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Powder Flow 2009 - London

The fluidisation behaviour of pharmaceutical powders and their influence on particle deaggregation

Pharmaceutical Surface Science Research Group,

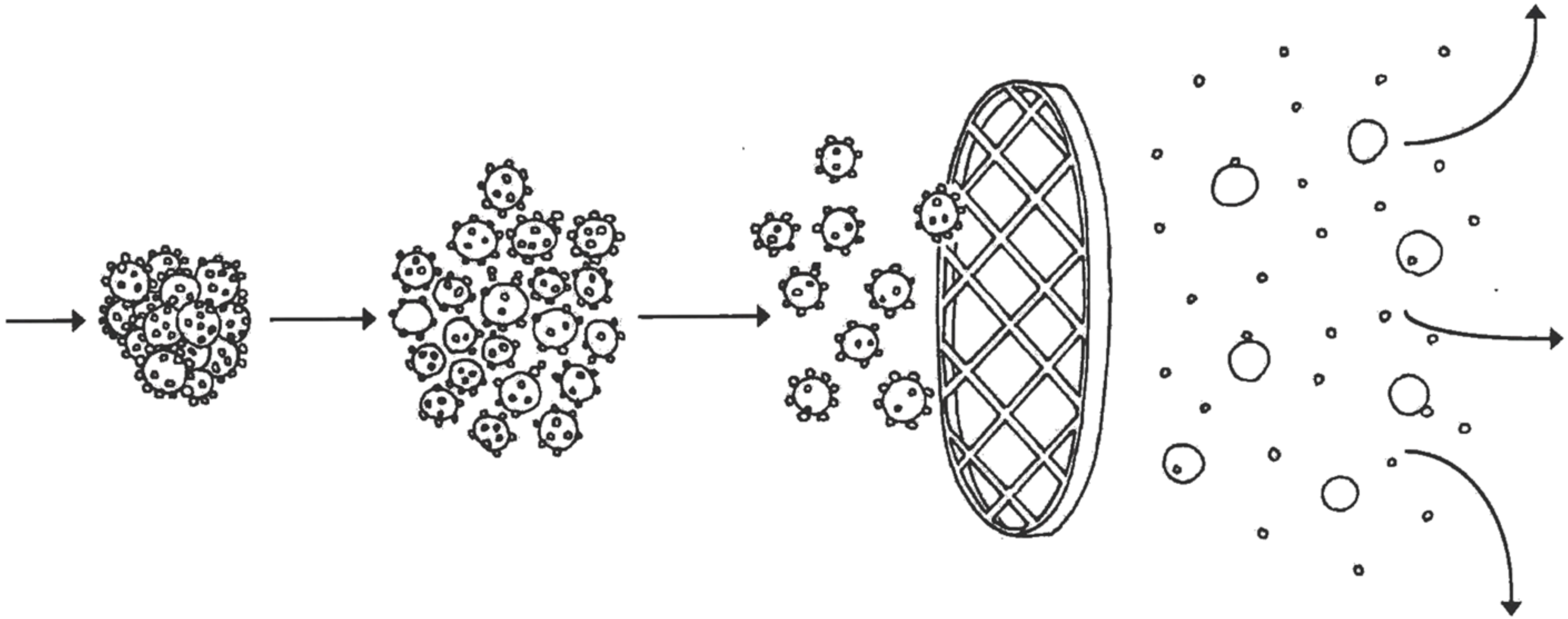
Department of Pharmacy and Pharmacology,

University of Bath

Contact: Dr Robert Price

E-mail: r.price@bath.ac.uk

Fluidisation of inhalation powders (Drug and Carrier)

