Adhesion of powders to metal surfaces during compaction

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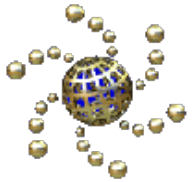

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Sticking team - 15 February 2023

Beatrice Toni Csaba Vishal Pradyumna Ahmad

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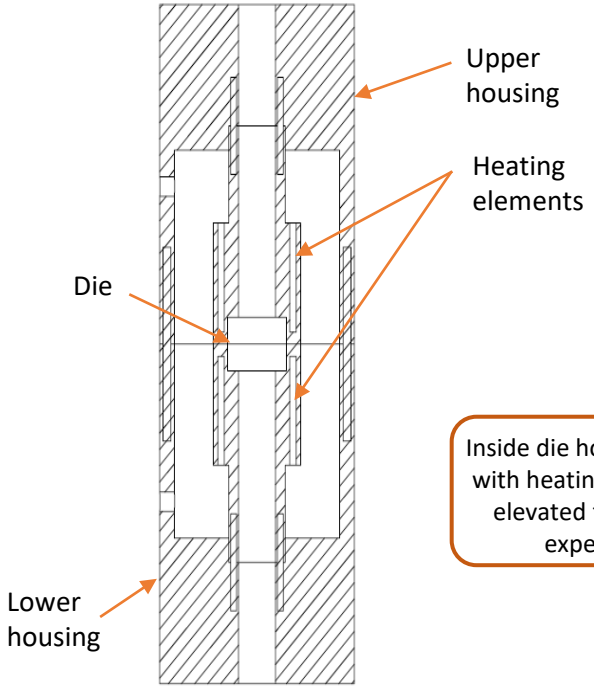
Part 1: Experimental characterisation of sticking

Materials

Material	Formula	Type	Sticking/Not Sticking	Parameters				
				Pressure (MPa)	% RH	Temperature	Strain rate	20 successive tabletting
				20, 50, 75, 100, 150, 200, 250	33%, 75%	50 °C	Impact test	
Ibuprofen	$CH_{13}H_{18}O_2$	API	Sticking	✓	✓	✓	✓	✓
Acetylsalicylic Acid (Aspirin)	$C_9H_8O_4$	API	Sticking	✓	✓	✓	✓	✓
Paracetamol	$C_8H_9NO_2$	API	Not Sticking	✓	✓	✓	✓	✓
Mannitol	$C_6H_{14}O_6$	Excipient	Sticking	✓	✓	✓	✓	✓
NEOSORB (Sorbitol)	$C_6H_{14}O_6$	Excipient	Sticking	✓	✓	✓	✓	✓
Maize Starch B	$(C_6H_{10}O_5)_n + (H_2O)$	Excipient	Not Sticking	✓	✓	✓	✓	-
Microcrystalline Cellulose (MCC)	$(C_6H_{10}O_5)_n$	Excipient	Not Sticking	✓	✓	✓	✓	-

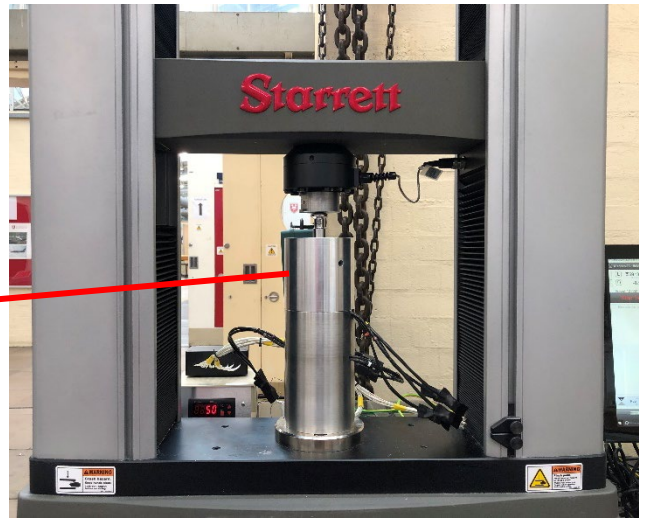
Equipment

1. Slow speed compactions at different pressures
2. High speed compactions using impact tester
3. Compactions at different relative humidity
4. Compactions at elevated temperature

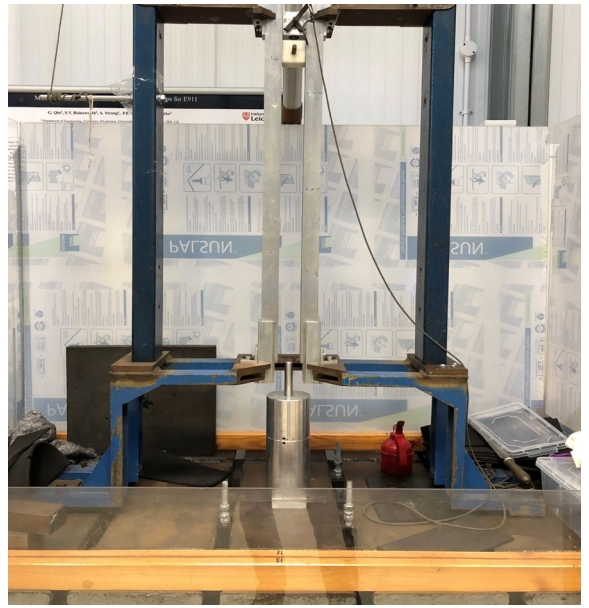


Inside die housing installed with heating elements for elevated temperature experiments

Standard B Tooling



Compaction test machine for slow speed compaction



Impact tester for high speed compaction

Humidity chambers

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Ibuprofen

20 MPa

150 MPa

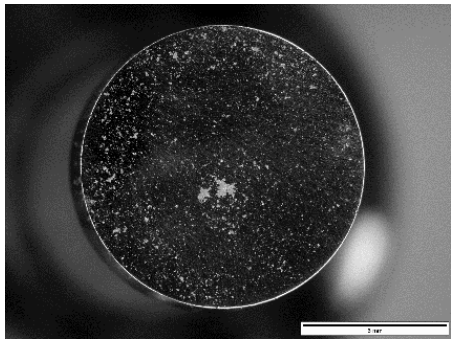
RH- 33%

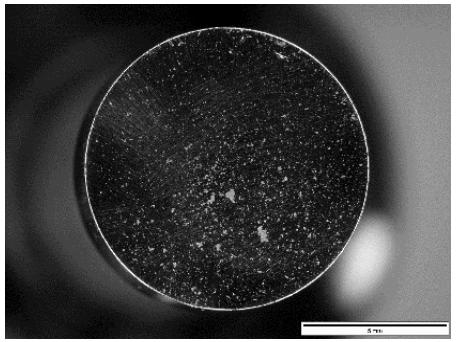
RH- 75%

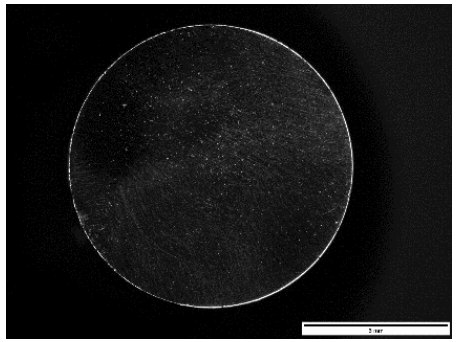
RH- 33%

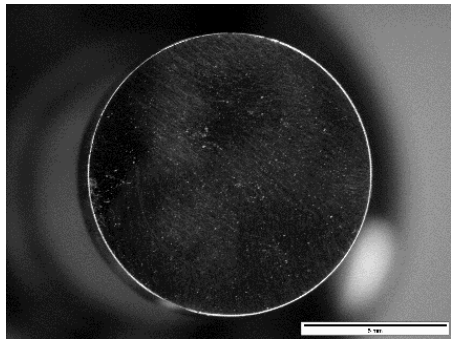
RH- 75%

Room temperature

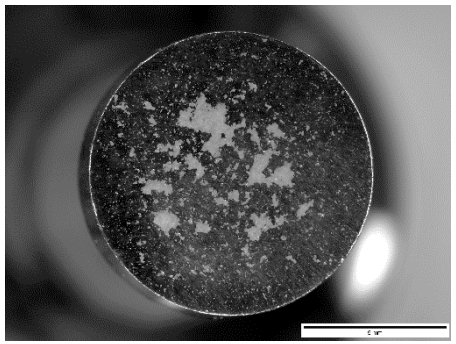


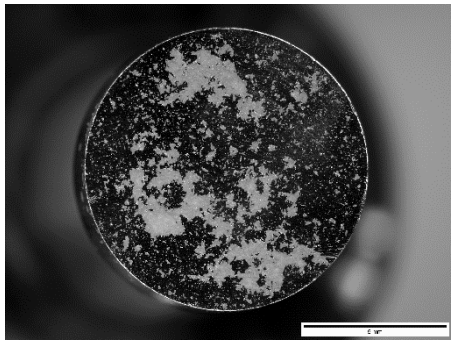


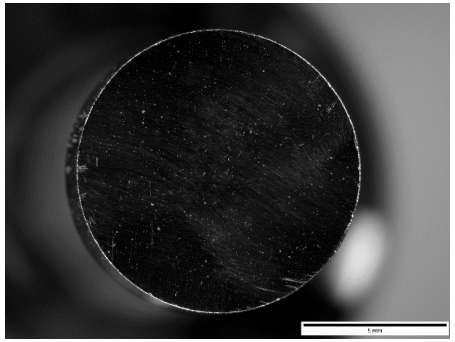


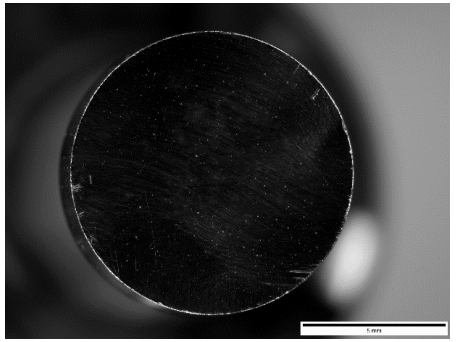


At 50 °C









At both humidity levels and elevated temperature, ibuprofen exhibited less sticking than expected during low speed compaction. However, at high speed, sticking was severe.

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Aspirin

20 MPa

150 MPa

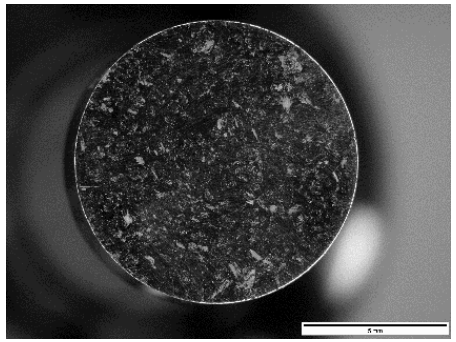
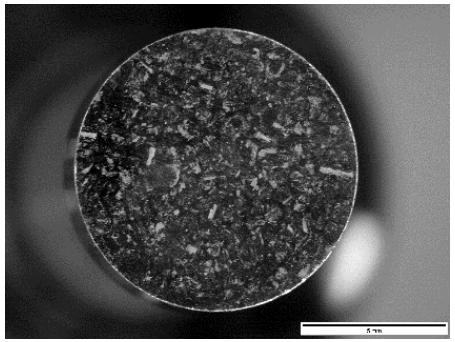
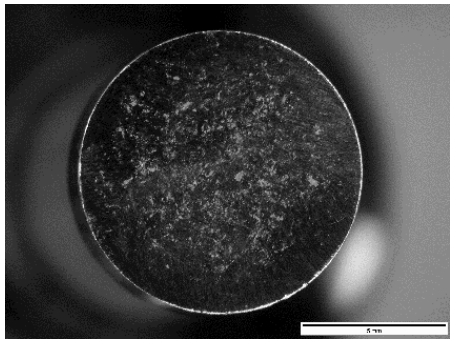
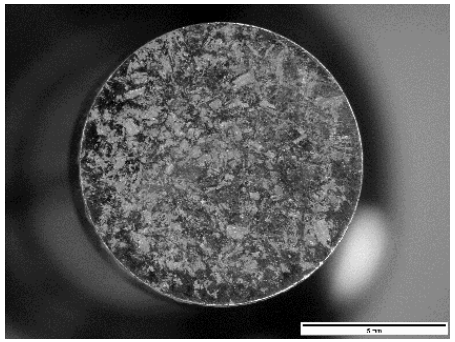
RH- 33%

