Downstream Processability of Crystal Habit-modified Active Pharmaceutical Ingredient

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Supporting Information

1. Size and shape-related particle parameters

Figure SI 1 below illustrates the concept of major and minor axis used to define length and width of the particles.[1] The major axis passes through the center of the mass of the particles at an orientation corresponding to the minimum rotational energy of the shape. The minor axis passes through the center of mass at right angles to the major axis.

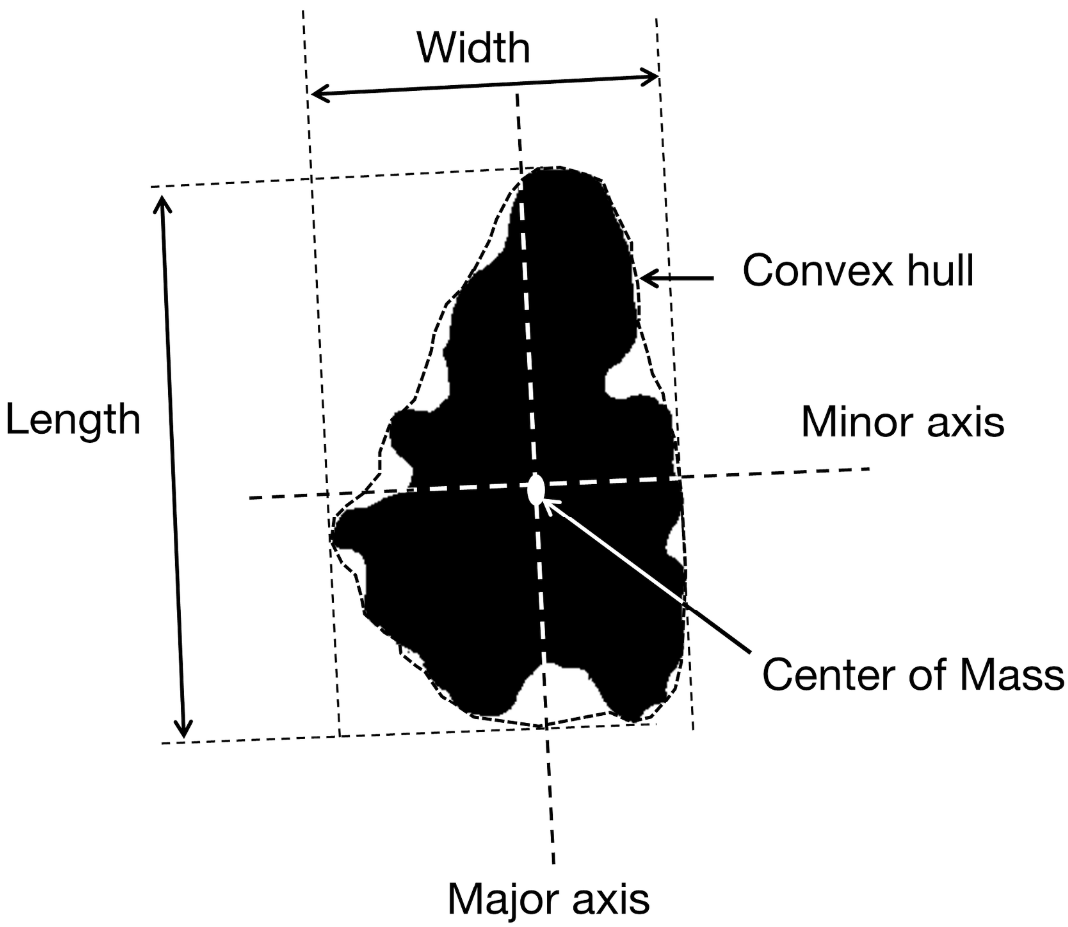


Figure SI 1: Spheroid crystal with major, minor axes, and convex hull indicated with a dotted line. The convex hull is an imaginary line inscribing particles, formed by touching the outer edge of the particle. The convex hull is necessary to calculate convexity and solidity as defined in **Table SI 1.**

Table SI 1: Definition of size and shape-related parameters used to characterize crystals.