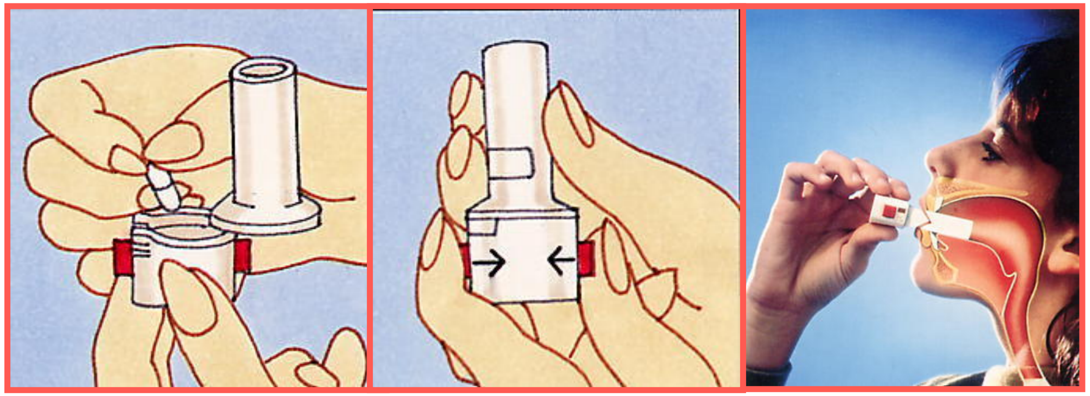


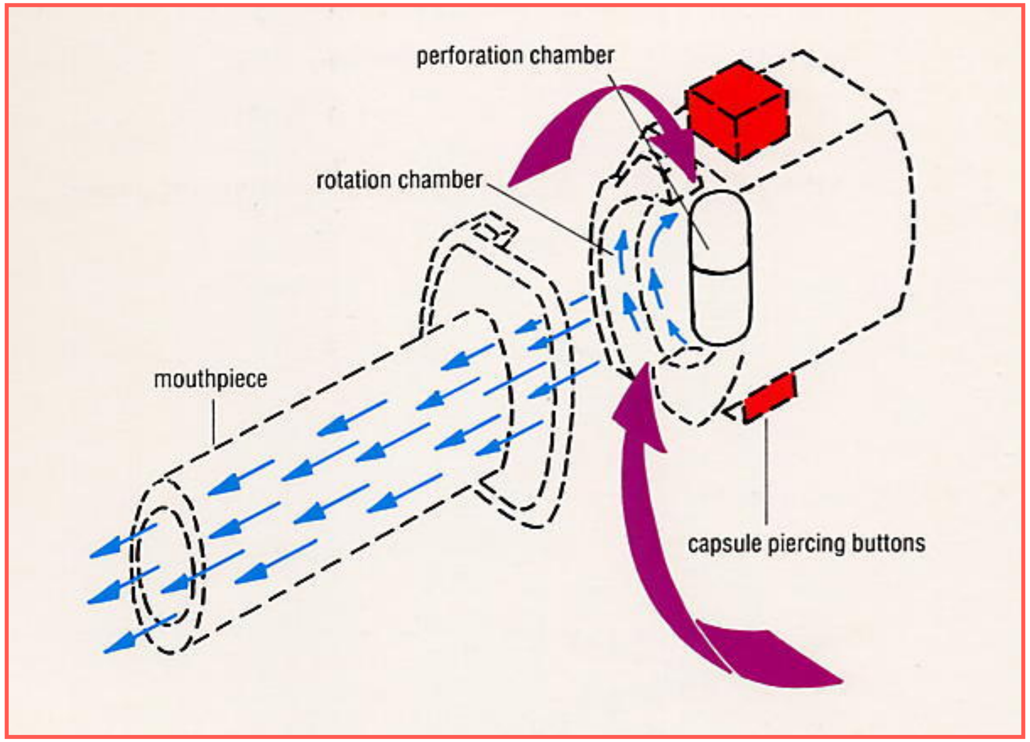
Static Powder Bed

Dilated Powder Bed

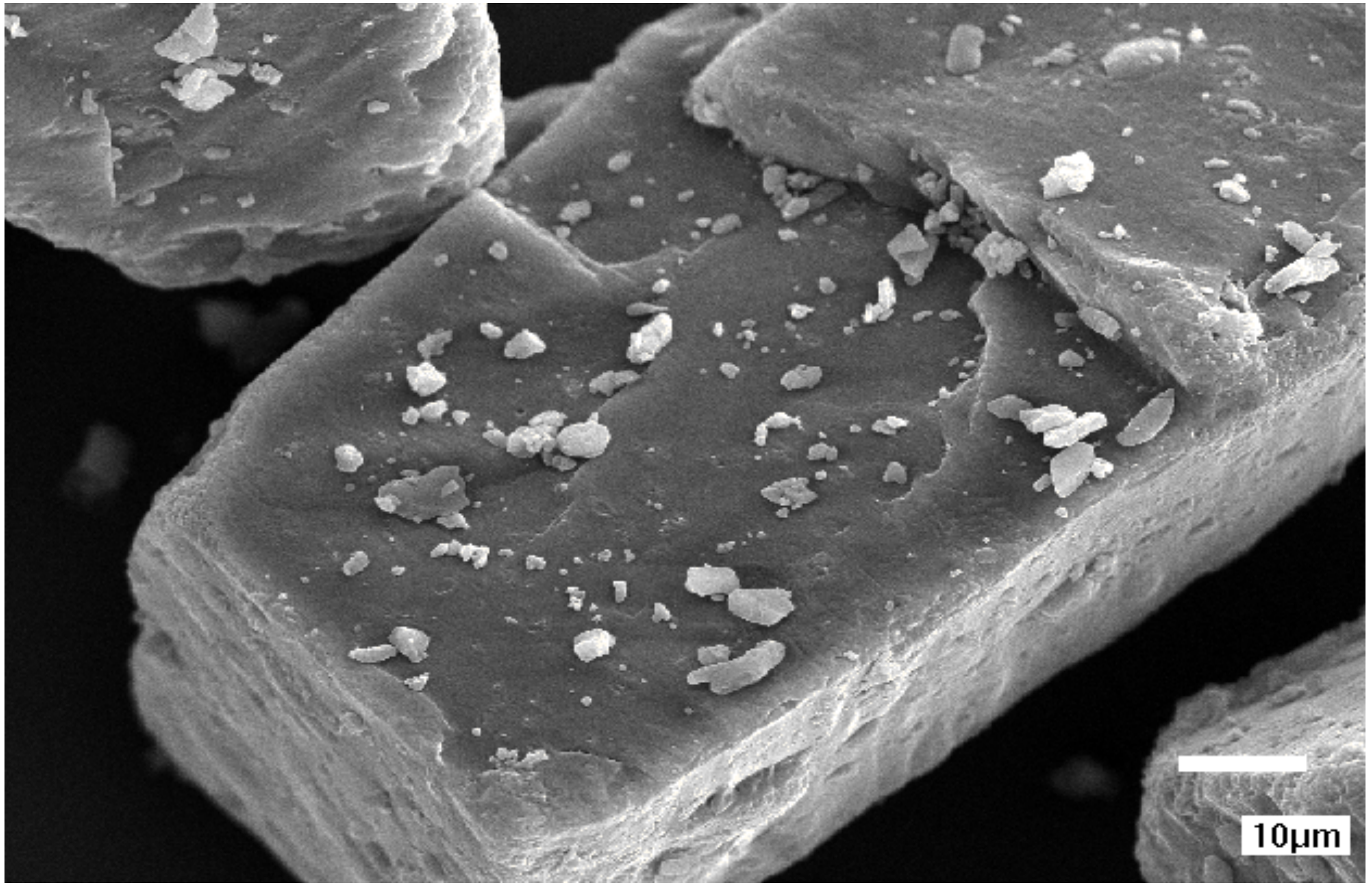
Aerosol Generation

Dispersion of Drug Particles

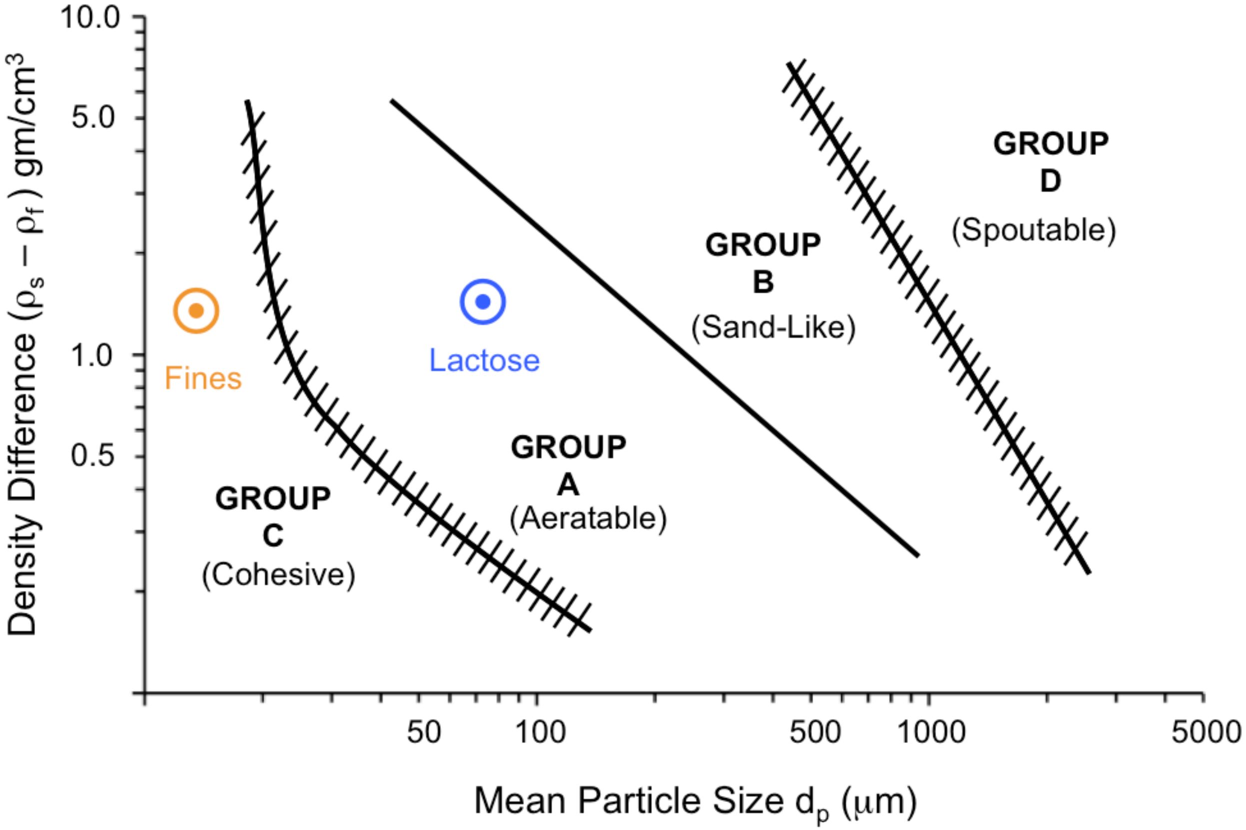



perforation chamber
rotation chamber
mouthpiece
capsule piercing buttons

Influence of the excipient fines on the fluidisation and deaggregation of DPI formulations



Geldart powder classification

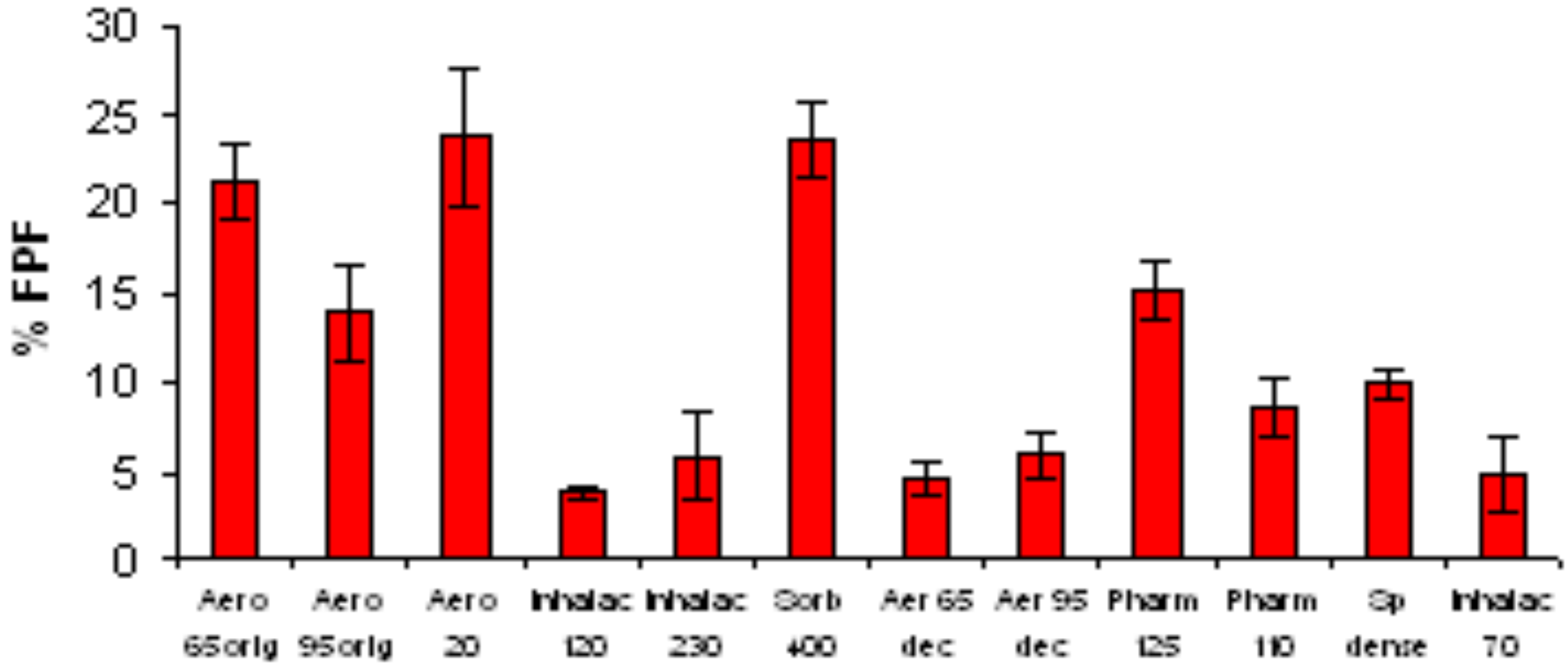


We are interested in the influence of the addition of fine Group C powders to aeratable Group A powders

Effect of adding Fines (Group C) to Geldart A-type powder on deaggregation

- Removing intrinsic fine particles from Group A powders decreases deaggregation efficiency
- Addition of fine Group C powders increases deaggregation efficiency
- Increasing the amount of Group C powders increases deaggregation efficiency
- Different fine powders have similar influence:
  - Lactose, PEG, mannitol, sorbitol, glucose, erythritol
- **Appears to dominate all other influences on performance**

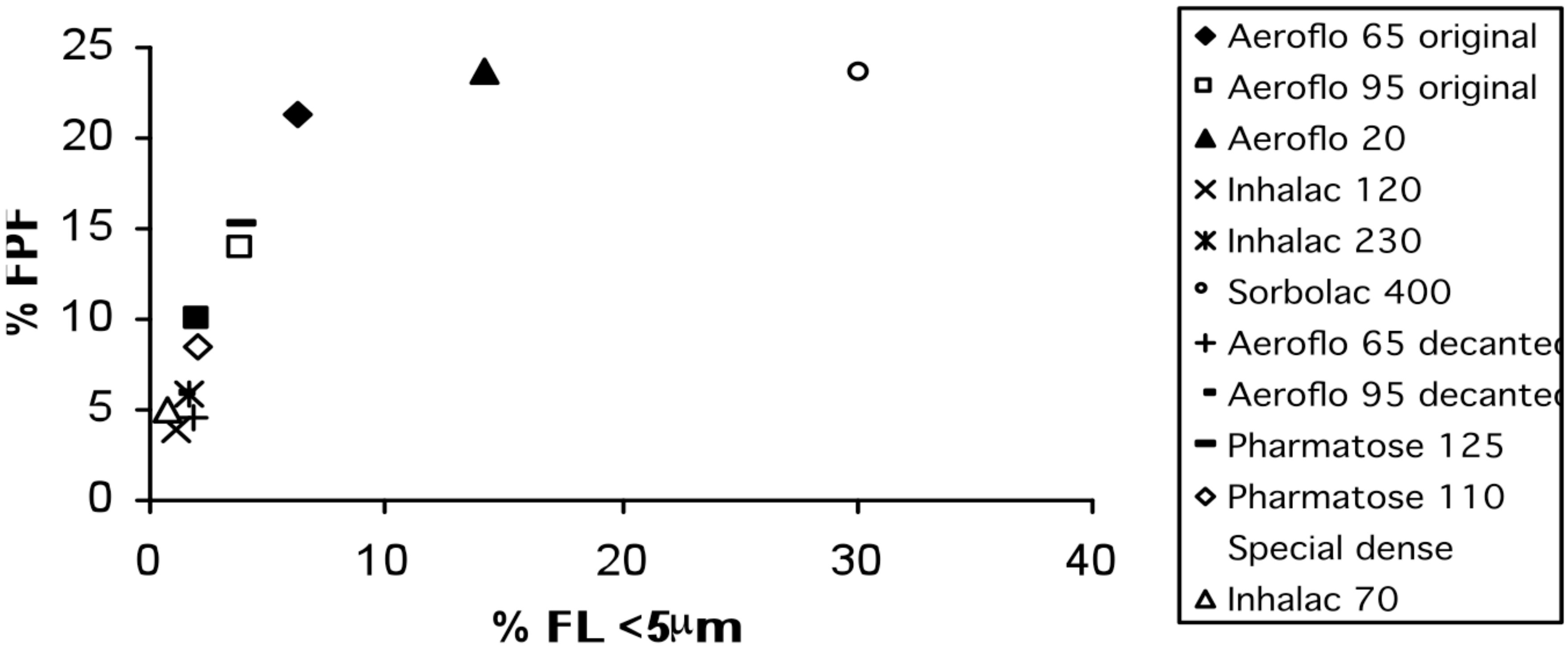
Deaggregation efficiency of drug from different grades of lactose