RH- 75%

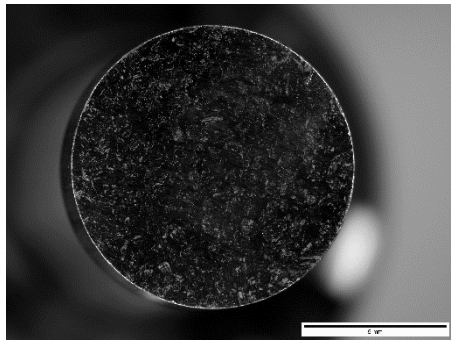
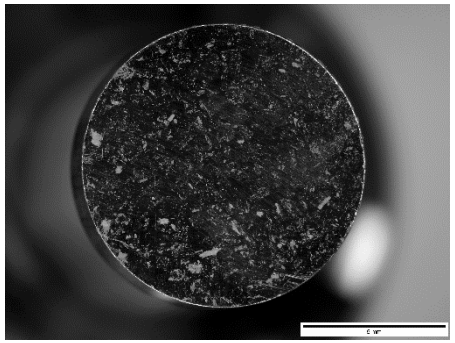
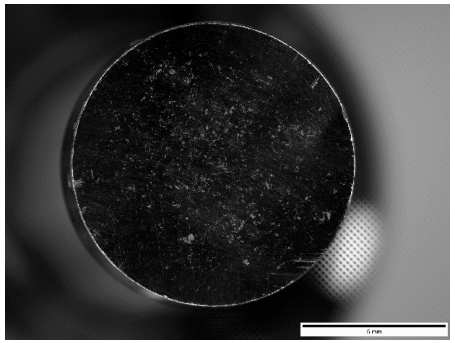
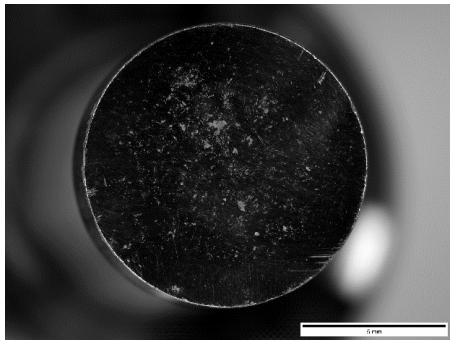
RH- 33%

RH- 75%

Room temperature

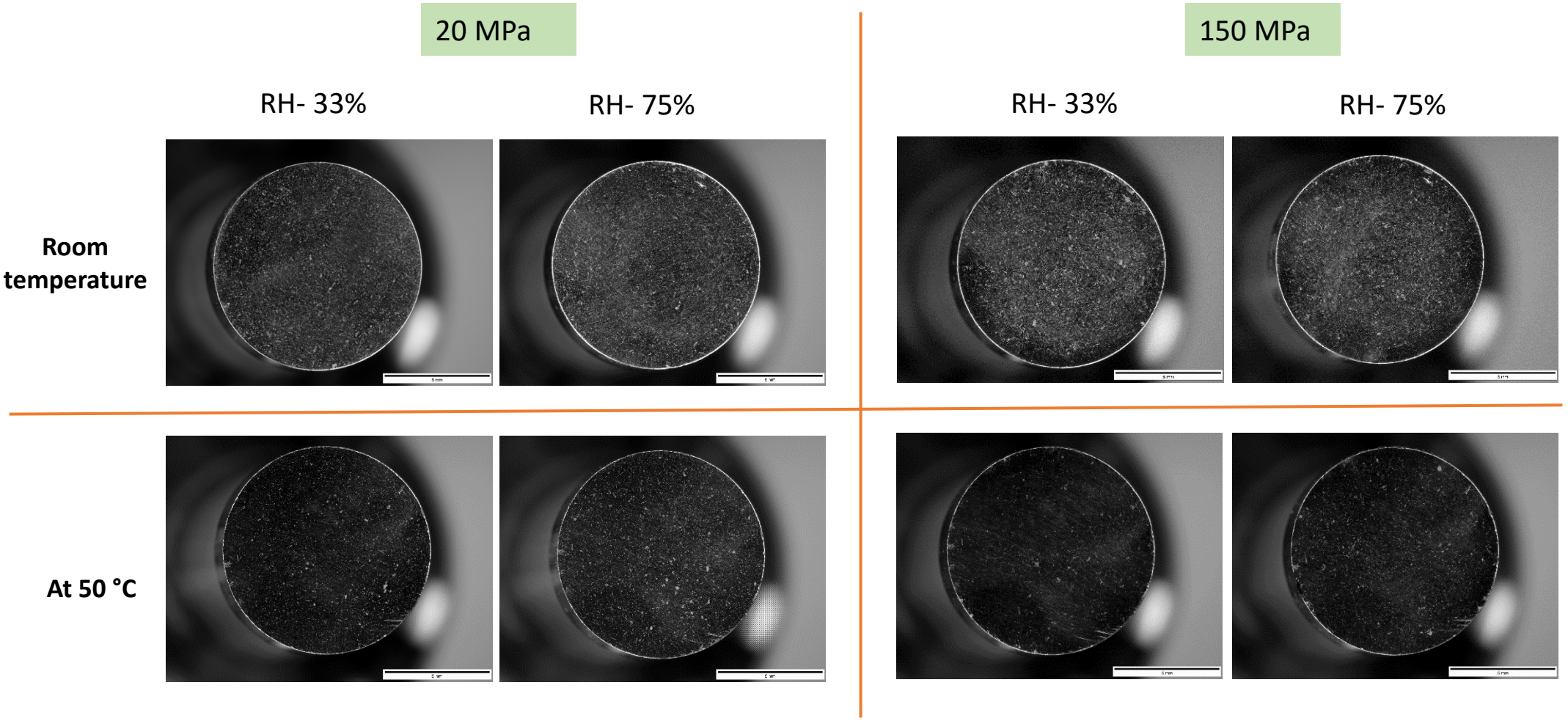





At 50 °C

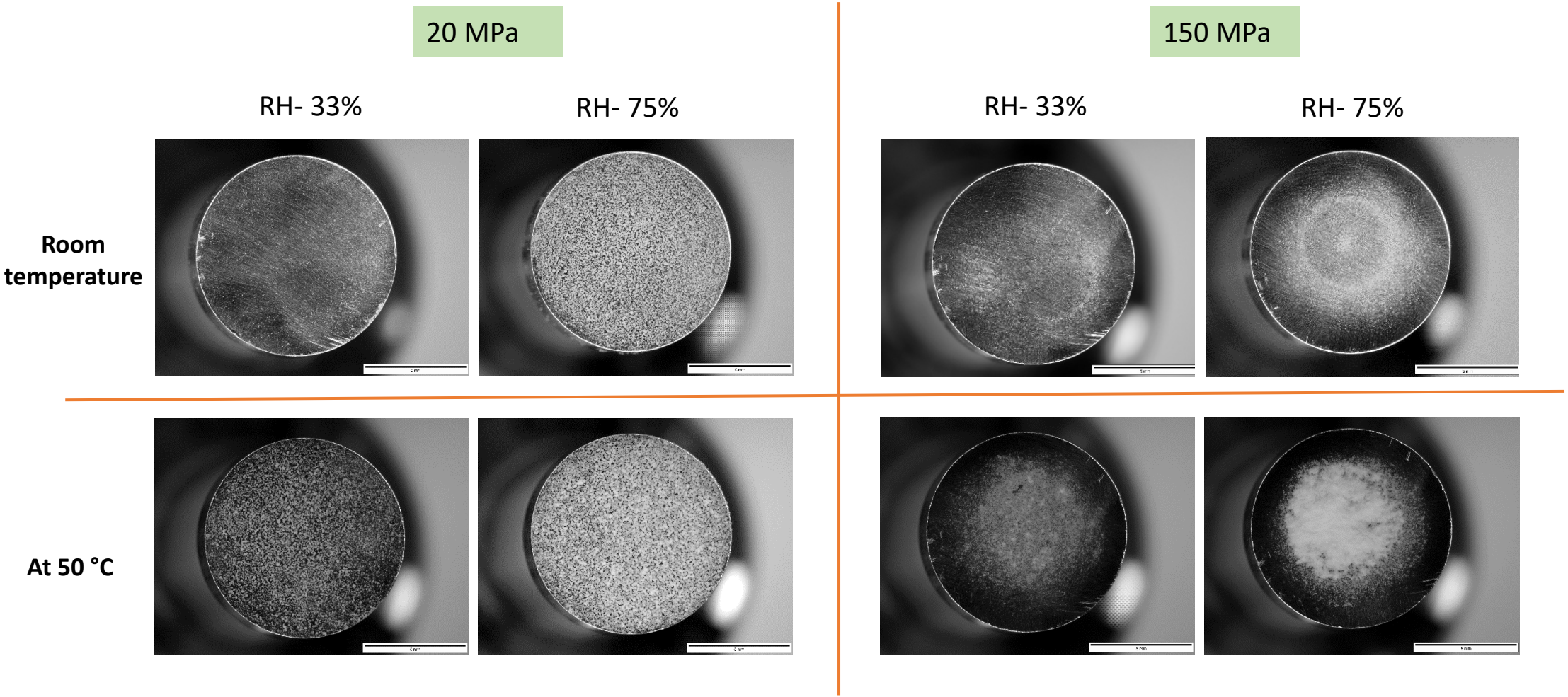
Exhibited more sticking than the other APIs at both humidity levels. However, at 75% RH sticking was severe, and, unexpectedly, sticking was reduced at elevated temperature.

Paracetamol



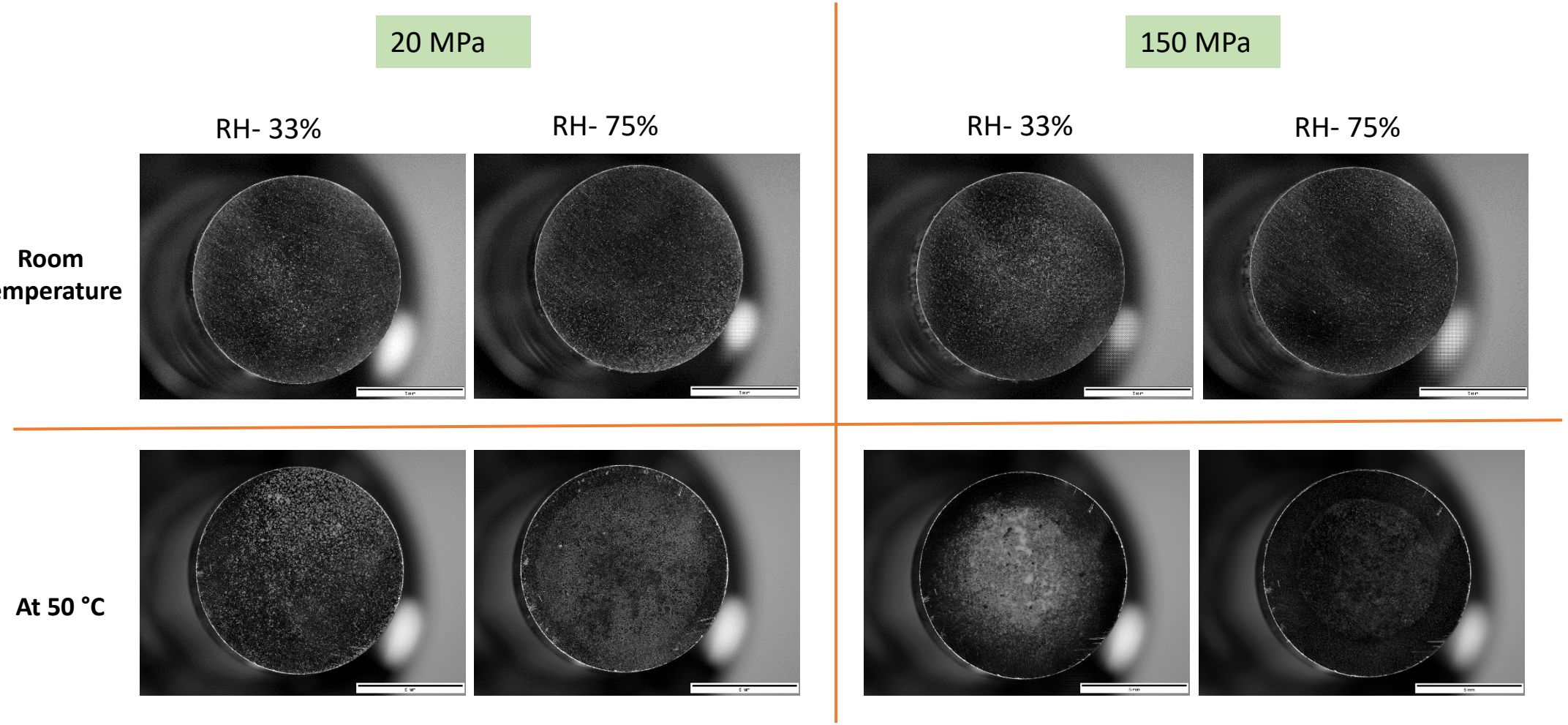
Though it showed more hazing at room temperature (the powder was easy to remove with the help of lab tissue) at elevated temperature hazing was reduced significantly at both humidity levels.