Shape Parameters*	
Aspect ratio	The ratio of the width to the length of the crystal.
Circularity	The ratio of the circumference of a circle equal to the crystal projected area to the perimeter of the crystal.
Solidity	Pixel area of the crystal divided by the area enclosed by the convex hull.
Convexity	The perimeter of the convex hull of the crystal, divided by its perimeter. The convex hull can be considered as the border created by an imaginary rubber band wrapped around the crystal, represented by the dotted outline in **Figure SI 1**
HS circularity	It is circularity squared. It is used to compare particles with similar circularity values.
Size Parameters	
Circle Equivalent diameter	The diameter of a circle with the same area as the projected area of the crystal image.
Area	The visual projected area of the crystal.
Length	All the possible lines between two points on the perimeter are projected on the major axis of the crystal. The longest of those lines is the length of the crystal.
Width	All the possible lines between two points on the perimeter are projected on the minor axis of the crystal. The longest of this line is the width of the crystal.
Perimeter	The total length of the crystal boundary calculated by summing the length of the boundary pixels.

*Values of shape-related parameter ranges between 0 and 1

2. Powder ring shear tester

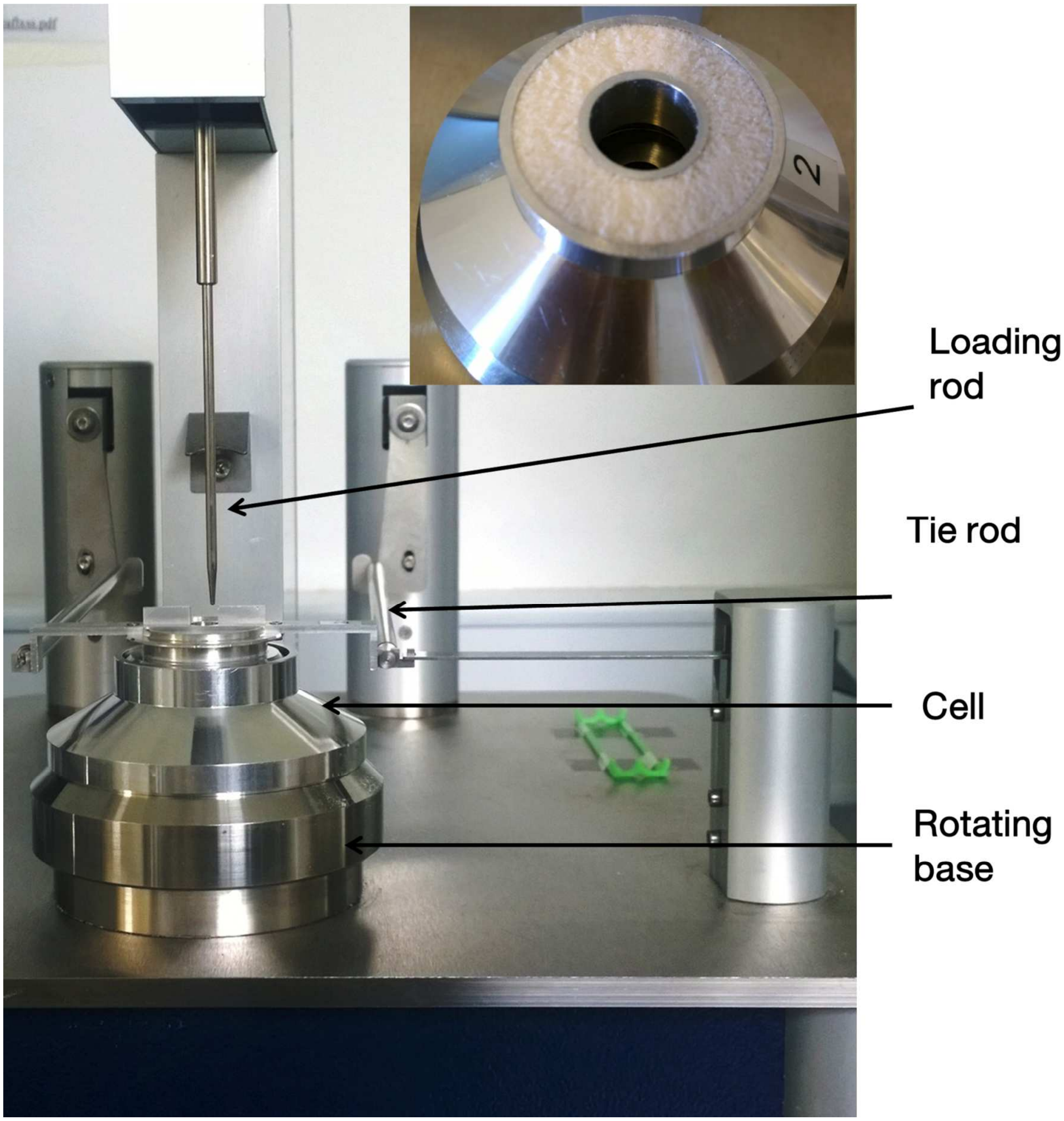