MONASH University
Pharmacy

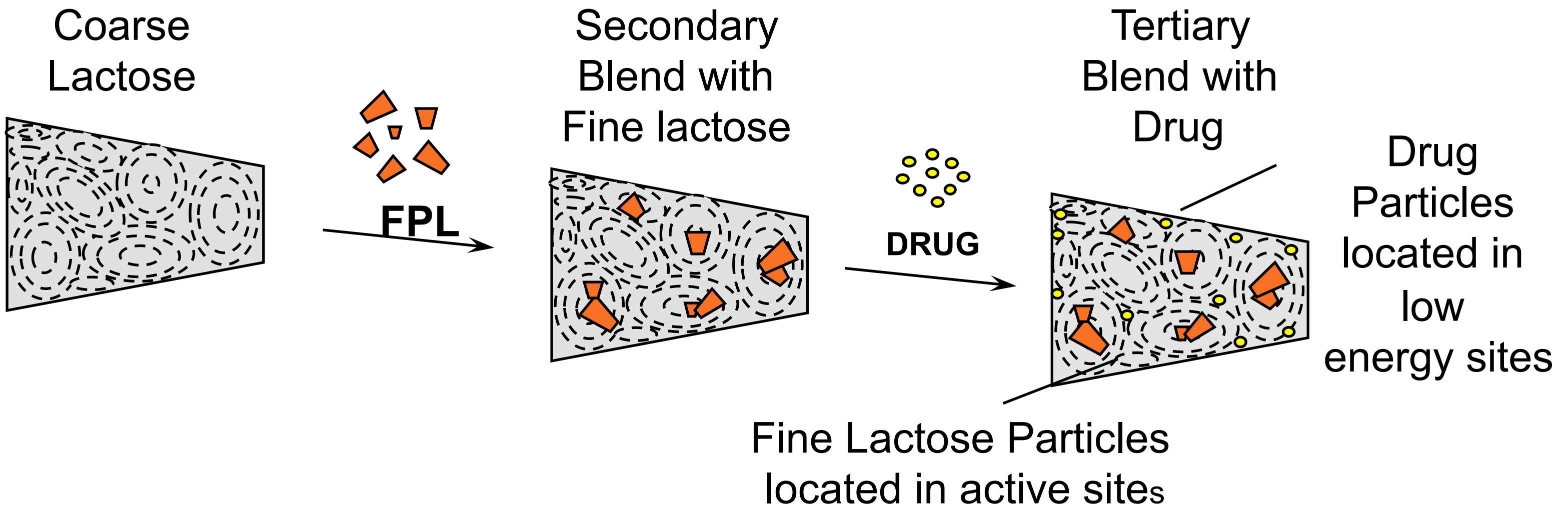
Courtesy of Prof. Peter Stewart

Influence of fine lactose particles on SX dispersion from Lactose carriers

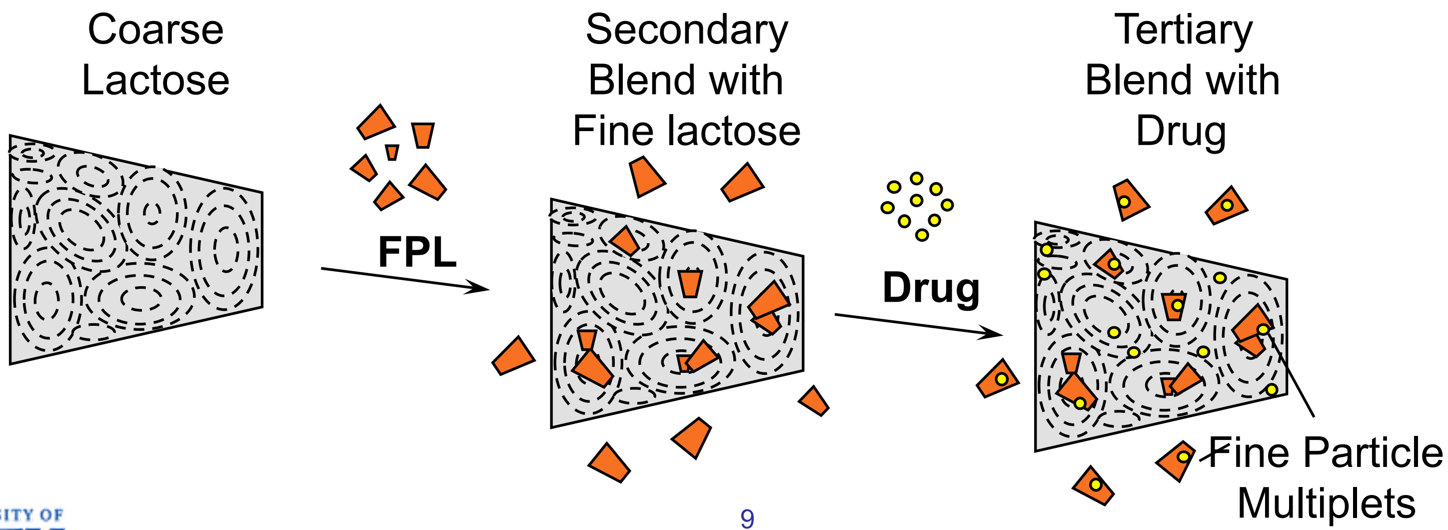


Courtesy of Prof. Peter Stewart

Hypothesis I: Passivation of Active Sites



Hypothesis 2: Fine Particle Multiplets



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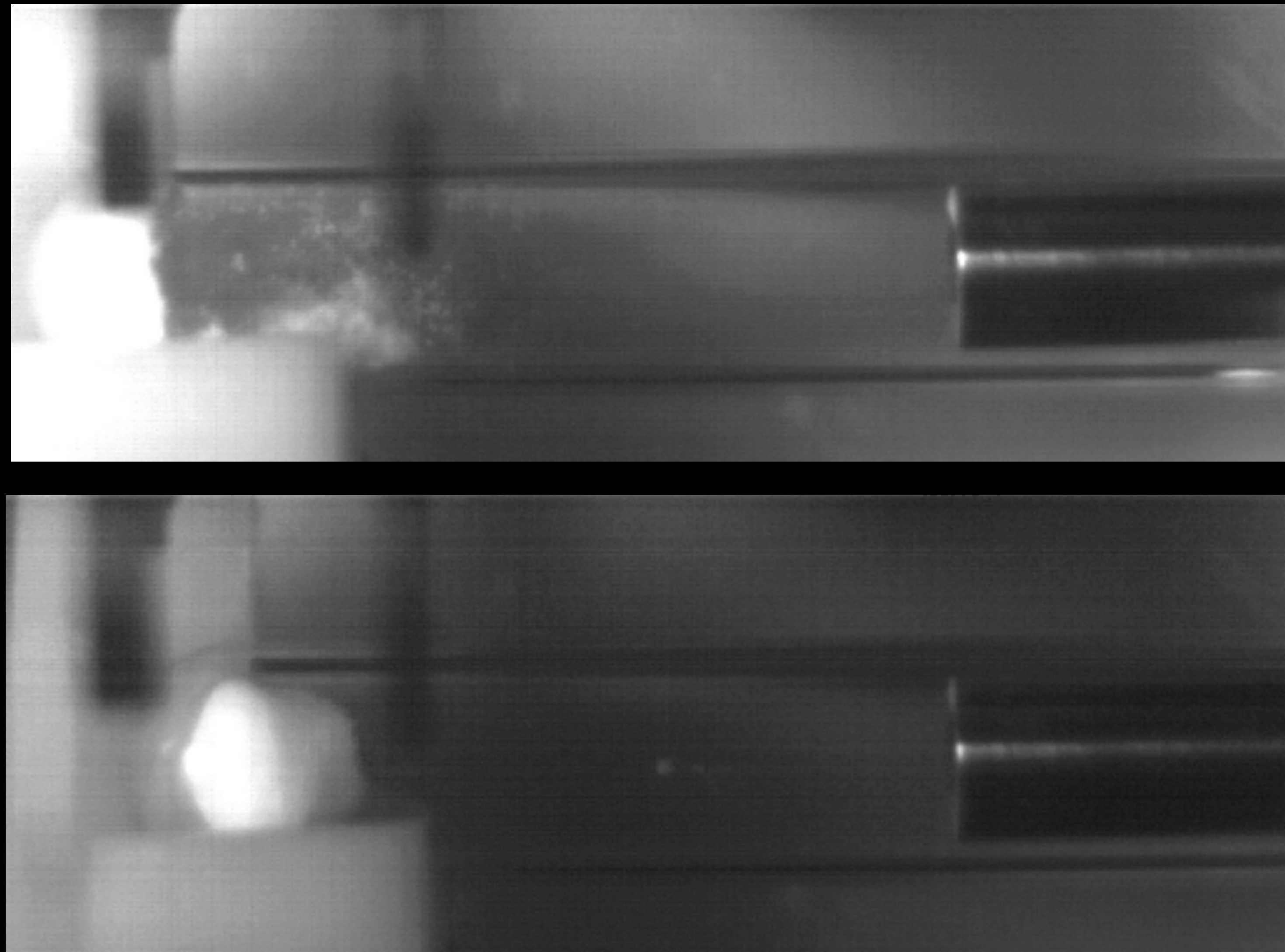
Hypothesis 3: Increasing the Tensile Strength of the powder

Fluidization of Cohesive Powders[1,2]

- The addition of fine Group C powders to an aeratable group A powder reduces rate of powder entrainment. Why?
- The adhesion of the fines to the larger particles makes the powder behaves more cohesive due to the increase of interparticulate forces.
- These forces are greater than hydrodynamic forces which leads to poor fluidization.
- Powders tends to fracture before breaking and flow and avalanche as agglomerates. This is the key to efficient deaggregation of the drug.