Mannitol



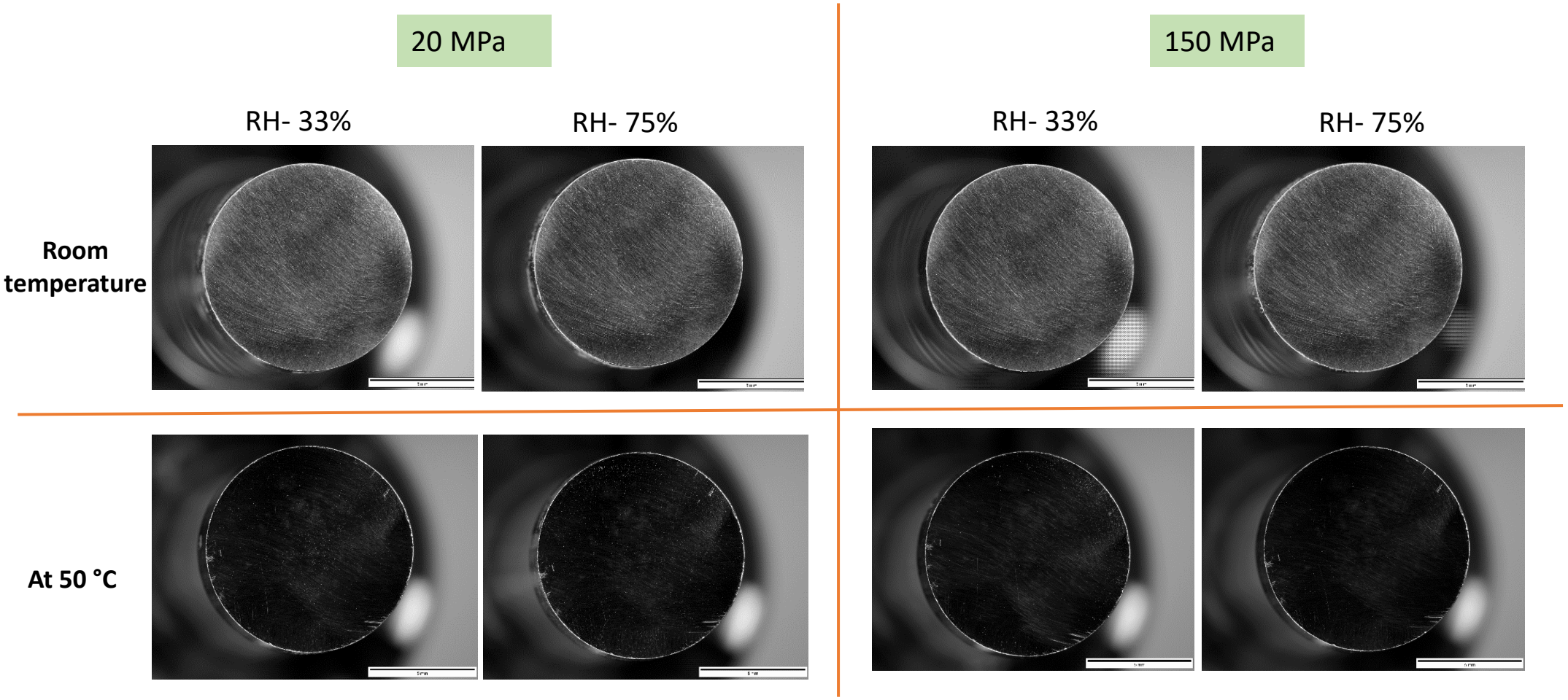
Mannitol showed more sticking at RH 75% compared to RH 33%. Also, at 75% RH and elevated temperature, sticking was increased further.

Sorbitol



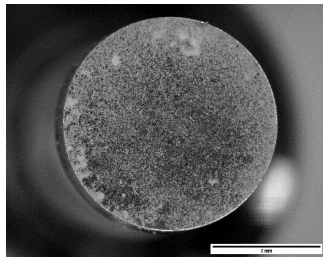
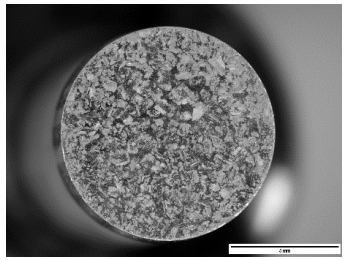
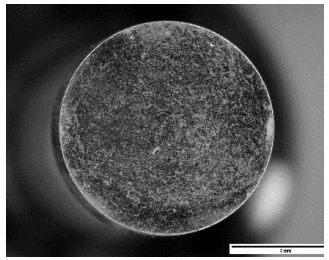
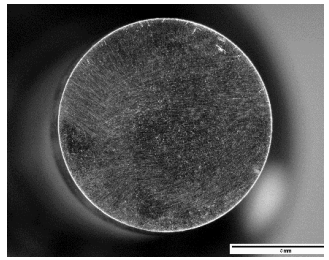
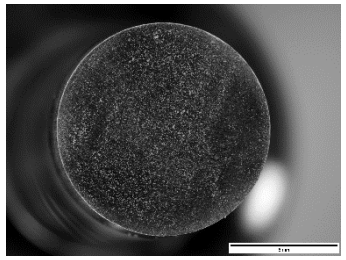
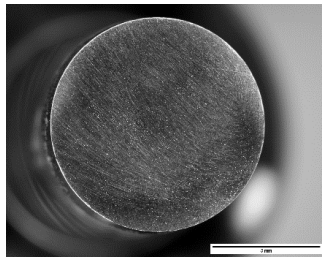
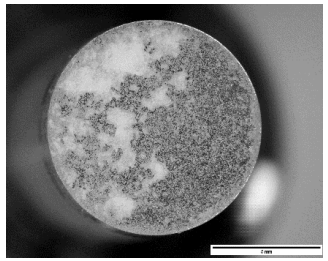
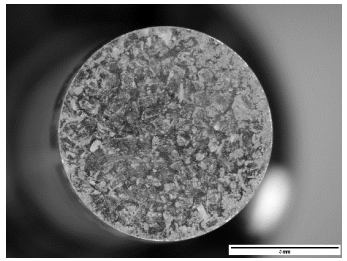
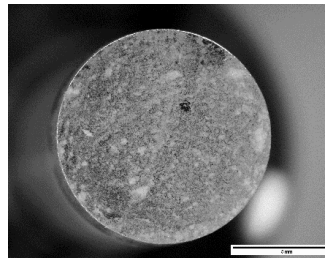
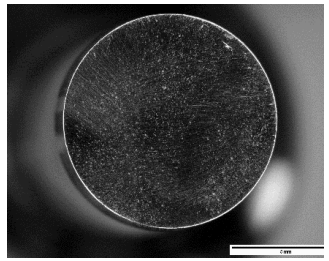
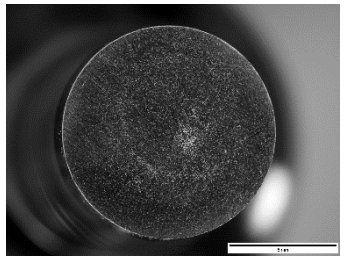
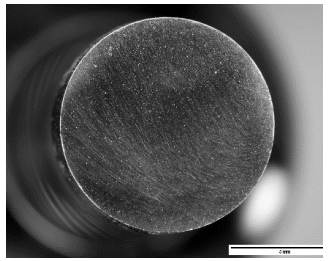
Little to no sticking was observed at room temperature for both humidity levels. However, at 50 °C a small amount of sticking was observed, which was reduced at RH 75%.

Maize Starch



Maize starch did not exhibit any sticking behaviour at either humidity level or at elevated temperature.

High speed compaction

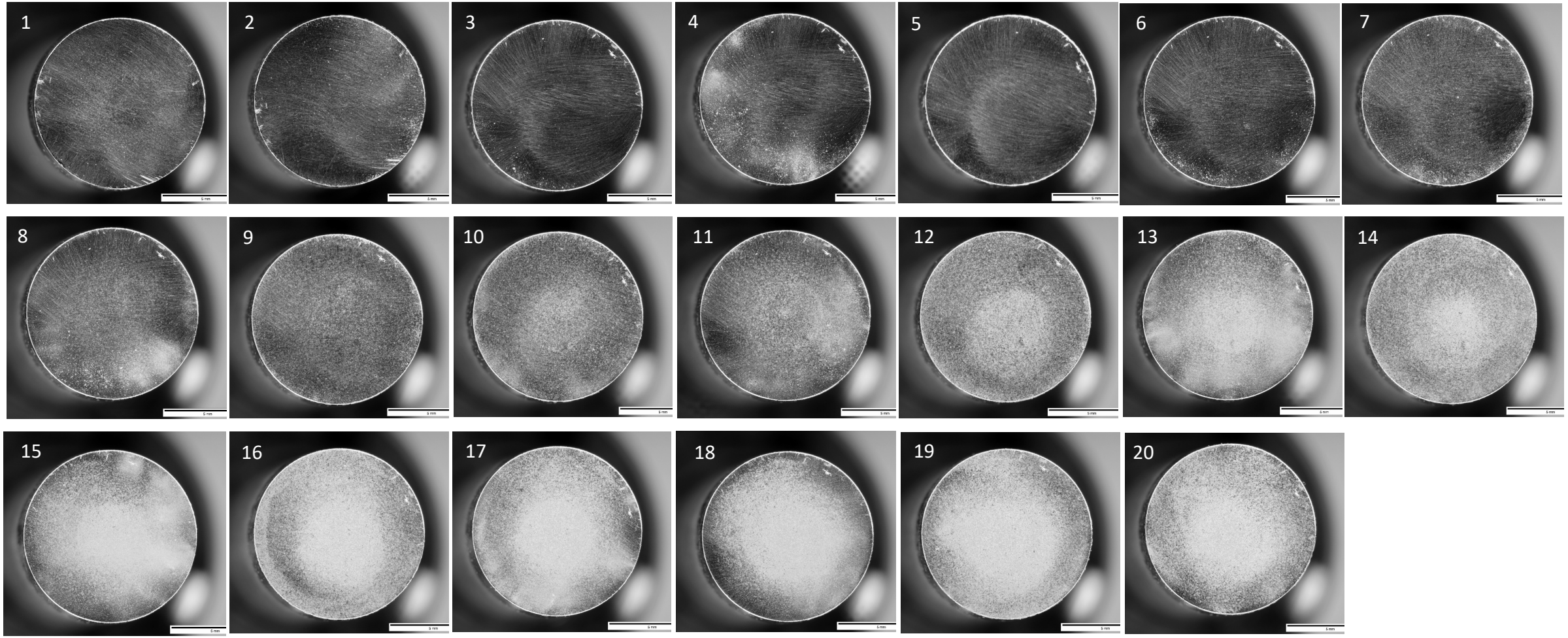
	Ibuprofen	Aspirin	Paracetamol	Mannitol	Sorbitol	Maize starch
RH 33%						
RH 75%						

- Ibuprofen, Aspirin and Paracetamol: severe sticking
- Mannitol, Sorbitol and Maize starch: compaction rate did not show a significant effect

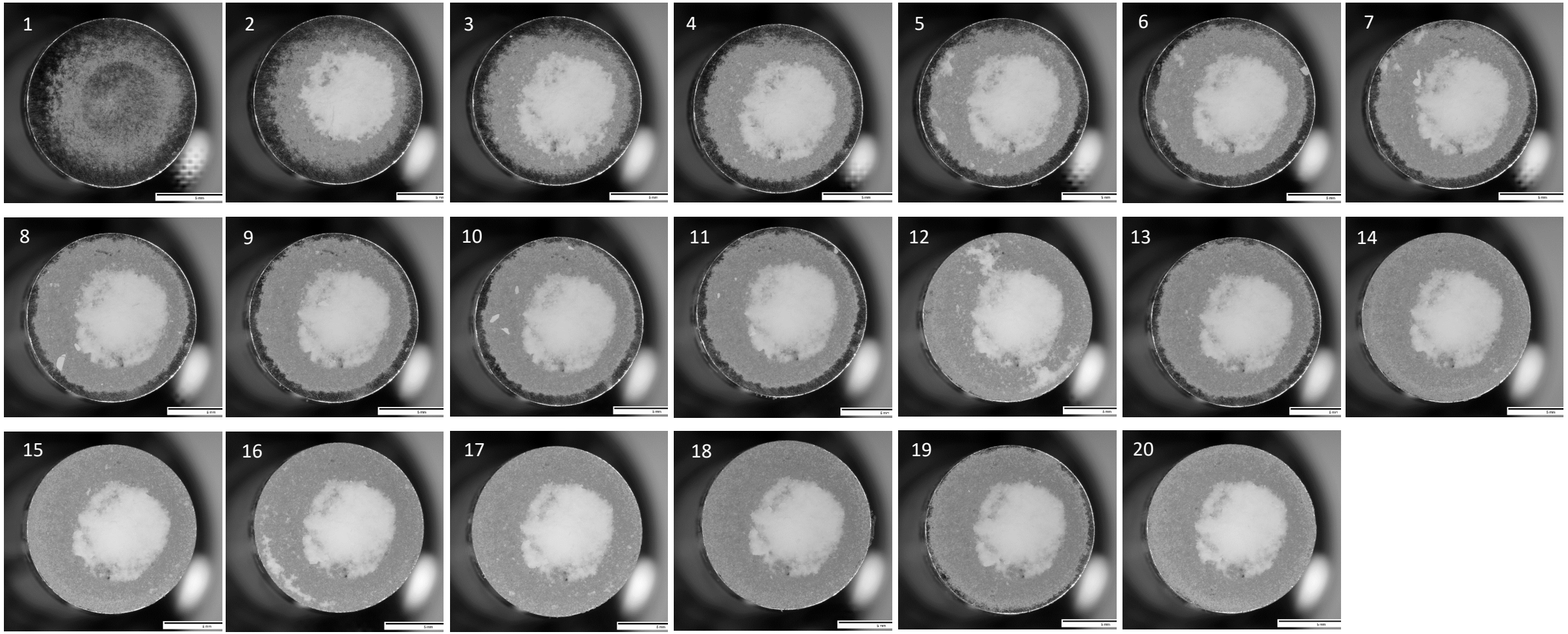
20 Successive tabletting

(at 150 MPa)