Figure SI 2: Schulz ring shear tester[2] with its major components used for determination of yield locus (a measure of stress needed to make powder flow after consolidation) and two Mohr's stress circle (**Figure SI 3**). The inset displays the shear cell (volume 3.5 ml) filled with powder in annular space. Normal stress is applied through loading rod, while the base rotates at a fixed velocity. The lid is fixed during rotation through the attached tie rod, which in itself is removable. The load beams connected to tie rods measures the shear stress.

The pairs of normal stress and shear stress are used to construct a yield locus and two Mohr's stress circle (**Figure SI 3**). The greater Mohr's circle represents stress state in powder during consolidation and gives consolidation major principal stress (σ_1); while the smaller one describes stress state under unconfined compression and gives unconfined yield strength (σ_c). To quantify powder flow, the two parameters *viz*. effective angle of internal friction (φ_e) and flowability index (ff_c) can be calculated. Flowability index (ff_c) is the ratio of σ_c and σ_1, and the effective angle of internal friction is represented by the angle of effective yield locus (the straight line passing through origin and tangent to the greater Mohr circle).

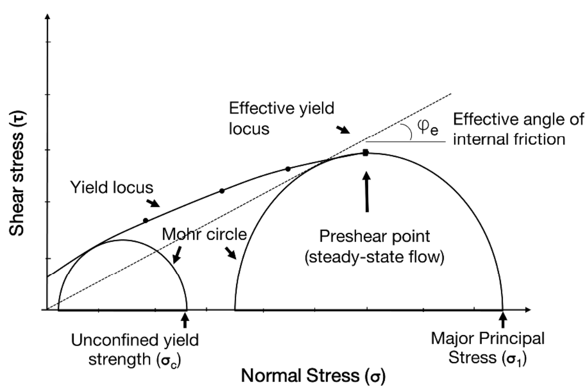


Figure SI 3: Typical yield locus and Mohr's stress circle to calculate flowability index and effective angle of internal friction with ring shear tester.