1. *Geldart, Harnby and Wong, Powder Technology 37 (1984) 25-37.*
2. *Baeyens, Geldart and Wu, Powder Technology 71 (1992) 71-80.*

Fluidisation behaviour



Can we characterise these effects and their role on formulation behaviour?

- Fundamental characterisation of the adhesive and cohesive interactions are too complicated
- The fluidisation is influenced by a number of factors, including:
  - Particle size, particle shape, distribution of interparticle and mechanical forces, contact restructuring, compaction, interstitial gas etc.
- Fluidisation will be inter-dependant on
  - The tensile strength of the lactose/ final blend structure
  - The energy required to overcome this resistance to flow (fluidisation energy)

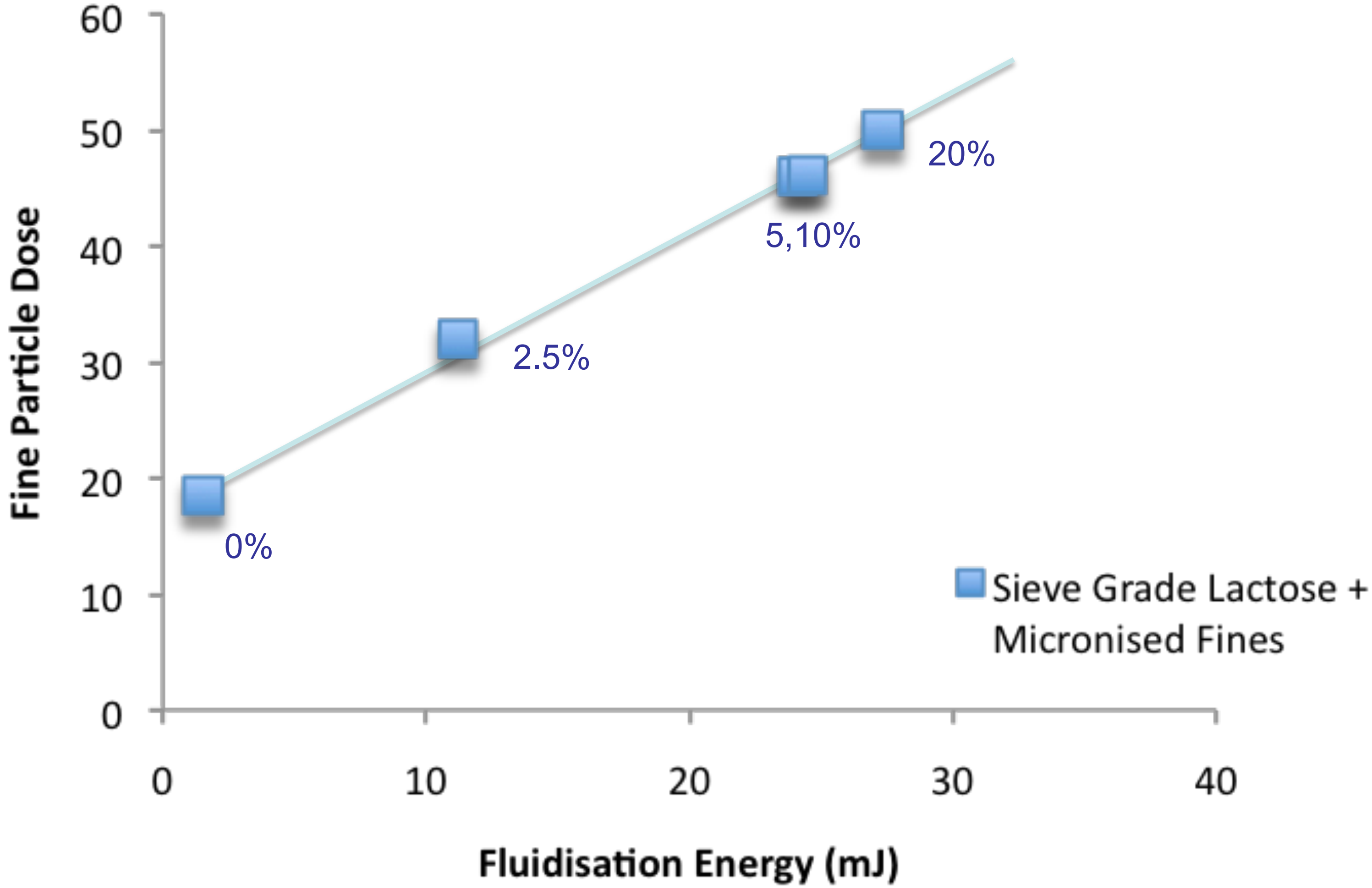
Case Study I: Effect of Fines Content on Powder Fluidisation Characteristics and Relationship to DPI Performance

- Addition of micronised lactose to commercial lactose (SV003) grade (0, 2.5, 5 and 10 % $^{w}/_{w}$).

- Formulations: Budesonide and lactose with the different levels of fines.

- Cyclohaler was used to disperse blends from size 3 HPMC capsules containing 25 mg of blend, into a NGI (with pre-sep) 82 $L.min^{-1}$.

Influence of Fines on FPD and Fluidisation of Budesonide



Case Study II: Influence of batch-to-batch variability of lactose batches on fluidisation and DPI Performance

- Four batches of sieved grade lactose (SV003) and milled grade lactose (ML001) were used as received from various pharma companies.
- Formulations: Budesonide with different batches of lactose were prepared via low shear blending
- Cyclohaler was used to disperse blends from size 3 HPMC capsules containing 25 mg of blend, into a NGI (with pre-sep) 82 $L.min^{-1}$.

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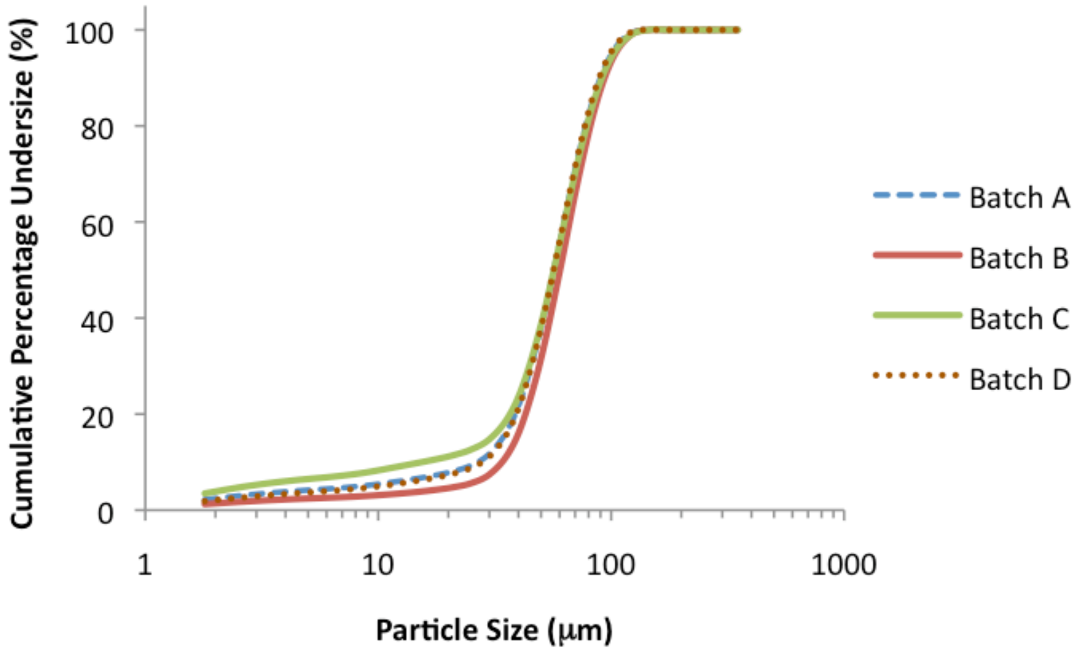
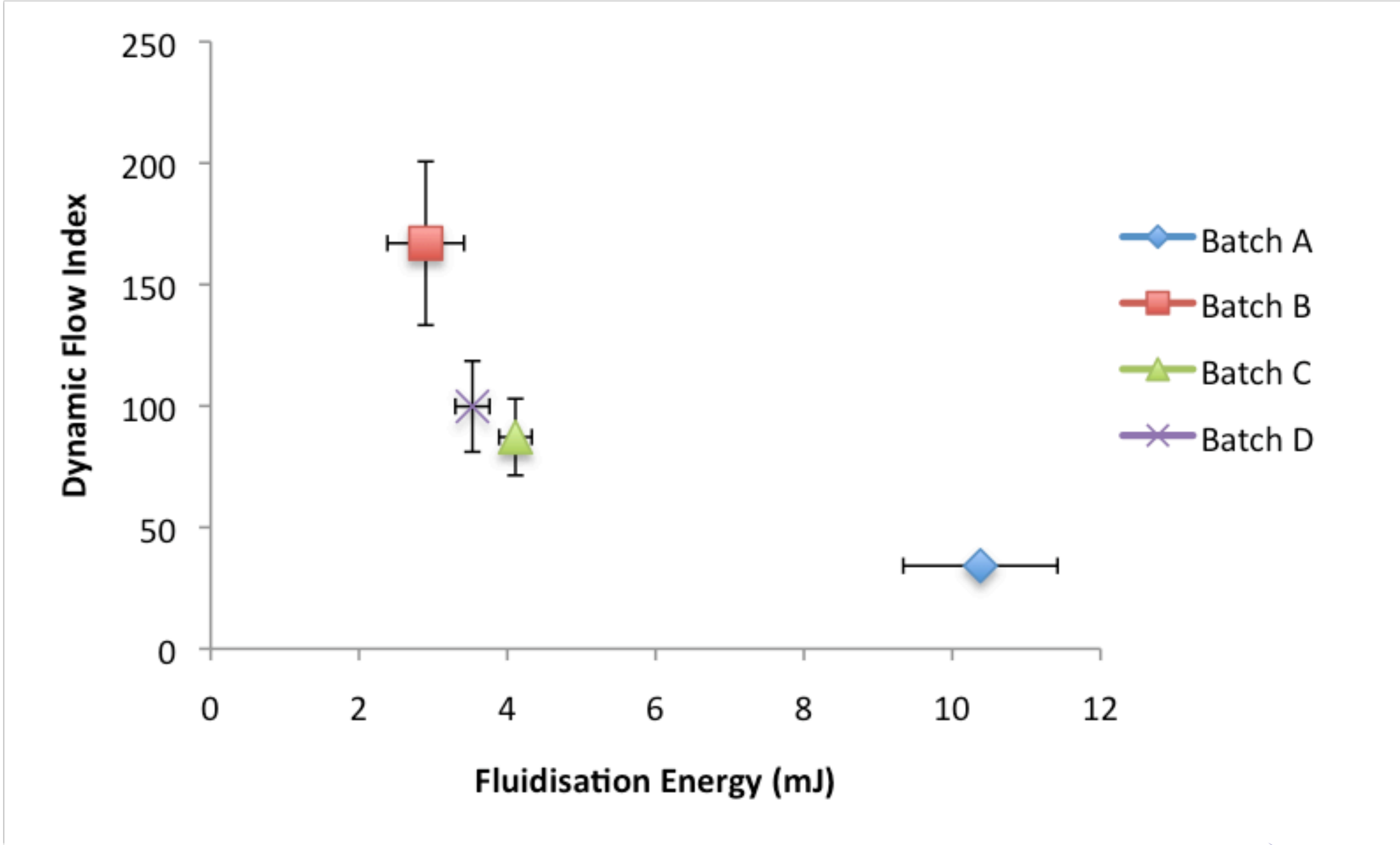
PSD analysis of sieved grade (SV003) DMV lactose batches