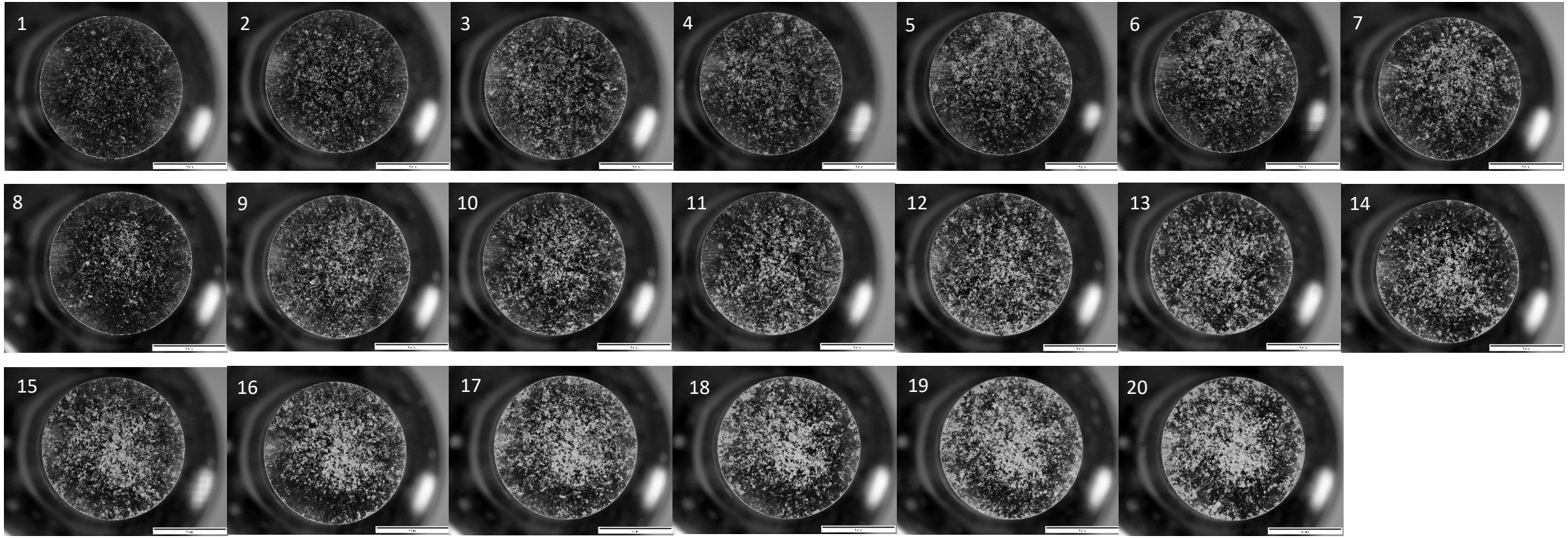
Mannitol at 150 MPa – RH 33%



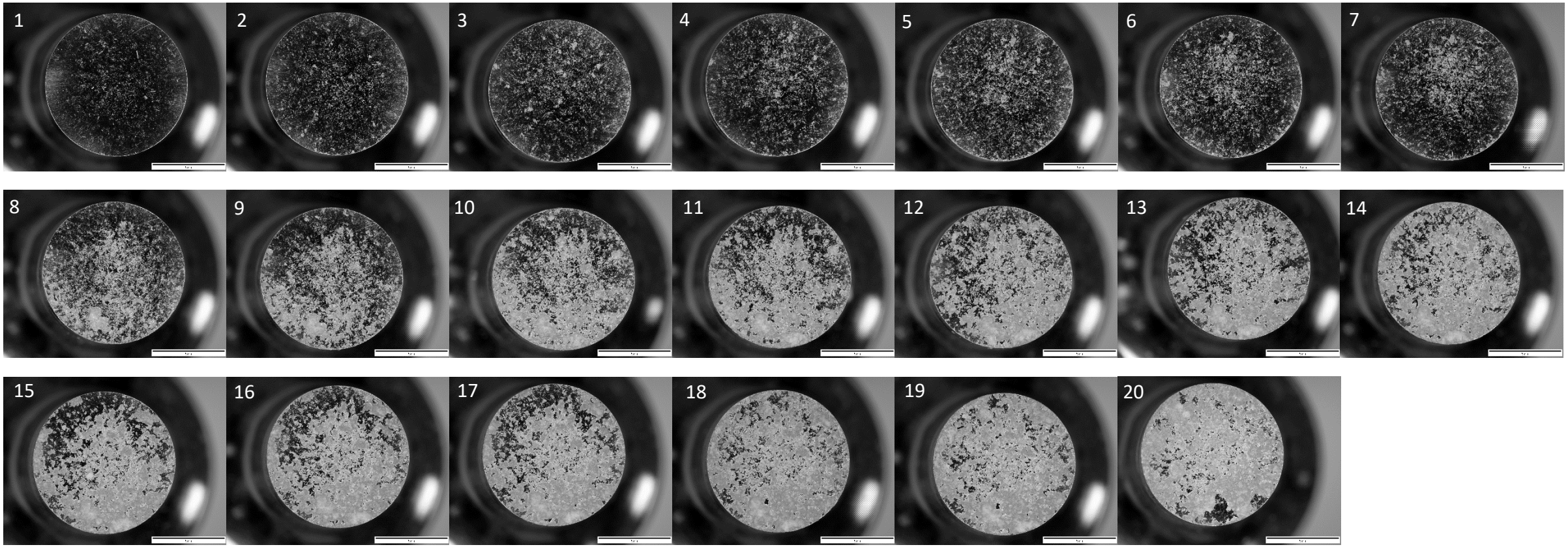
Mannitol at 150 MPa – RH 75%



Aspirin at 150 MPa – RH 33%

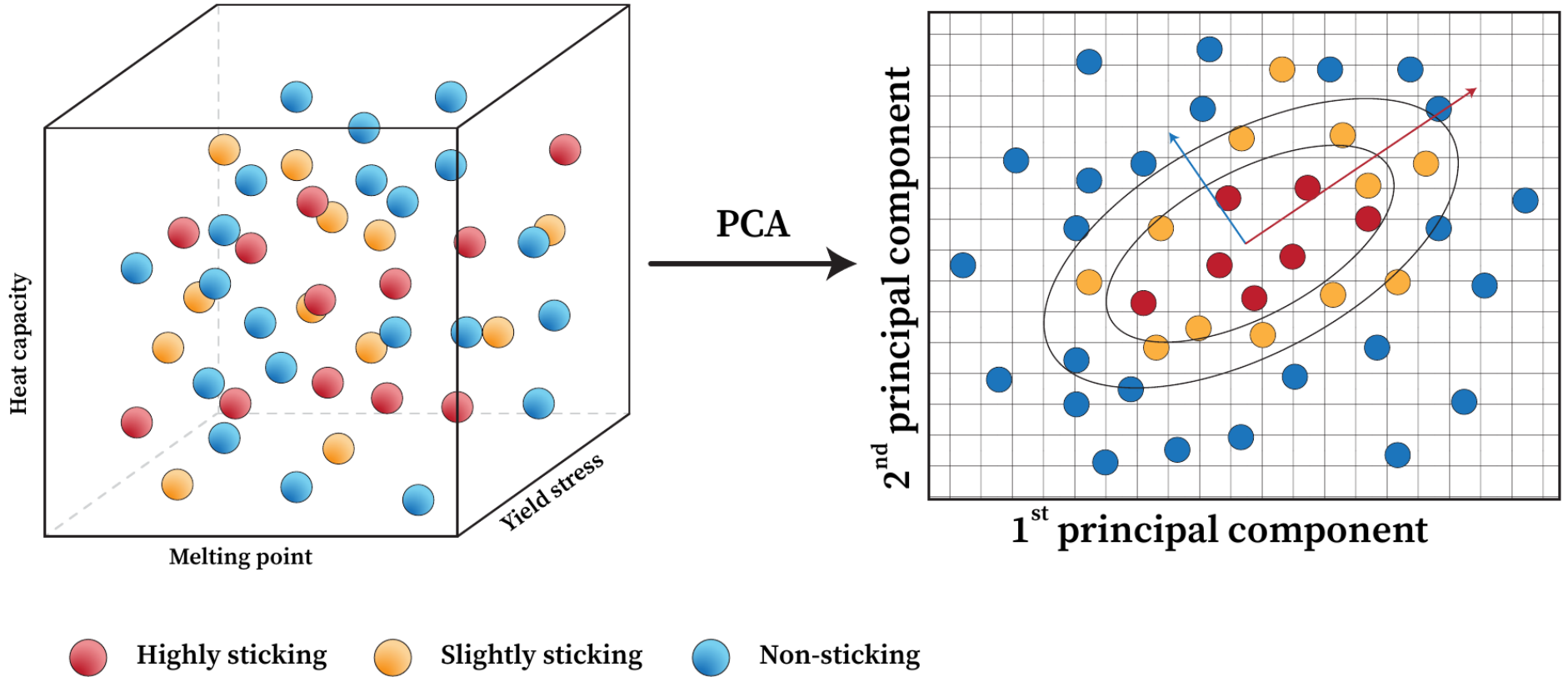


Aspirin at 150 MPa – RH 75%



Part 2: Principal component analysis (PCA)

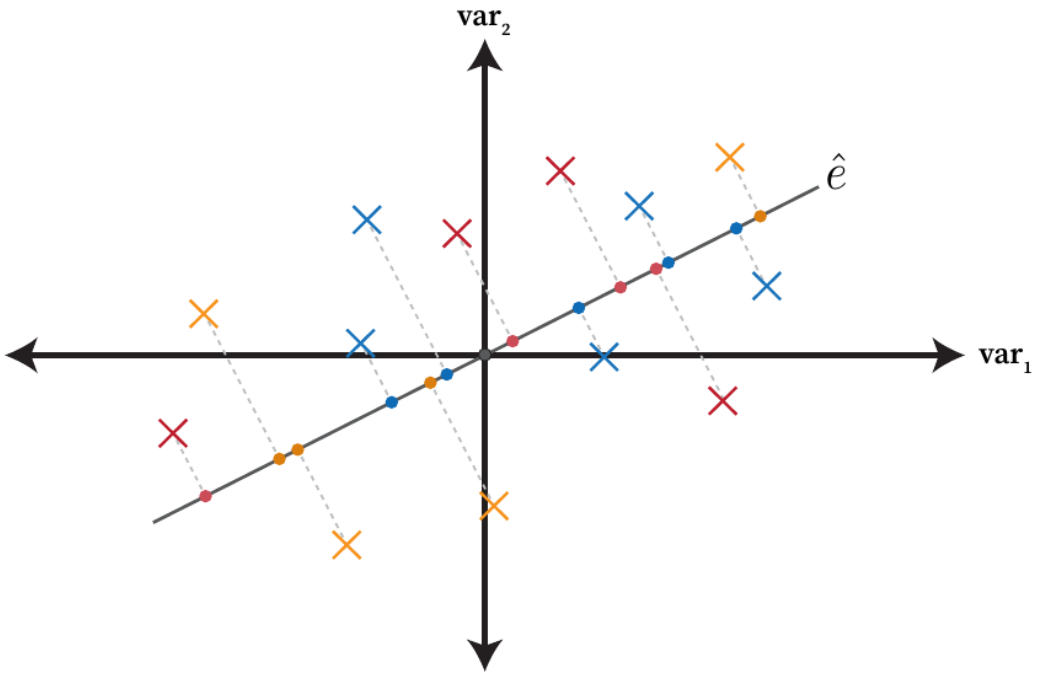
PCA: relate material properties to sticking

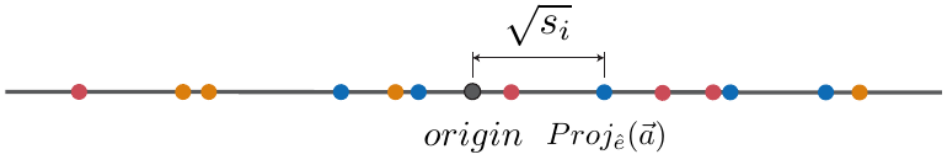


Notes:

1. The physical, mechanical, thermal etc. properties represent a small number of material data points for PCA
2. Method not applicable for a new chemical entity
3. Therefore a more direct method is needed to predict sticking for a given molecule