3. Flow rate analyzer (FlowPro)

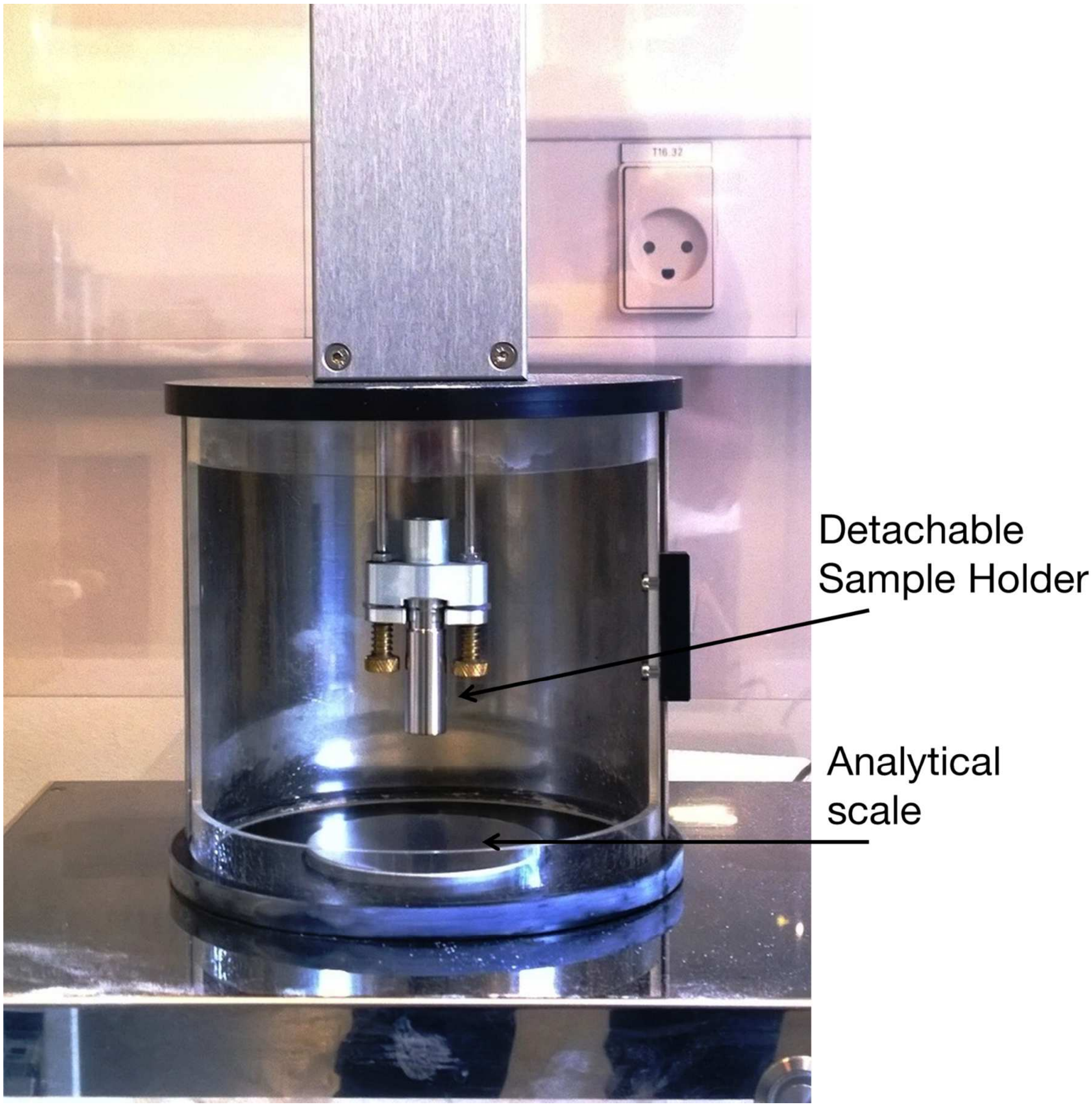


Figure SI 4: Flow rate analyzer[3] with its principal components. The detachable sample holder is inside the enclosure. The sample holder can oscillate vertically at a frequency of 1 Hz with the help of lever attached to it.

Flow rate analyzer consists of a cylindrical sample holder (volume 5 cm^3) that is open at the top, but with an orifice (diameter 3 mm) underside, an analytical balance, and a motor connected to a computer.

