

Powder compaction incurs rearrangement, deformation and breakage of particles which can induce a range of bulk and surface changes in crystalline solids with practical implications upon sticking. Such physical and chemical changes in particle properties include the introduction of defects, amorphisation and polymorphic transformations. To characterise these phenomena, we invite industrial partners to propose an IFPRI collaboration with Professor Jerry Heng at Imperial College to provide the necessary academic oversight for this key element of Sticking 2.

WP2: Principal Component Analysis (PCA) to link molecule to crystal and crystal to sticking

As illustrated in Figure 2, in Sticking 2 we link molecule to sticking in two stages, by including the relationships developed in WP1 and applying the PCA methodology developed in Sticking 1. The molecule is described by Mordred descriptors and the crystal is described by habit and physical, thermal and mechanical properties, and surface energy, including heterogeneity.

WP1 and WP2 will provide the framework for improved predictive capability compared to Sticking 1.

WP3: Verification of sticking hypotheses

Three main mechanisms prioritised for investigation in Sticking 1 are:

Temperature. Sticking can be understood as a coupled thermo-mechanical problem with two sources of heat: 1) Powder compaction involves dissipative processes that generate heat and 2) At the tool interface heat is also generated due to friction. As sticking (gradual deposition of the material to the tool surface) progresses the properties of the materials and surfaces evolve, e.g. phase transformations due to stress, strain rate, temperature. We propose to examine the 5 manometer asperity scale using AFM and XPS.

Humidity. We propose experimental characterisation of sticking of detergents. In Sticking 1 we developed chambers with controlled RH using salt solutions systems to condition powders to 9 different RH level. The equipment includes continuous monitoring of RH and temperature in the chambers.

Breakage. Brittle materials or granules break during compaction, creating new surfaces. These new unlubricated surfaces give cohesion/strength to compact but can also lead to sticking to the metal punch. Examples: mannitol, sorbitol.

A numerical modelling framework was developed at Leicester during other projects (inputs include particle size, PSD and particle strength). The model combines a DEM database established by Cantor (2018) to determine the forces applied to the particles during densification and a population balanced method developed by Ovalle (2016) to update PSD. The proposed work will combine the existing framework and breakage experiments and sticking observations as illustrated in Figure 4.

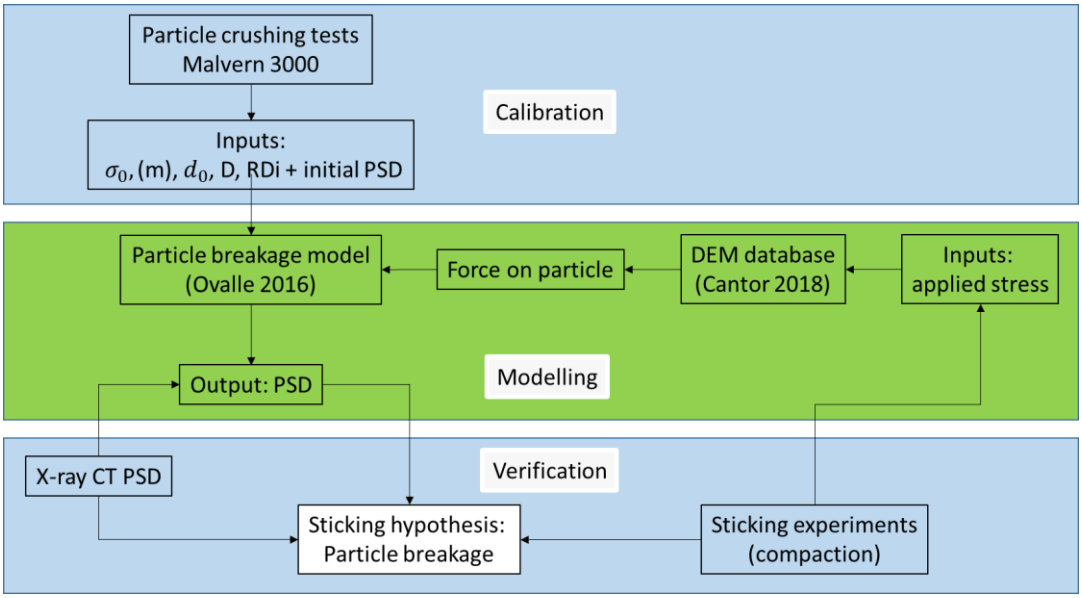


Figure 4: Experimental characterisation of breakage and model development

We propose to:

1) characterise particle breakage using a Malvern laser diffraction analyser with dry feeder using the method of Rajniak et al. (2018)
2) characterise particle breakage during die compaction using X-ray CT (fixture design and manufacturing is under way).