Principal Component Analysis (PCA)





$$origin = \frac{1}{n}\sum_{i=1}^{n}(\vec{x_i}\cdot\hat{e}_{var_1}, \ldots, \vec{x_i}\cdot\hat{e}_{var_m})$$

$$\vec{a}_i = \vec{x}_i - origin$$

$$s_i = Proj^2_{\hat{e}}(\vec{a})$$

$$Proj_{\hat{e}}(\vec{a}) = \vec{a}\cdot\hat{e}$$

$$S = \sum_{i=1}^{n} s_i$$

$$\hat{e}_{opt} = \{\hat{e}_i \in V : \ S(\hat{e}_i) > S(\hat{e})\}$$

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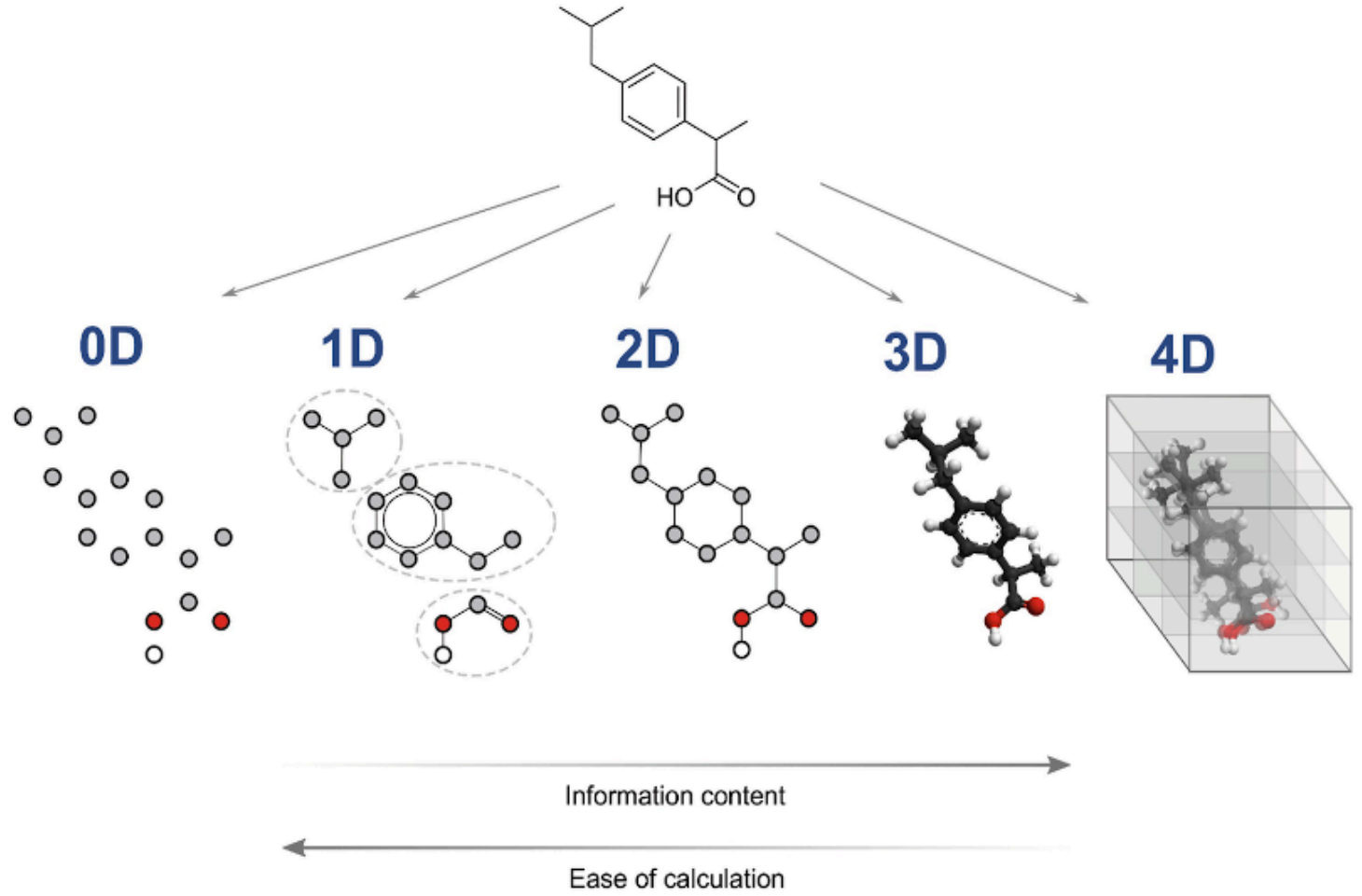
Mordred chemical descriptors

Mordred is a descriptor-calculation software that can calculates 1800+ two and three dimensional descriptors.

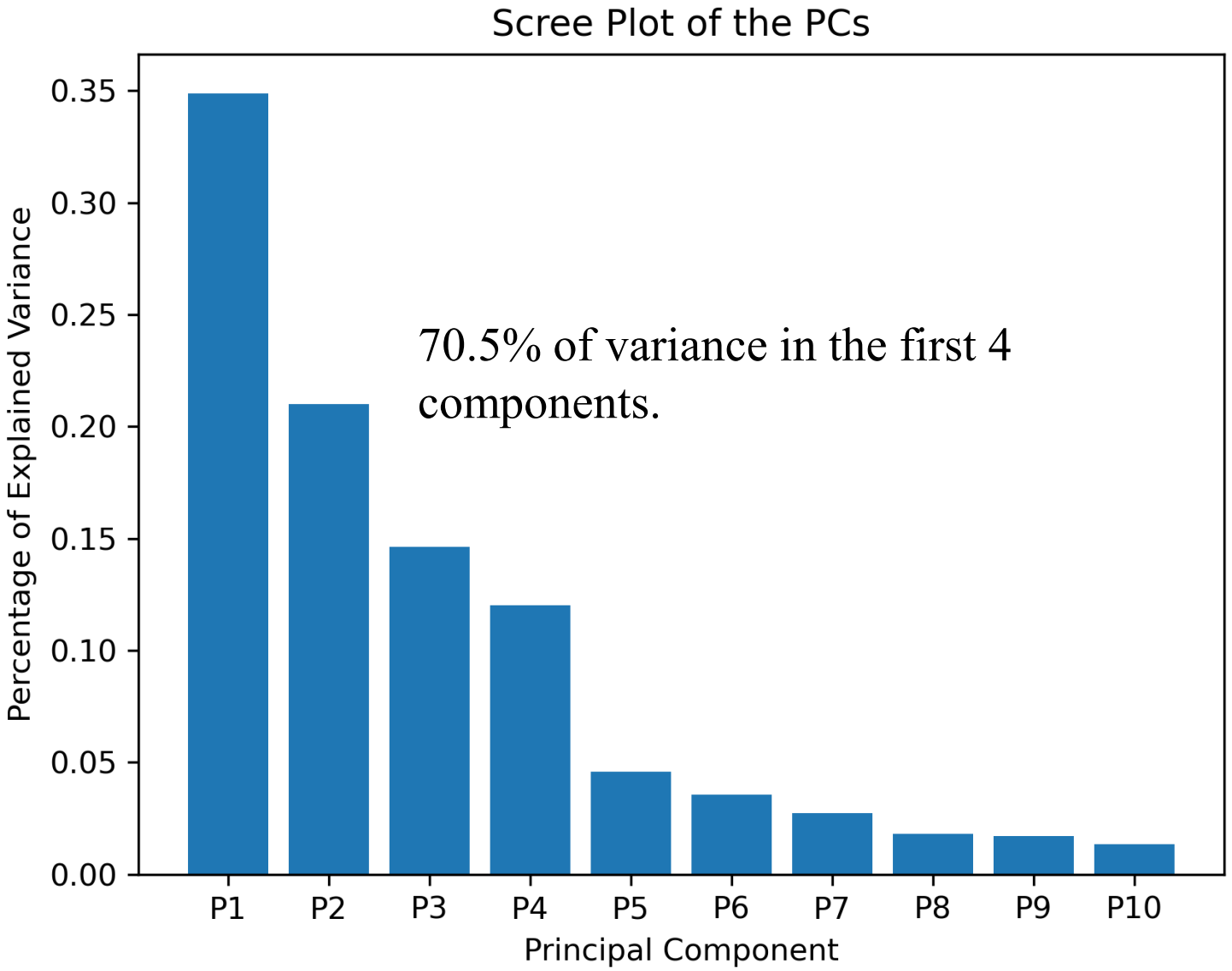


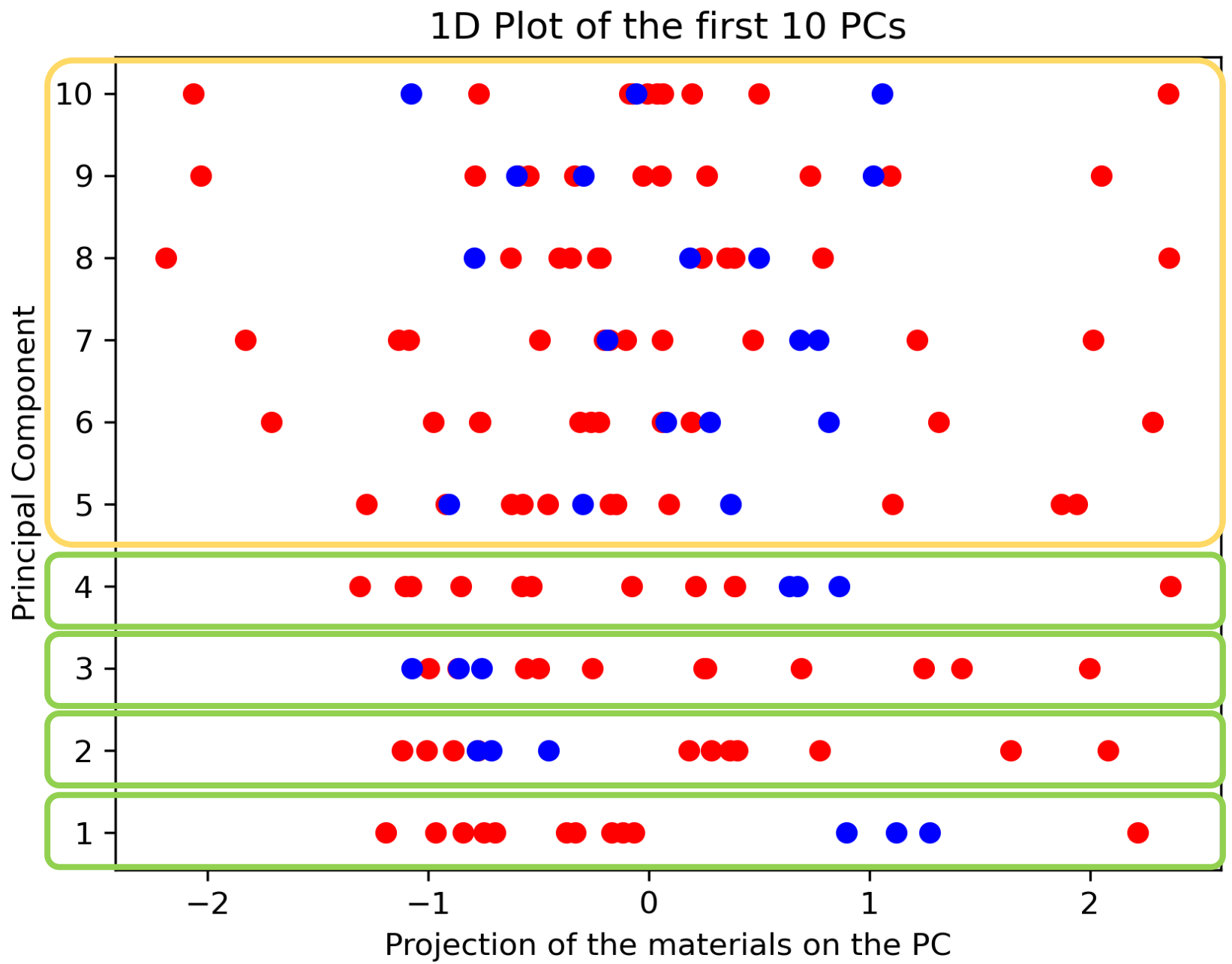
Steps for extracting Molecular Descriptors

Material	Chemical Formula	Smiles Representation
Ibuprofen	C13H18O2	CC(C)Cc1ccc(cc1)[C@@H](C)C(=O)O
Ketoprofen	C16H14O3	CC(c1cccc(c1)C(=O)c2ccccc2)C(=O)O
Aspirin	C9H8O4	O=C(C)Oc1ccccc1C(=O)O
Paracetamol	C8H9O2	CC(=O)Nc1ccc(O)cc1
Mannitol	C6H14O6	O[C@H]([C@H](O)CO)[C@H](O)[C@H](O)CO
Sorbitol	C6H14O6	OC([C@H](O)[C@@H](O)[C@H](O)CO)CO
MCC	C14H26O11	COC1OC(CO)C(OC2OC(CO)C(OC)C(O)C2O)C(O)C1O
PEG 3350	H(OCH2CH2)nOH	C(CO)O
Ascorbic Acid	C6H8O6	OC[C@H](O)[C@H]1OC(=O)C(O)=C1O

Molecular formula → SMILES representation → Mordred descriptors

PCA with Mordred descriptors





No clear materials separation.

Clear separation of the materials.

