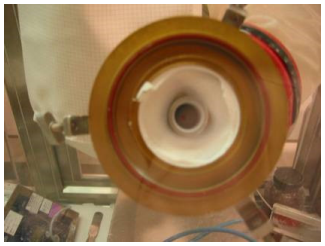
The Use of BRITEST in Drug Product Development

The Challenge

Micronisation issues during late stage development were identified with several new drug candidates intended for inhalation. Such issues have an immediate impact on late stage development but also potential issues later upon transfer to Operations.



One such inhalation compound showed no indication of potential issues, when micronised using a small scale spiral jet mill in the development facility. However, upon transfer to another facility for further development, hard cake built up in the micronisers. This had an immediate impact on operability and yield and was also indicative of further potential issues upon scale-up to full-scale production.

The Approach

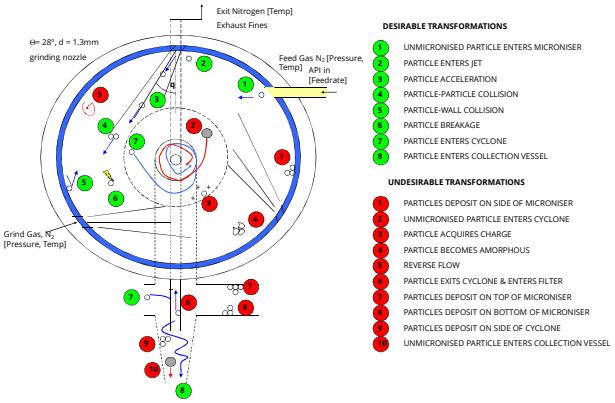
A multi-disciplinary team was put together including staff from both development sites. Britest tools were used to identify key material attributes, equipment and process parameters which impact upon the micronisation unit operation.

Micronisation Driving Force Analysis

+ Increase in parameter causes a positive effect on the process
- Increase in parameter causes a negative effect on the process

Material Properties	D1 Vern'l Particle Enters Microniser	D2 Particle Enters Jet	D3 Particle Acceleration	D4 Particle Particle Collision	D5 Particle-Wall Collision	D6 Particle Breakage	D7 Particle Enters Cyclone	D8 Particle Enters Collection Vessel	U1 Particles Deposit on Side of Microniser	U2 Vern'l Particle Enters Cyclone	U3 Particle Acquires Charge	U4 Particle Becomes Amorphous	U5 Reverse Flow	U6 Particle Exits Cyclone & Enters Filter	U7 Particles Deposit on Top of Microniser	U8 Particles Deposit on Bottom of Microniser	U9 Particle Deposit on Side of Cyclone	U10 Vern'l/Particle Enters Collection Vessel	Notes
Input PSD/Level of Fines	-			+		+		+		-				-				-	- Recommended MMD is ≥ 30µm - If input particle size too small, no mic w ill occur, particles straight to filter - Feeding issues if input particle size too high
Bulk Density	+																		- Potential feeding issues for low bulk density materials
Melting Point				+															- Recommended m.p. >80°C
Hygroscopicity							-					+							- Recommended m.c. < 2% - Potential for moisture absorption in collection vessel after processing
Crystal Morphology	+			+	+	+			-			-							- Ideal morphology is spherical. - Needles shaped particles problematic: inconsistent collisions, difficult to feed, difficult to assess PSD, may produce higher content of amorphous material
Crystal Surface Attachment Energy				+		+													
Yield Pressure/Hardness						+			-	-		-							Assume required energy input is greater than yield pressure required for particle breakage.
Cohesivity	-			-															
Adhesivity					-				+						+	+	+		
Electrostatic Properties	-			-				-			+						+		
Elasticity (Youngs Modulus)				+		+						-							If particle yield pressure is not exceeded, elastic energy will be converted to heat.
Glass Transition Temperature									+			+			+	+	+		
Tendancy to Soften				-					+			+			+	+	+		Possible to use DMA (Dynamic Mechanical Analysis) to assess this?

Rich Picture – Micronisation Process



The Solution

Post-Study Materials Property Investigation

- Glass transition temperature
- Calculations of propensity to amorphise
- Nano-indentation
- Identification of techniques to measure 'stickiness', e.g. Dynamic Mechanical Analysis (DMA) and link with slip planes
- Investigation of shear planes and crystal structure

Root Cause Identified:

High energy levels in the micronisers and the relatively low glass transition temperature of the API resulted in formation of amorphous material which adhered to the wall of the micronisers, causing build up and resulting in loss of yield and performance.

Benefits of Using a Britest Approach

- The Britest study brought together the team and independent technical experts to assess the process in a structured way
- Key material properties were identified and measured as a result of the study
- The root cause of the micronisation problem was identified for this project
- Micronisation generic learning was gained
- Longer term benefits are expected from development of a generic workflow and guidance document for micronisation

Supporting organisations in gaining value from process understanding