SV003	%<5µm	FPD
Batch A	4.16	39.04
Batch B	2.41	22.40
Batch C	6.48	28.09
Batch D	3.67	23.08

Powder rheometric analysis of the sieved grade (SV003) lactose



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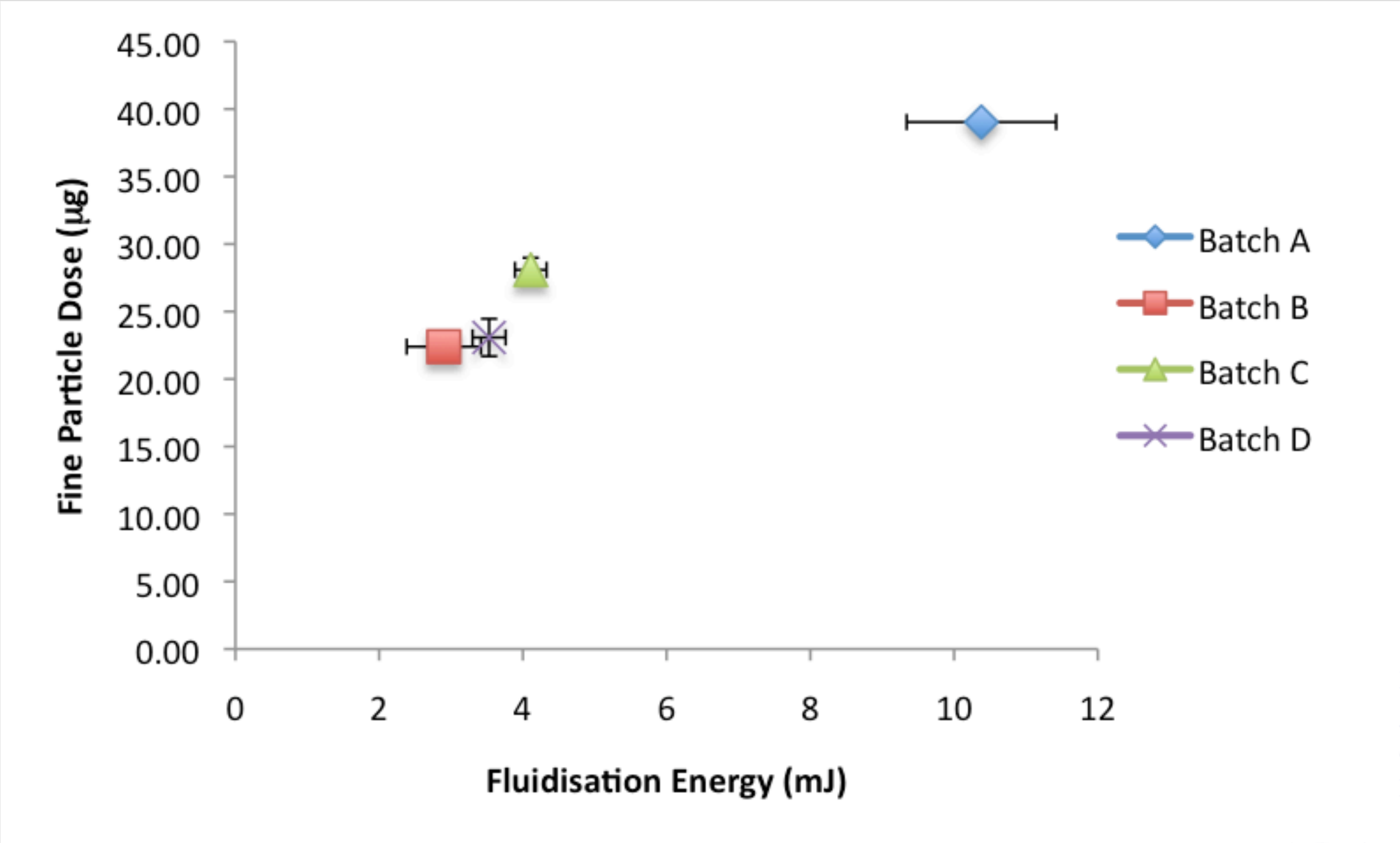
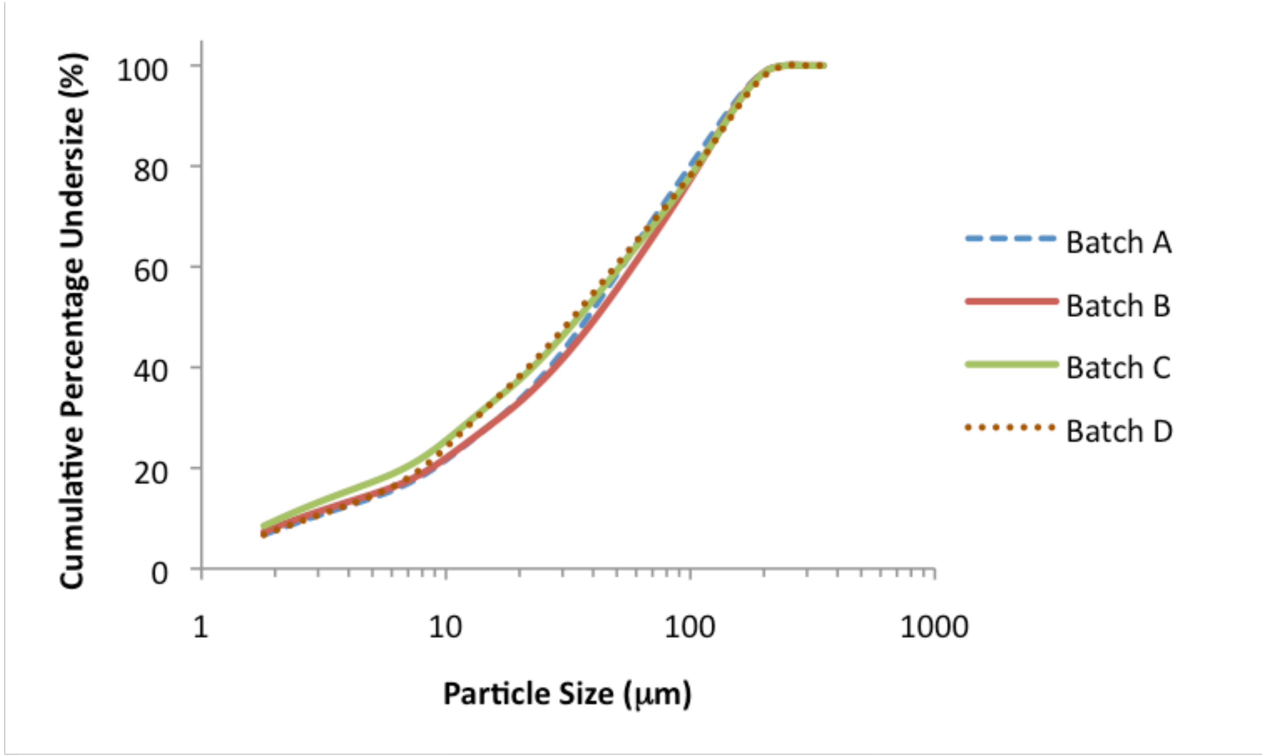
Relationship between performance and fluidisation energy



PSD analysis of milled grade (ML001) DMV lactose batches



SV003	%<5µm	FPD
Batch A	14.06	38.1
Batch B	14.79	49.2
Batch C	17.21	42.1
Batch D	14.45	41.7