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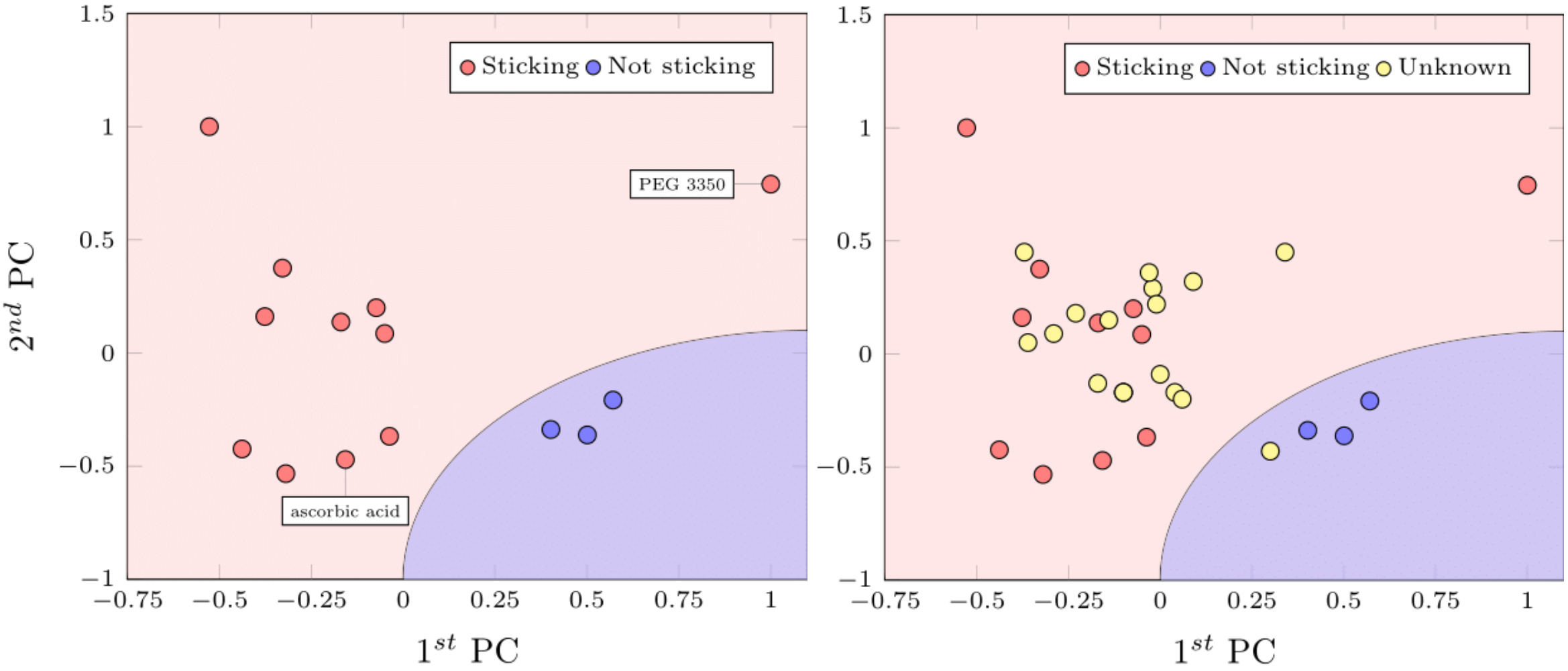
PCA - 1^{st} and 2^{nd} Components



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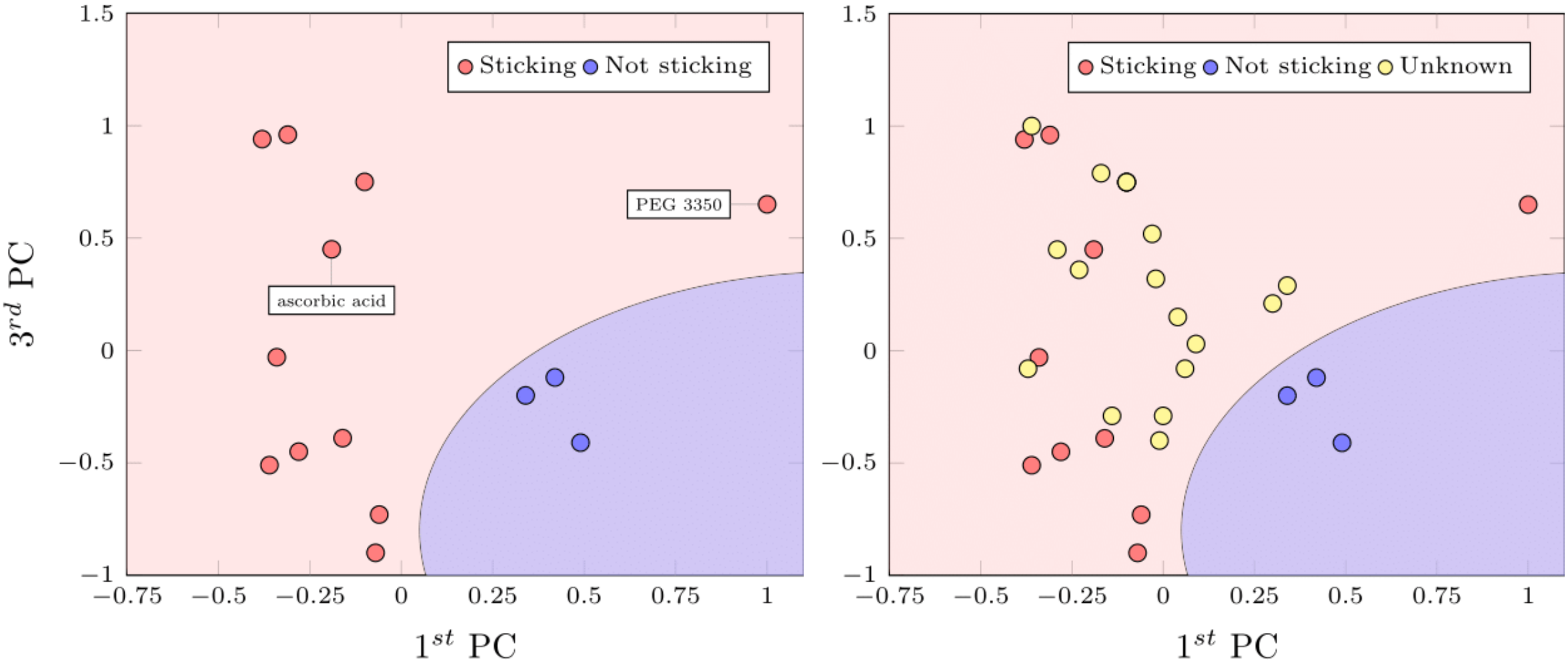
PCA - 1^{st} and 3^{rd} Components



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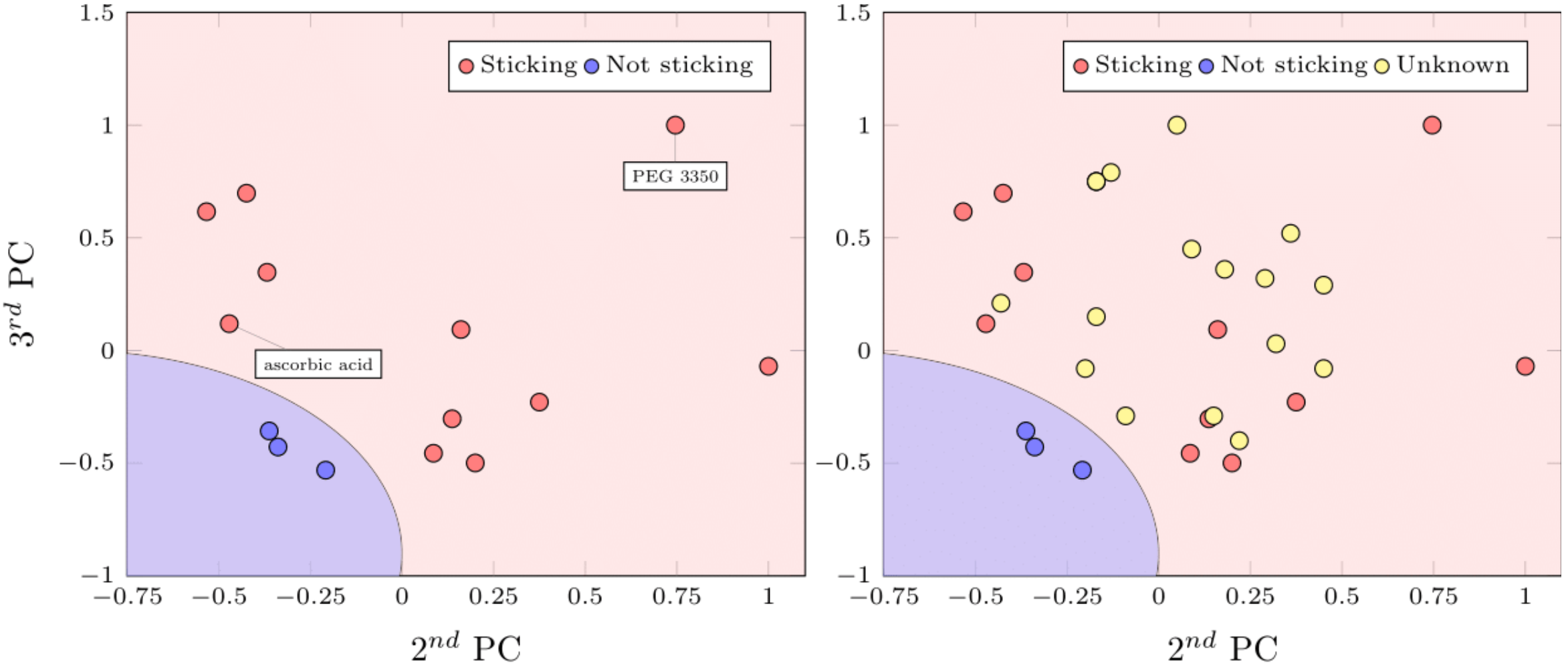
PCA - 2^{nd} and 3^{rd} Components



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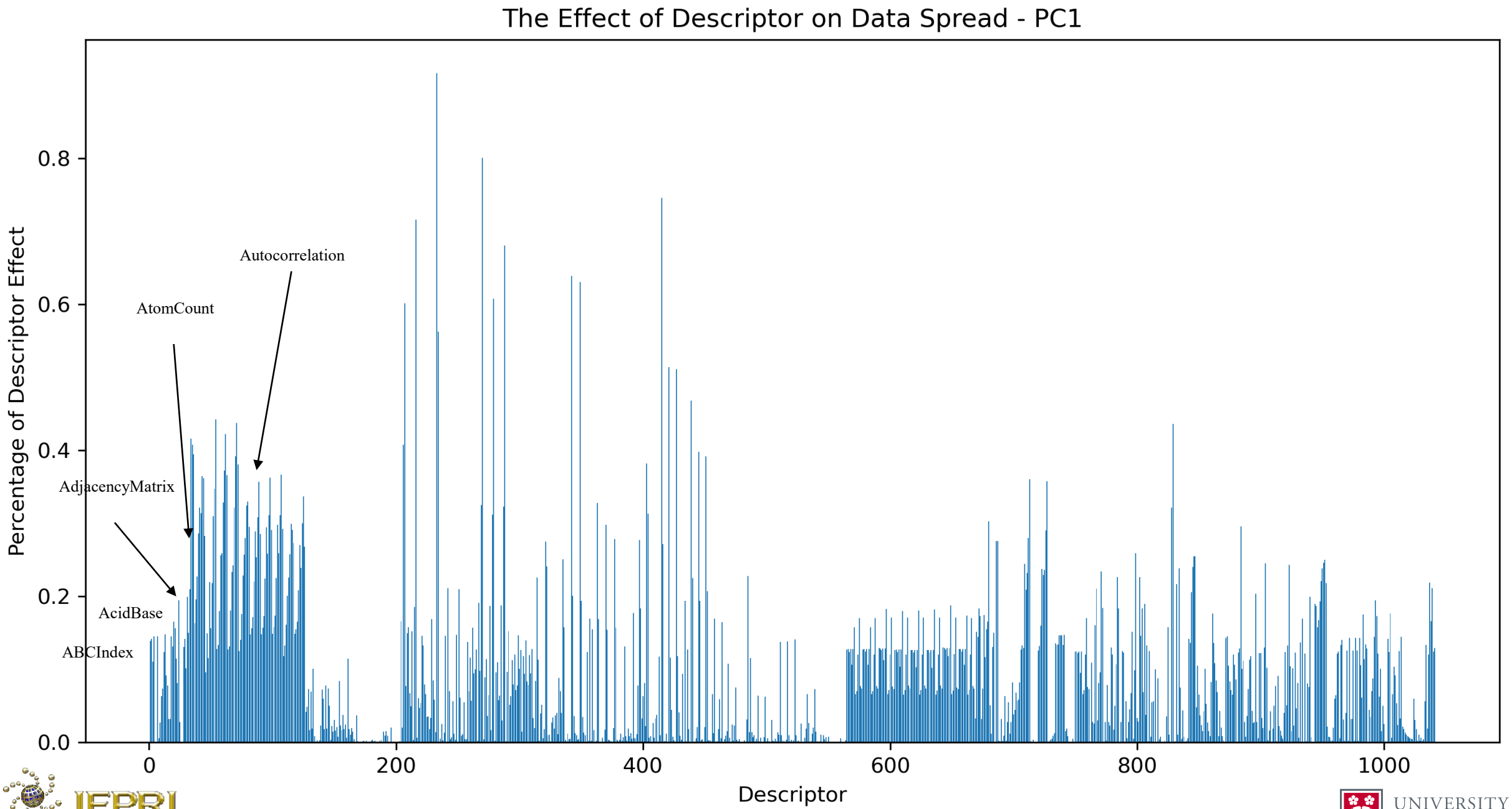