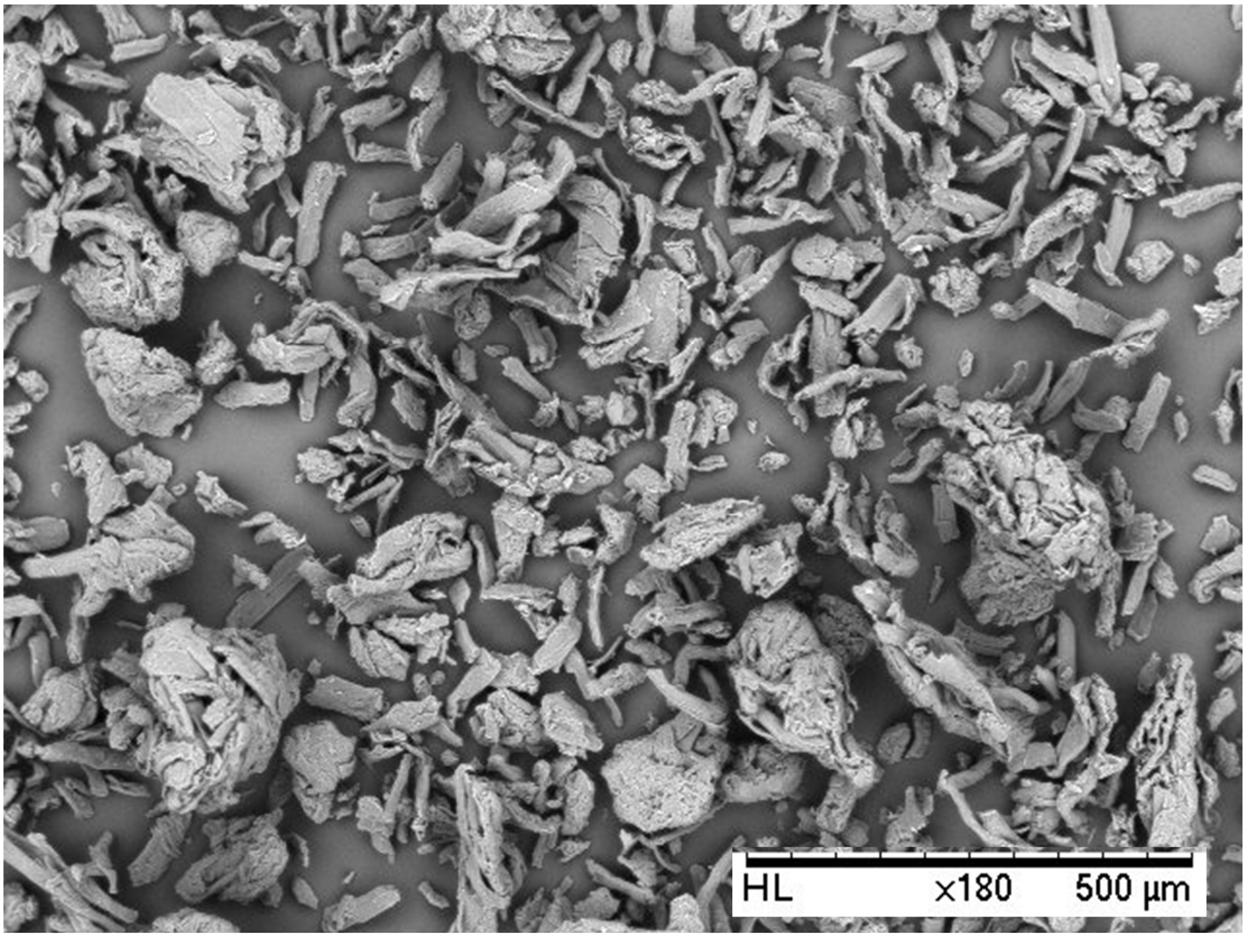
4. Flow properties and tabletability indicator values measured for six crystal habits

In the following table, data used to construct spider chart in Figure 7 of paper are given.

Table SI 2: Different flow properties and tabletability parameters used to construct spider chart.

Indicators/Habits	Needles	Plates	Rectangular bars	Rhombohedrals	Spheroids	Elongated hexagons
Flowability (*ffc*)	2.0	5.8	4.7	7.5	19.9	22.5
Flow rate (mg/s)	1	7	2	24	206	315
Bulk density (g/ml)	0.14	0.19	0.27	0.54	0.53	0.63
Effective angle of internal friction (degree, ^{o})	49.6	37.3	40.4	36.1	35.8	32.5
Tablet Tensile strength (MPa) at 0.9 solid fraction	2.86	1.4	0.79	0.46	0.89	0.36

5. Scanning electron microscopy Image of Microcrystalline cellulose PH 102



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