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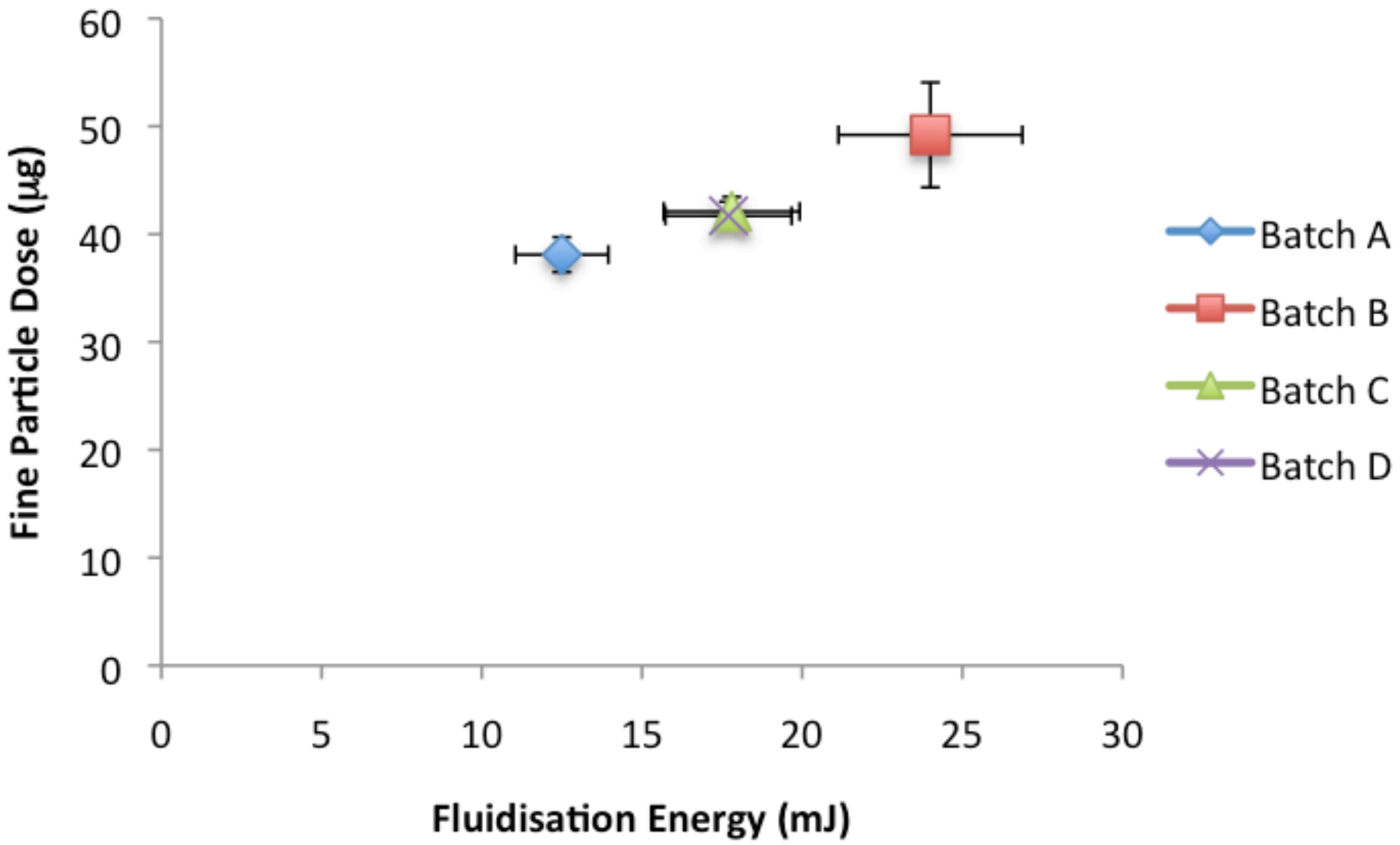
Relationship between performance and fluidisation energy of the ML001 batches



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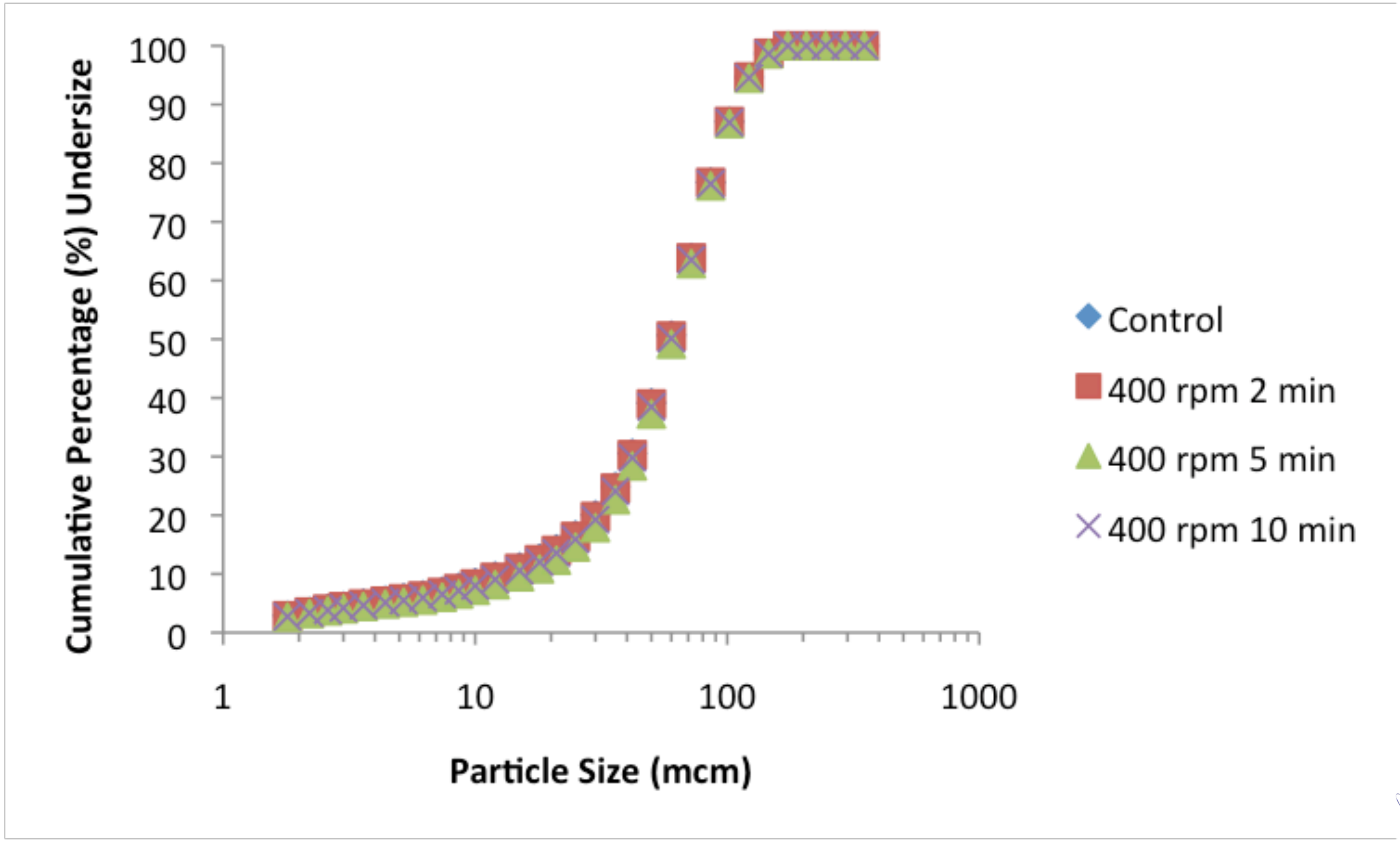
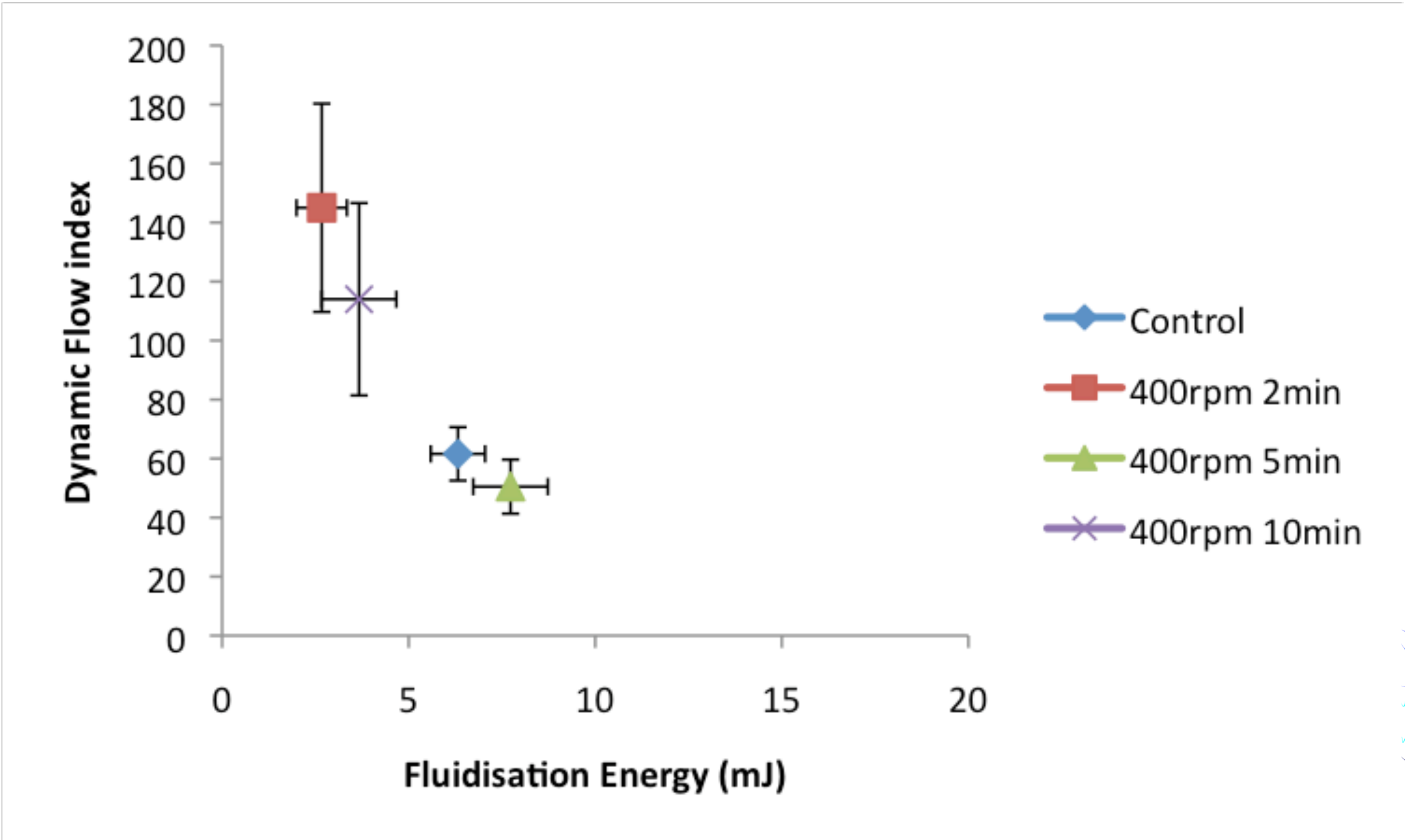
Case Study III: Influence of processing conditions on excipient characteristics and product functionality

- Influence of High shear processing effects on Milled and Sieved Grade Lactose
- High shear granulator set at 400rpm and processing time varied from 2, 5 and 10min.
- Processed lactose were subsequently formulated with Budesonide via turbula blending.
- Cyclohaler was used to disperse blends from size 3 HPMC capsules containing 25 mg of blend, into a NGI (with pre-sep) 82 $L.min^{-1}$.