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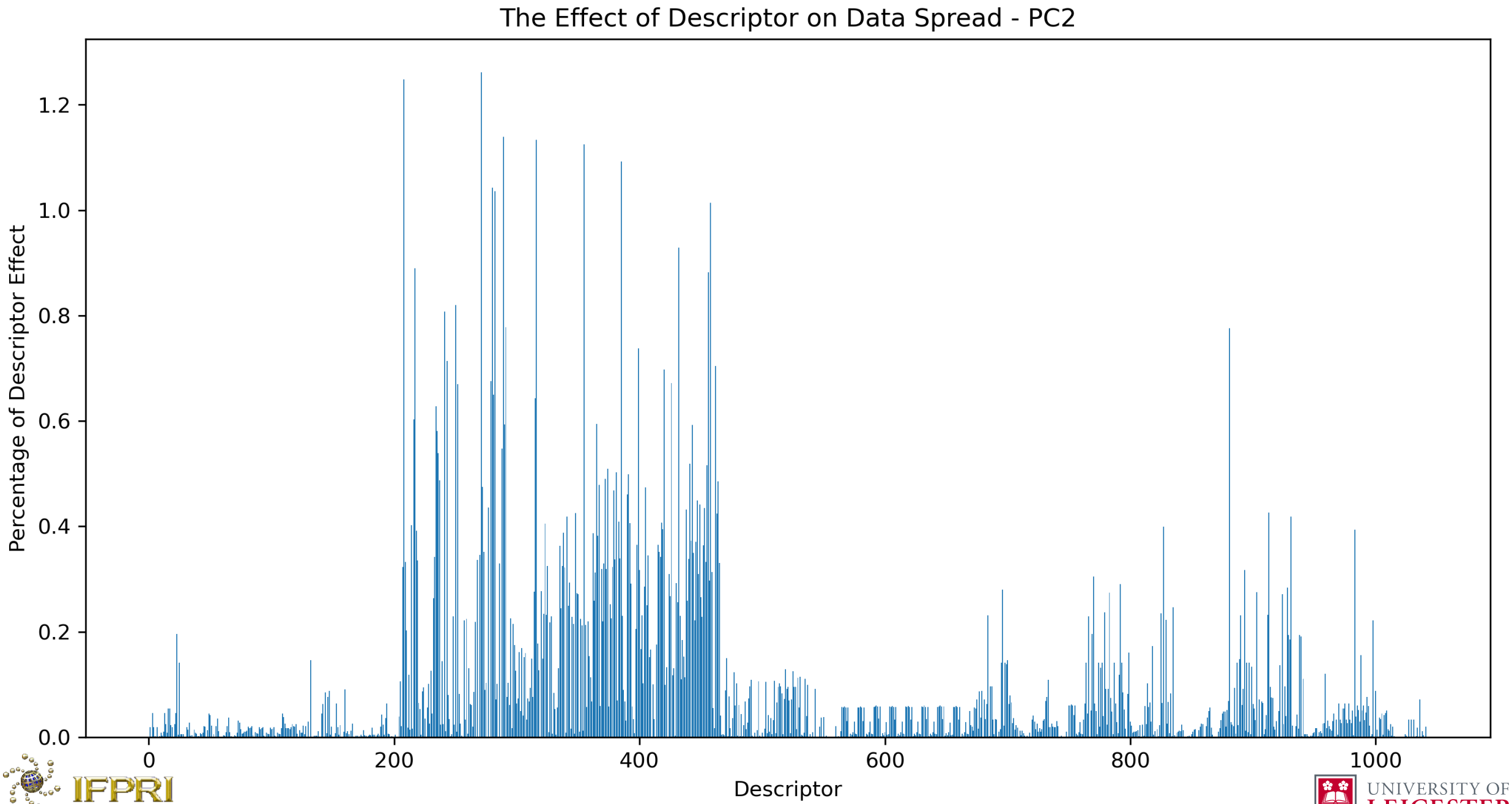

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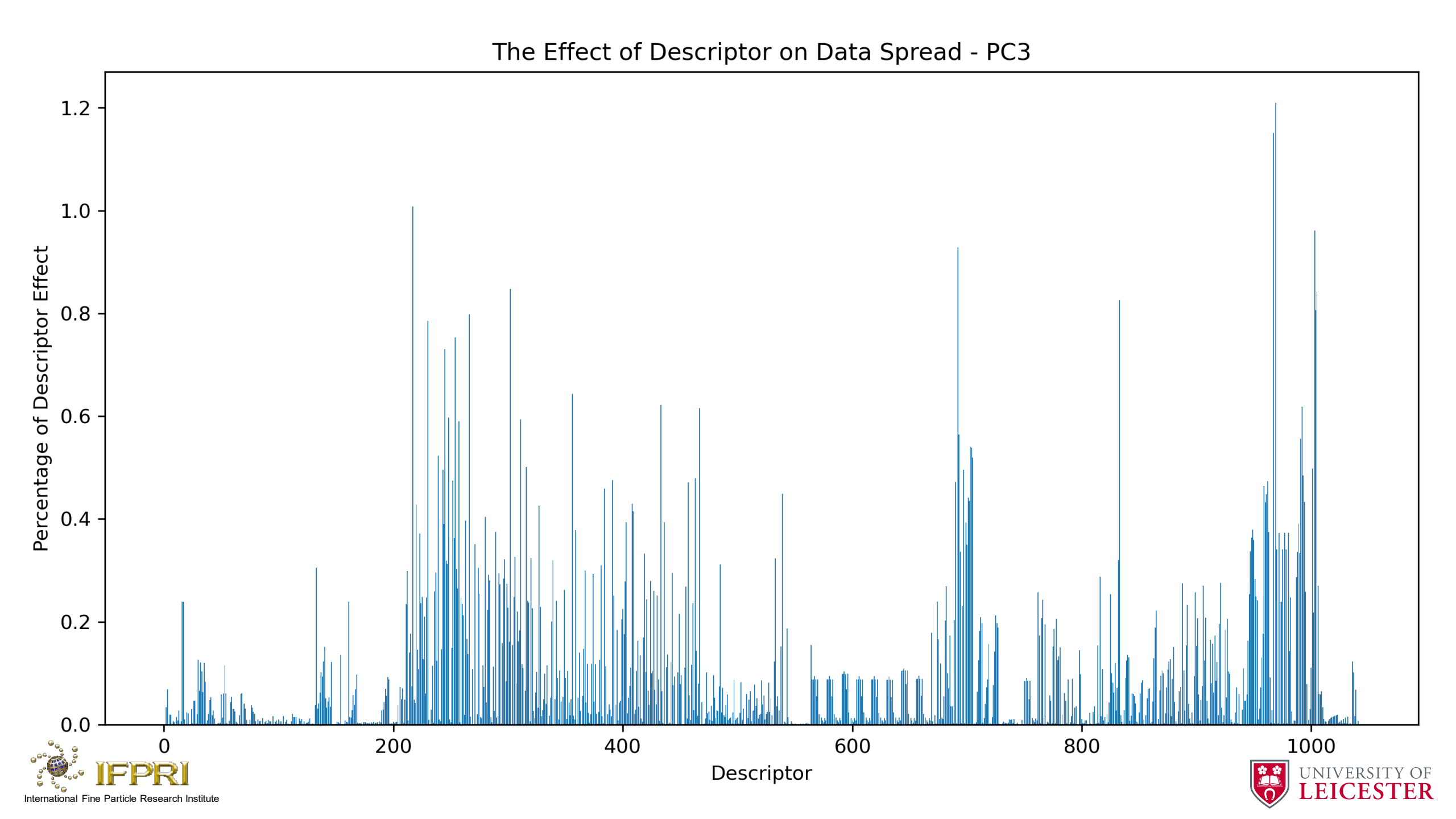

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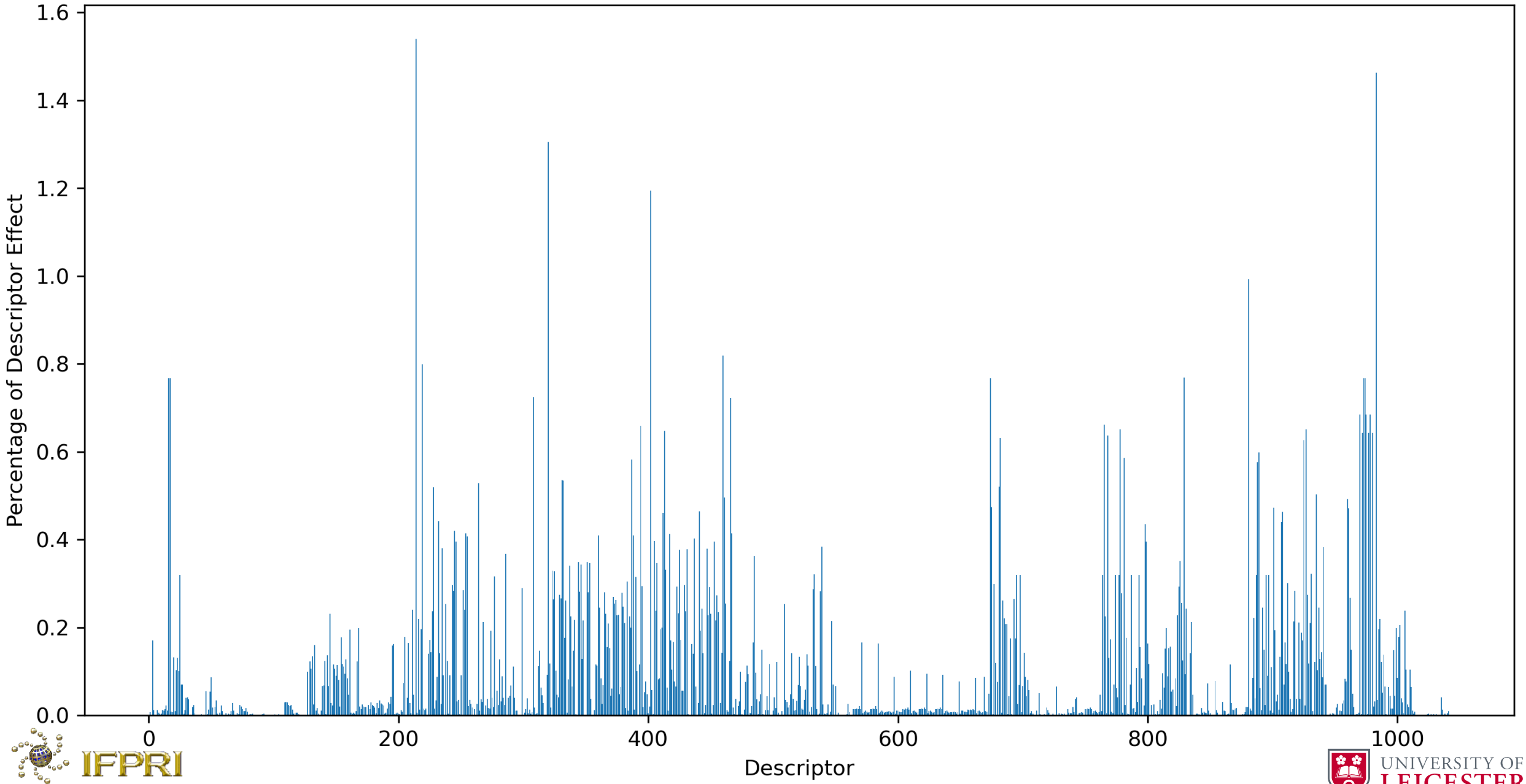

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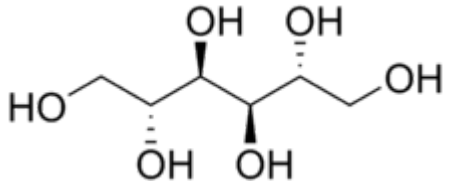
Summary and project deliverable

- Database of sticking behaviour:
  - Comprehensive characterisation of 7 materials
  - Hypotheses/mechanisms: compaction pressure, rate, temperature, humidity
  - Mordred descriptors
  - PCA to predict sticking of a new molecule
- Work remaining:
  - Identify key Mordred categories (20+ => 5): polarity, acid/base, autocorrelation
  - Identify key Mordred descriptors (1800 => 100): molecular weight, no. of H donors/acceptor, no of cyclic structures
  - Refine sticking prediction maps
  - Consider particle and bulk properties (e.g. physical, mechanical and thermal properties)
- Deliverable: Python package:
  - Input: SMILES representation (new molecule)
  - Output: yes/no sticking prediction and representation on map
  - Database updated by user with their materials

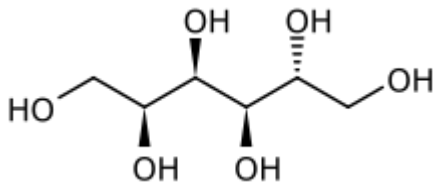
Mannitol and Sorbitol

Mannitol and Sorbitol have the same chemical formula $C_6H_{14}O_6$.

- Chemical structure: isomers: differ only in the orientation of the hydroxyl group on carbon 2.
- Mannitol



Sorbitol



- Sticking: mannitol is sticking, sorbitol is not sticking.
- Crystallinity: Mannitol is a crystalline material that exhibits a characteristic rhombic crystal shape, while sorbitol is amorphous. (typically sticking is more severe as the amorphous content increases)
- Meting point Mannitol 170 degC, sorbitol 100 degC. (typically sticking is more severe as the melting point decreases)
- 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.
- Stability: Mannitol is more stable than sorbitol (see RH and T effect above)

Differences:

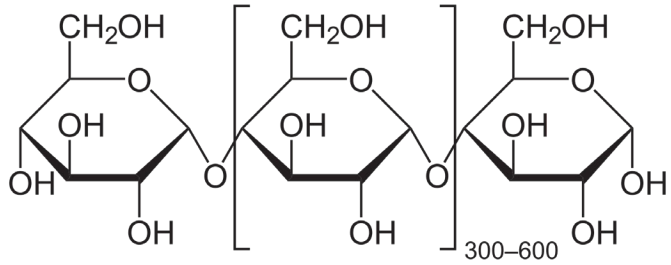
- Sublimation point: Mannitol 170 deg (same as melting point), Sorbitol 200 deg. => can this lead to cause of anomaly?