Experimental characterisation will be employed as needed to validate the sticking hypotheses. These include electron microscopy, roughness profilometry, AFM profilometry, Kelvin Probe AFM (work function), particle size measurement, energy-dispersive X-ray spectroscopy (EDS, EDX, EDXS or XEDS) elemental analysis and tensile pull-off force

measurement. In addition, we explored the applicability of several other experimental techniques to provide further understanding on sticking, including AFM with functionally coated probes, PF-QNM - Peak Force Quantitative Nanomechanical Imaging, XPS, Micro-FTIR to identify the functional groups that are attached to the surface of the punch. The indications were that electrostatic forces or mechanical interlocking of the particles with the surface roughness features are more likely than chemical bonds with the metal.

If required, during Sticking 2 we will have access to Electron backscatter diffraction (EBSD) (Leicester) to study crystal orientations, Rahman (Leicester) to provide information about bonds), Diffraction Contrast Tomography (Leicester), DMTA (Leicester), FDIGC (Imperial College), and drop test and shear test (Greenwich).

WP4: Mechanistic model from particle properties to sticking

We propose to develop a framework to quantify the adhesive forces between particles in the powder bed and between powder-metal surface. The framework is based on contact mechanics involving a contact strength parameter η (illustrated in Figure 5) requiring two inputs:

1. the strength of the tablets. Empirical data was already collected for all materials in Sticking 1 under all compaction pressure, temperature, humidity and compaction rates. We propose to analyse the data in more detail, extract a suitable descriptor of the contact strength between particle-particle, and establish correlations between compaction (pressure, rate) and environmental parameters (temperature, RH).
2. the strength of the interface particle-tooling will be characterised using AFM. In Sticking 1 we described the use of AFM for surface topography and Kelvin Probe AFM to distinguish between the surface features. Here we propose the use of AFM probes where the tips are made of API particles, and also silicon probes functionalised with different functional groups in order to characterise the adhesive forces directly.

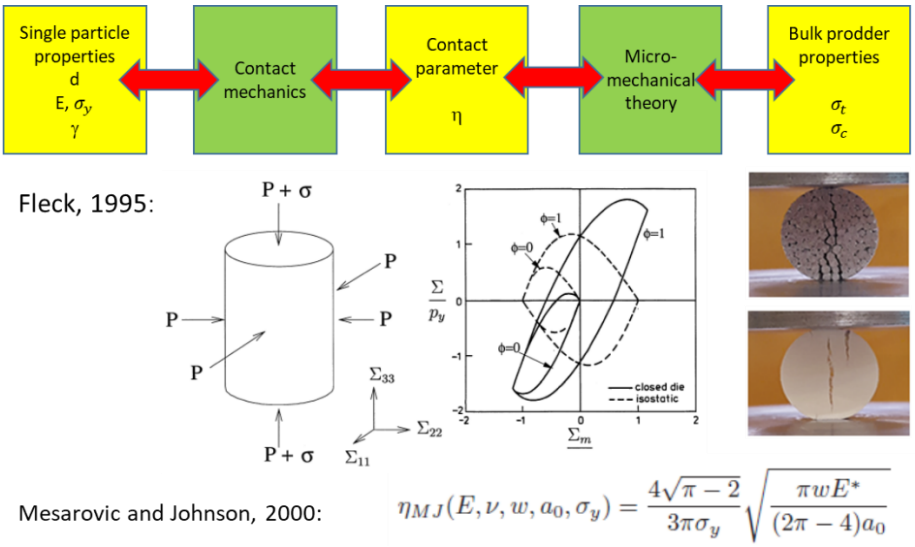


Figure 5: Framework for linking particle to bulk powder compressibility/compactibility

The two components above will feed into the mechanistic model.

WP5: Risk, mitigation strategies, and predictive tool development and validation

Currently sticking is mitigated mostly by lubrication, however, lubrication has detrimental effects on tablet strength and bioavailability. We will refine the sticking regime maps and develop strategies for mitigating sticking through formulation design, addressing specific mechanisms linked to temperature, humidity and breakage.

With input from the industrial partners, we propose to examine the remaining uncertainties and develop a risk based predictive tool.

This WP will includes additional empirical sticking characterisation work for validation purposes:

1) Evaluation of **formulated and lubricated** mixtures (prepared using a Turbula mixer or a shaking device)
2) **Progressive material deposition** over multiple compression events under production conditions using a small scale production press.

The integration of the proposed WPs is illustrated in Figure 2. We welcome input to further refine the programme to accommodate industry need.

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