No significant effect on Particle Size Distribution of SV003



Rheological characteristics of processed SV003 lactose



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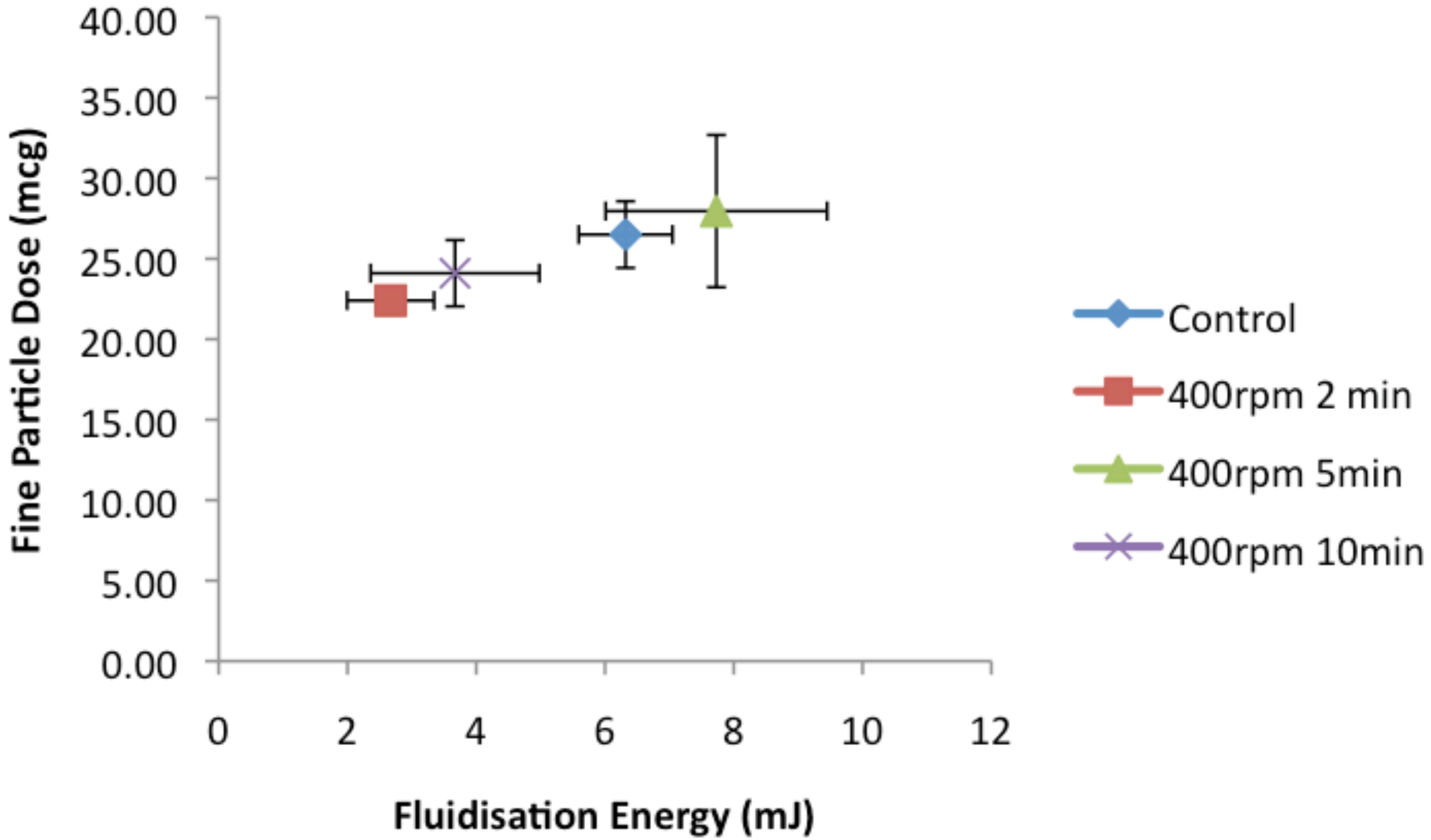
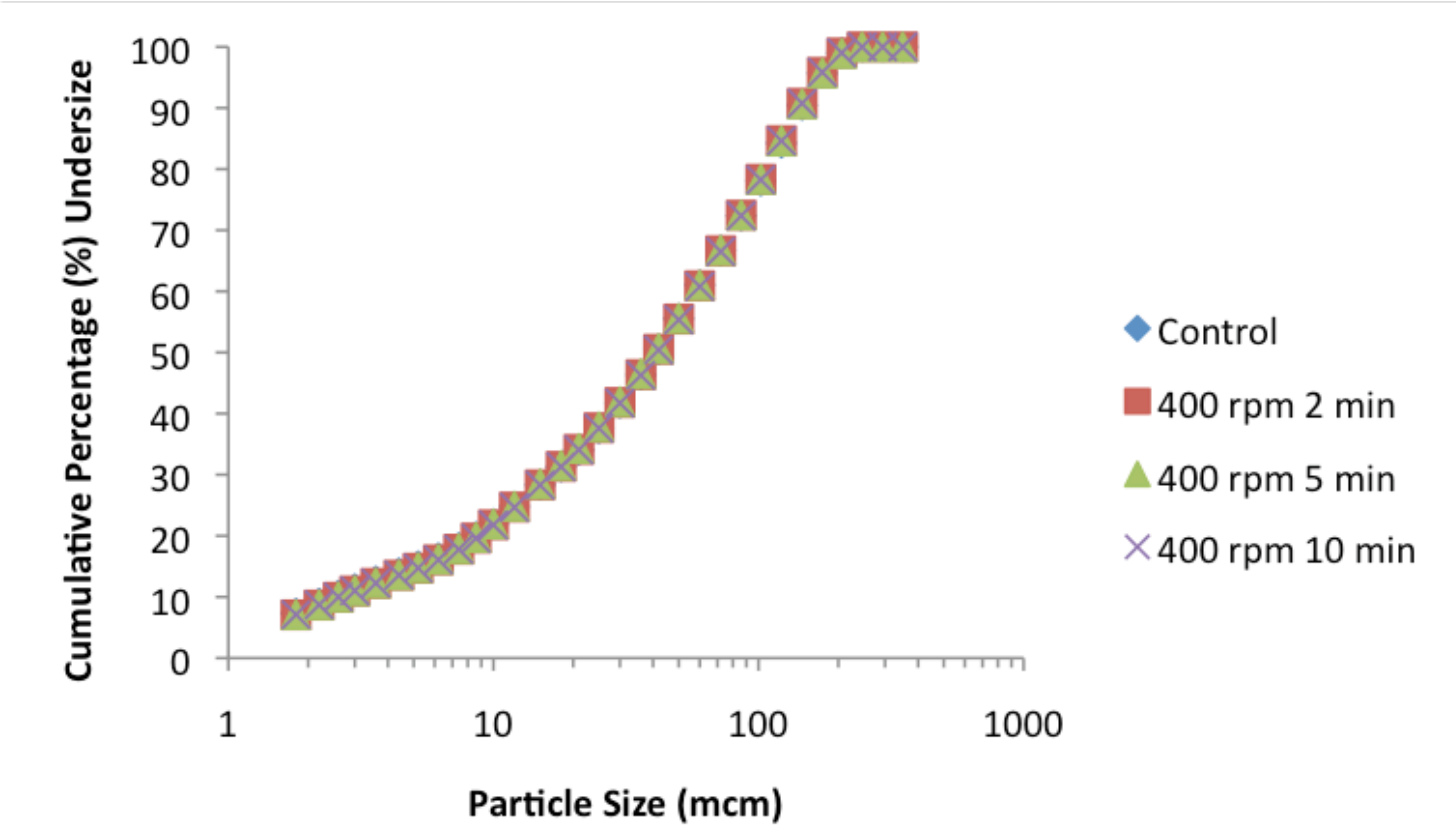
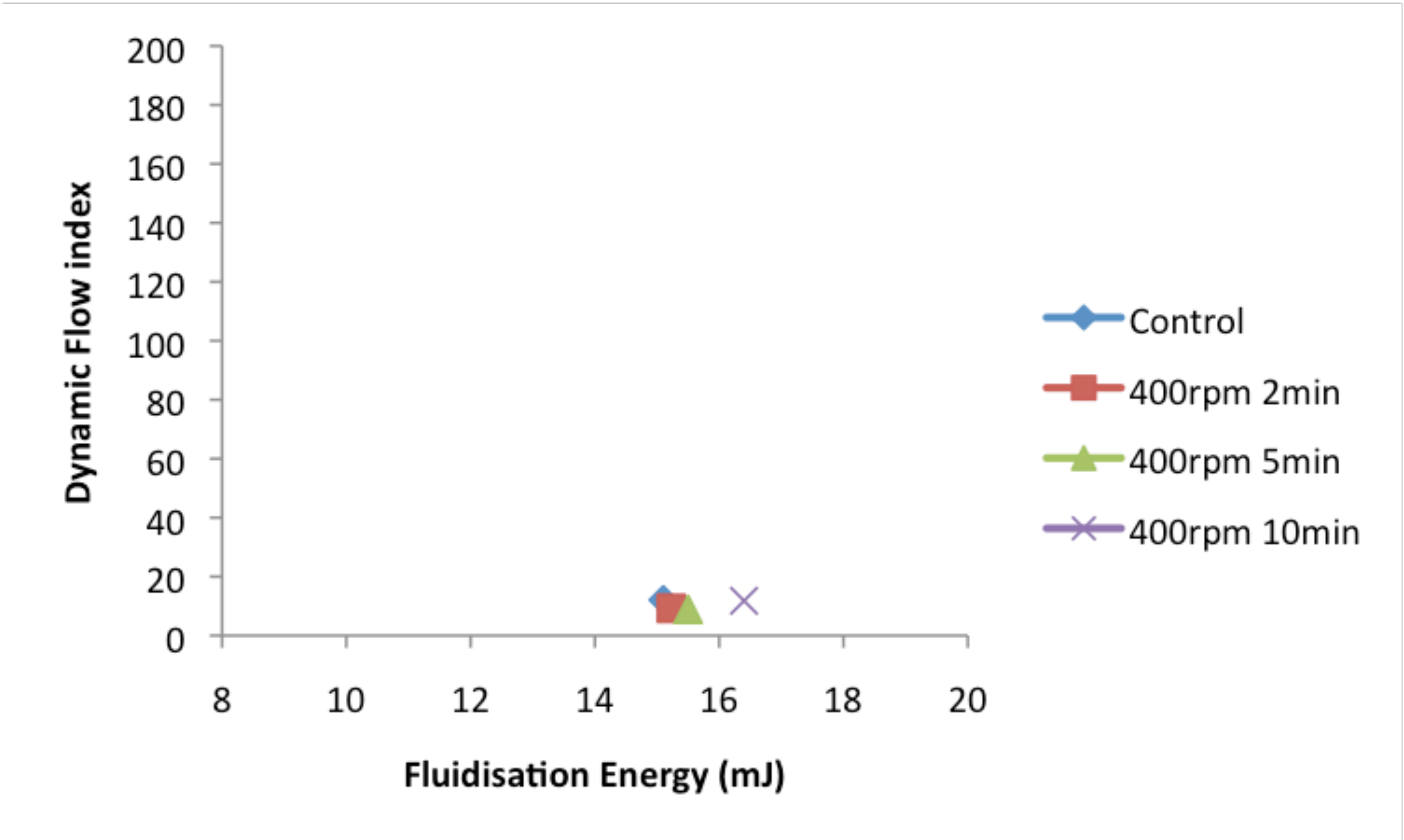
Relationship between performance and fluidisation energy of processed SV003 batches