Other properties:

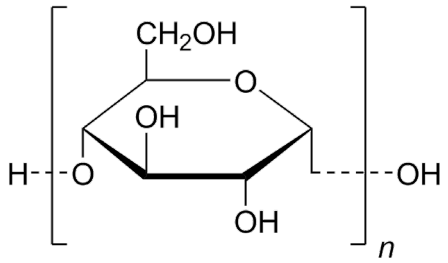
- Sweetness: Sorbitol is much sweeter than mannitol
- They both have the same boiling point 295 degC. – this need checking.

Starch and Maltodextrin

Starch (amylose): $(C_6H_{10}O_5)_n + (H_2O)$



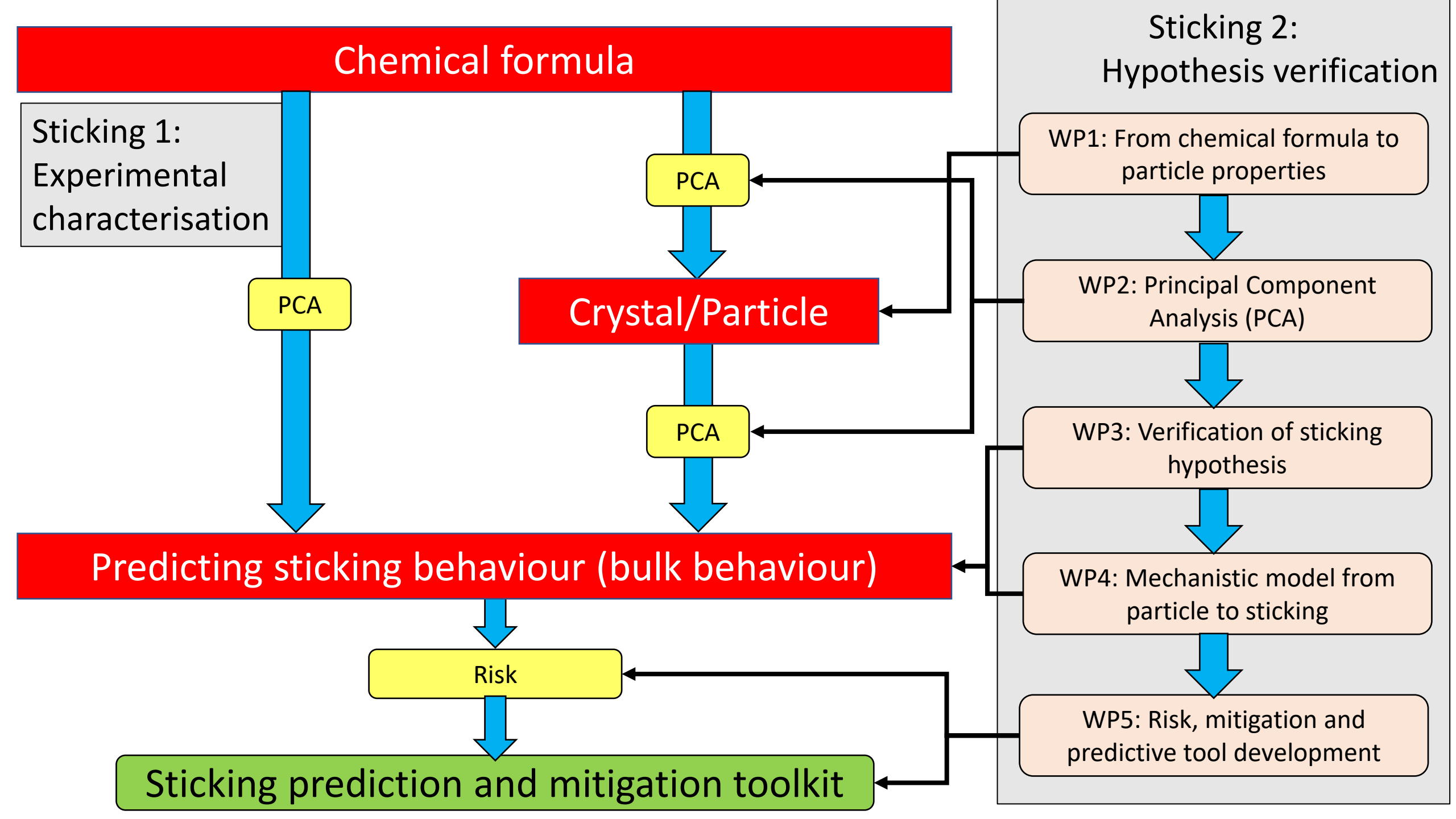
Maltodextrin: $C_{6n}H_{(10n+2)}O_{(5n+1)}$



α-1,4

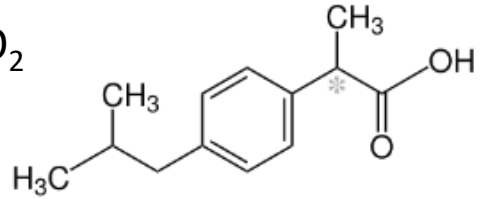
$2 < n < 20$

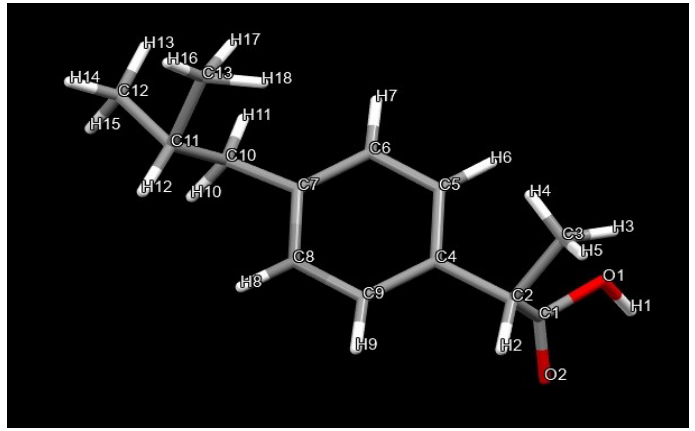
"Maltodextrins are classified by DE (dextrose equivalent) and have a DE between 3 and 20. The higher the DE value, the shorter the glucose chains, the higher the sweetness, the higher the solubility, and the lower the heat resistance." (wiki)


Chemical formula
Sticking 1: Experimental characterisation
PCA
PCA
Crystal/Particle
PCA
Predicting sticking behaviour (bulk behaviour)
Risk
Sticking prediction and mitigation toolkit
Sticking 2: Hypothesis verification
WP1: From chemical formula to particle properties
WP2: Principal Component Analysis (PCA)
WP3: Verification of sticking hypothesis
WP4: Mechanistic model from particle to sticking
WP5: Risk, mitigation and predictive tool development

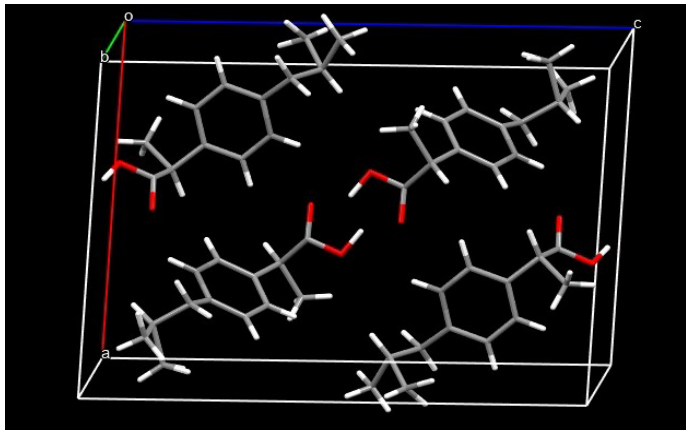
Ibuprofen

$C_{13}H_{18}O_2$

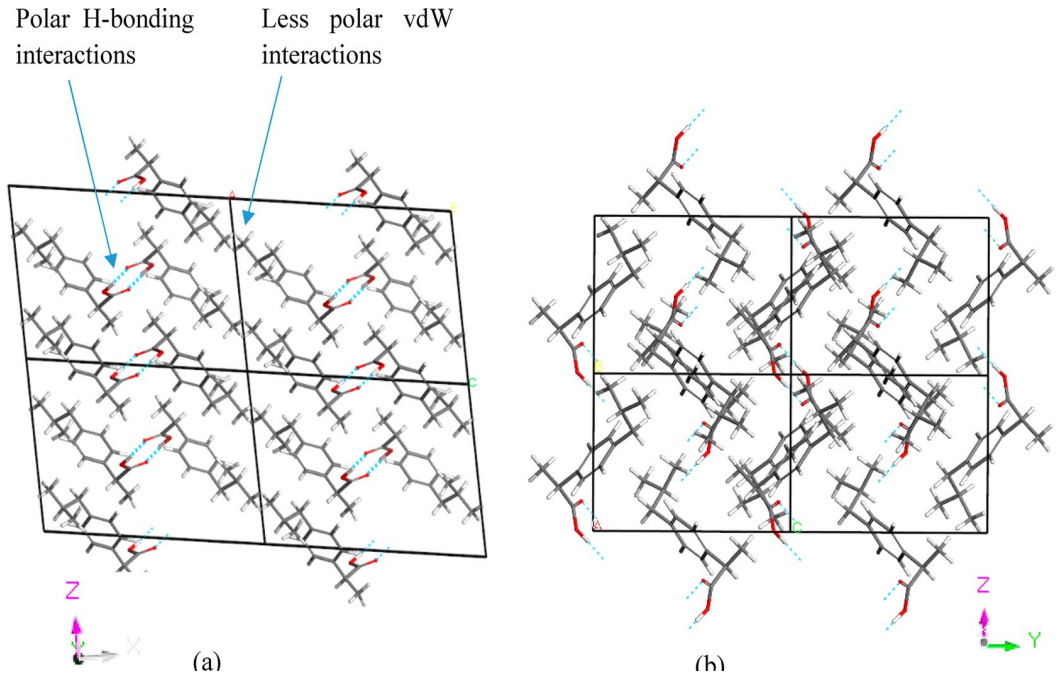


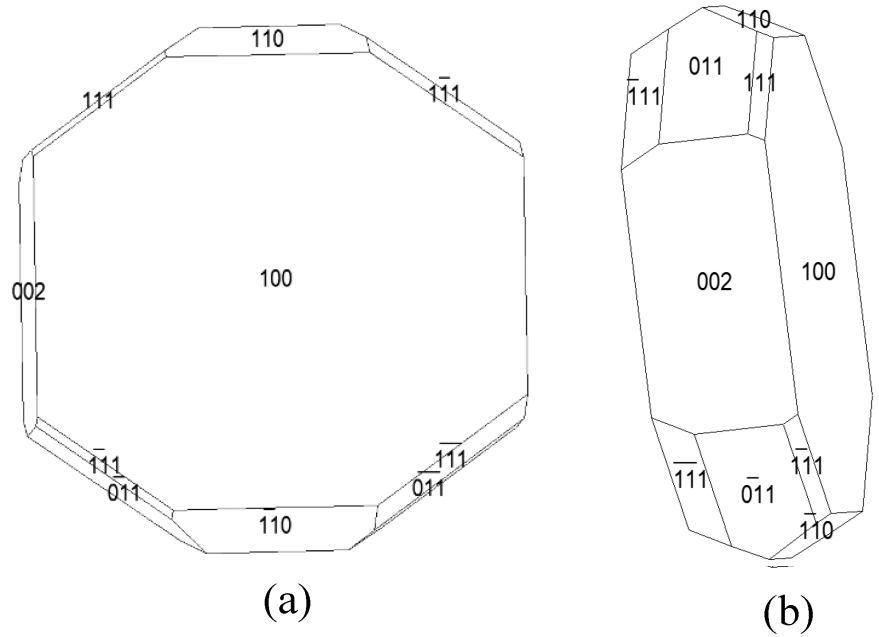


Molecular structure



Packing within unit cell

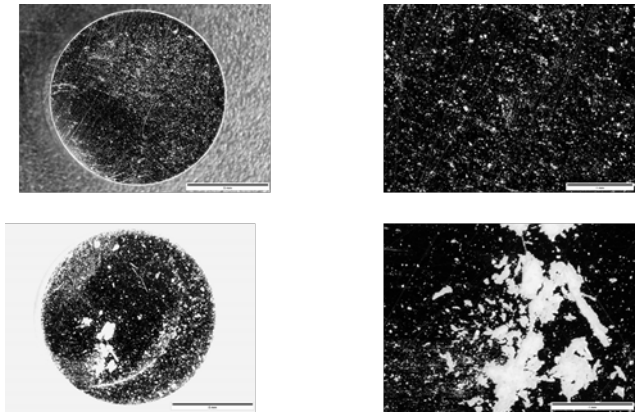




Thai T. H. Nguyen, Ian Rosbottom, Ivan Marziano, Robert B. Hammond, Kevin J. Roberts, Cryst. Growth Des. 2017, 17, 3088−3099

Ibuprofen 50 (as received from BSF) (Leicester SEM)

Hypothesis verification



Thank you for your attention