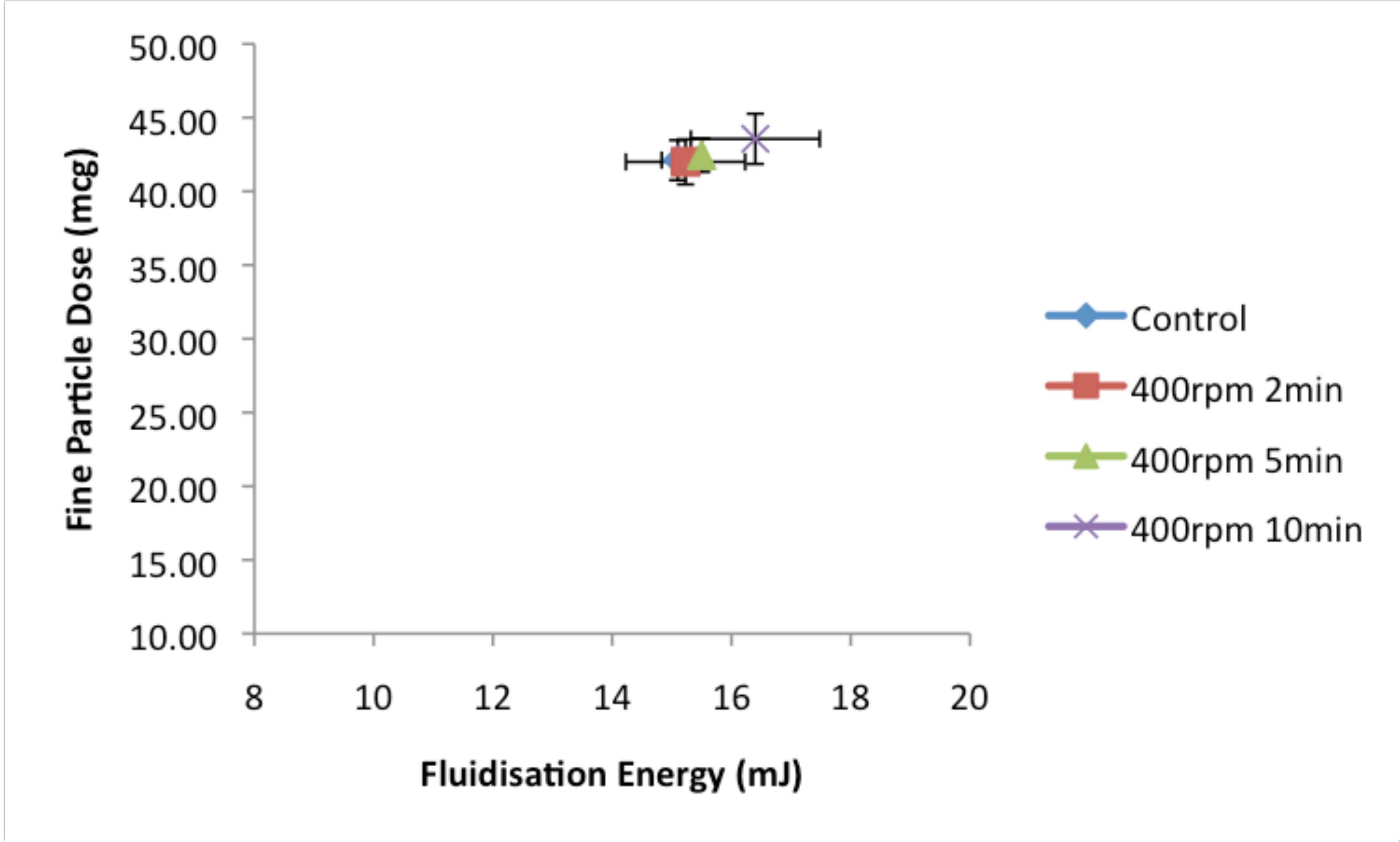
Processed ML001 Batches



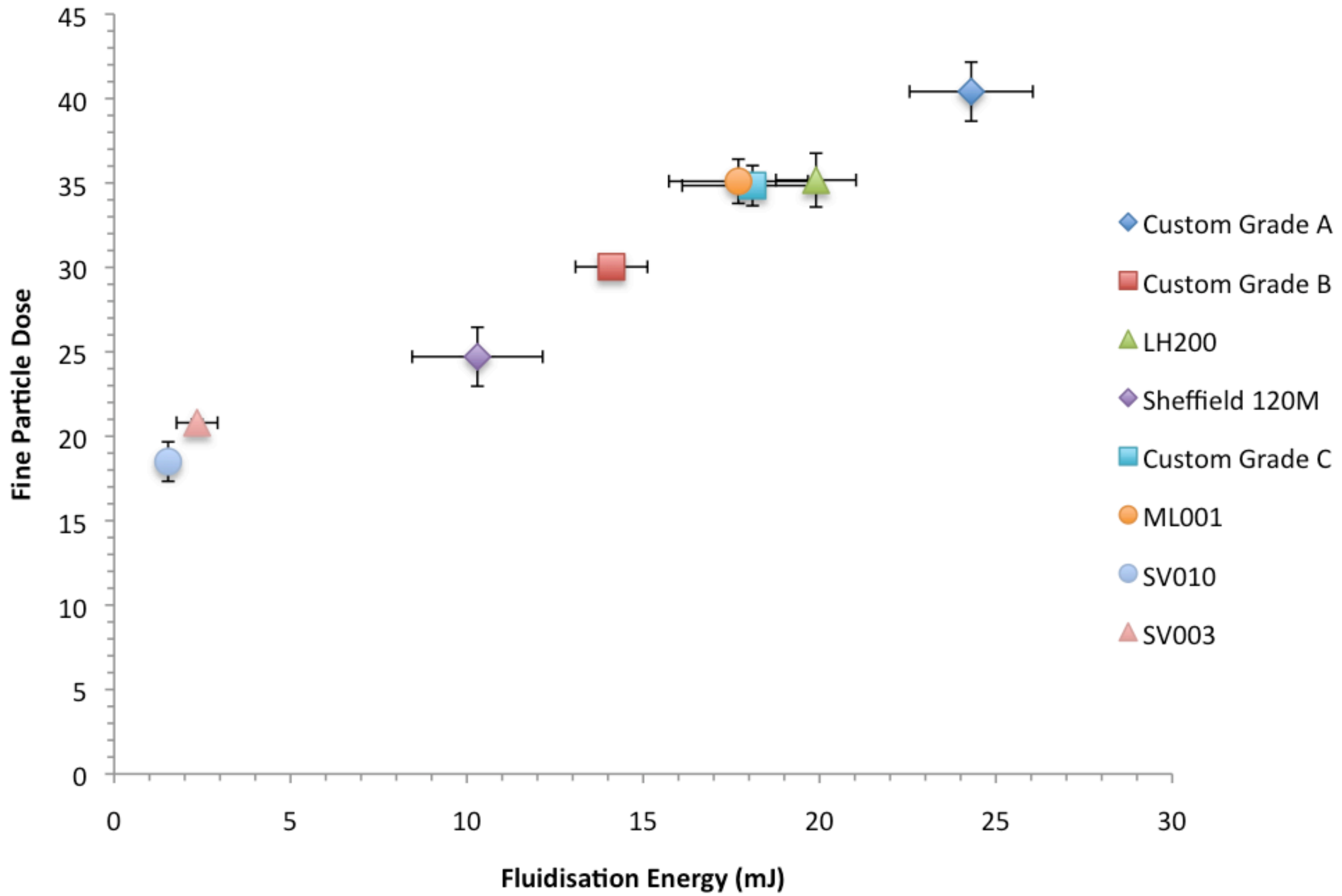
Rheological characteristics of milled grades of ML001



No influence on fluidisation and performance



De novo screening of lactose grades and batches



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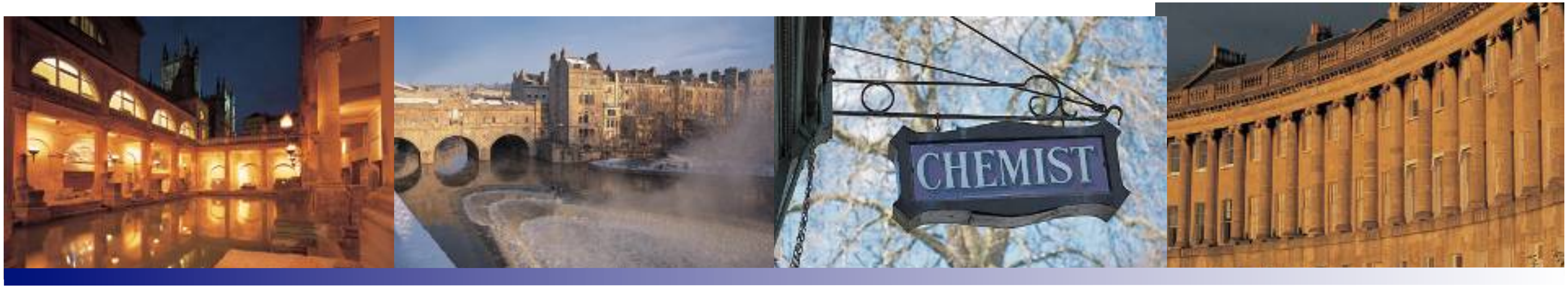
Conclusions

- The fluidisation of a carrier based DPI formulation is dependant on the cohesivity of the blend structure.
- The increase in drag force and particle-particle, particle-wall collisions with increasing tensile strength may aid the deaggregation of the active due to:.
  - Increase probability in inter-particle collisions within a high density aerosol.
  - Particle impaction is more likely to produce re-suspension than airflow alone.
- Re-suspension modelling, in conjunction with characteristic measurement of powder reactivity to an air flow, allows a means of investigating process control and understanding of DPI formulations.



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