ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Predicting the performance of powders in a loss in weight feeder

Work Package 3b Team

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Work Package Team

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Continuous processing and LIW feeders

Factors influencing flow (in LIW feeders?)

Particle size

- Larger particles, which are more amenable to gravity, flow better than smaller ones

Particle size distribution

- For a given particle "size" wider or even bimodal distributions can flow better

Particle shape

- Round particles flow better than needle ones, for a given particle size

Surface area

- Cohesion is an important determinant of flow, and higher surface area particles are more cohesive

Surface energy

- "Higher" surface energy particles likely to be more cohesive

Consequences of poor flow

Poor control of feeding into blender

- Inhomogeneity and material loss/efficiency loss
- Slow feeding leading to low efficiency

Possible decision to reject CDC as a manufacturing route

Need to preblend powder prior to filling

- Relative inefficiency in system
- No longer fully continuous
- Has been implemented commercially

FFC delineation

FFC	Flow Performance
FFC<1	Extremely cohesive and no flow
1<FFC<2	Very cohesive and non-flowing
2<FFC<4	Cohesive
4<FFC<10	Easy flowing
10<FFC	Free flowing

Some evidence that powder that is “too” free flowing will also function efficiently in a LIW feeder. Not usually a problem for API’s.

Assumptions and hypotheses

- Base assumption: material with a FFC of less than 3 is likely to perform poorly in a LIW and may require intervention
  - Projects in GSK and AZ have indicated this
- Can an FFC of ±3 be inferred from material tests using relatively small amounts of material? Available for constant updating – “internal” specification or target
  - Expand range to smaller, finer, materials
- Is it possible to set a target for powder properties which will allow reliable LIW feeding?
  - Work with Particle Engineers

Physical Work Programme

Test	Input or output	Data used
Shear Cell	Output	Flow function coefficient, using agreed precompression details
Particle size by image analysis	Inputs	Particle size, shape (size distribution, shape distribution)
BET	Input	Surface Area
Surface Energy	Input	Specific terms

A curated data set was preferred for this purpose

Morphologi G3

Application of Image-Based Particle Size and Shape Characterization Systems in the Development of Small Molecule Pharmaceuticals

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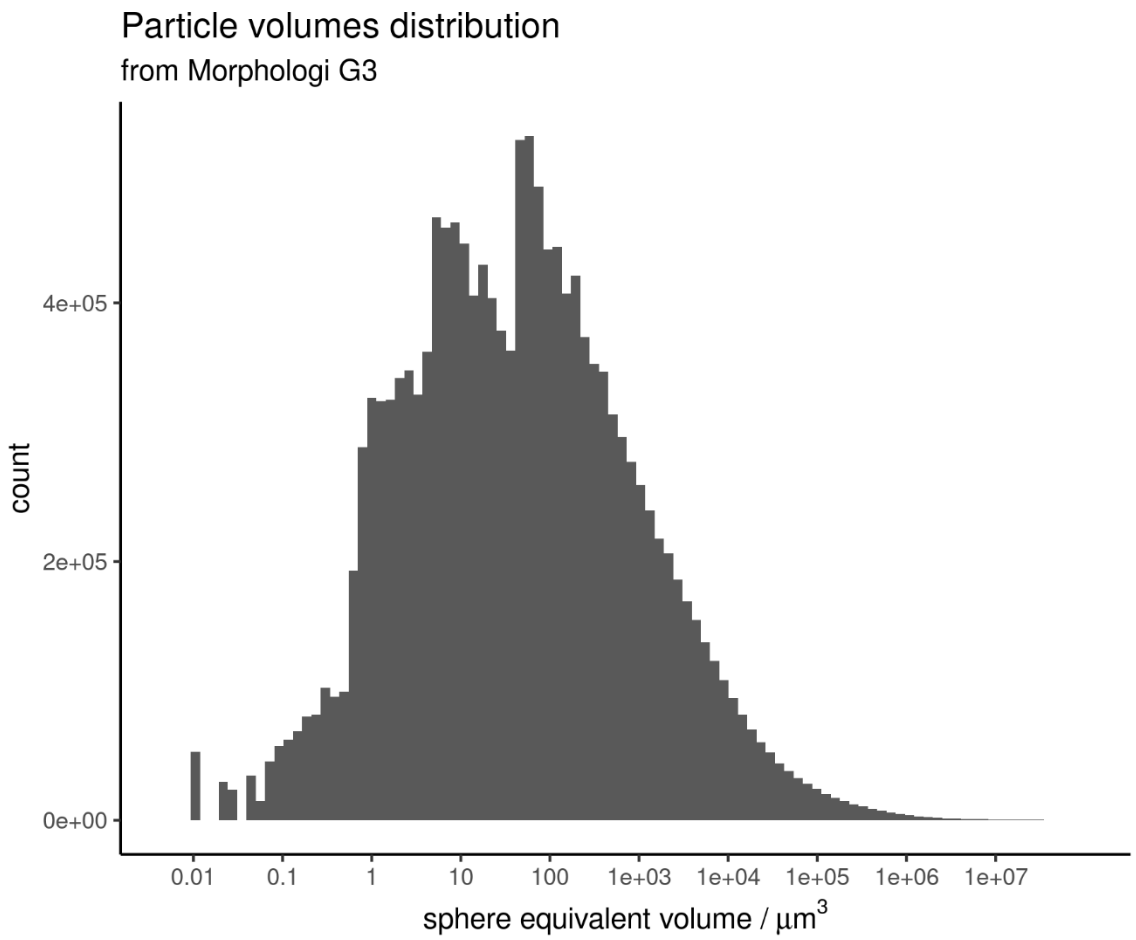
ADDOPT

Current status of data

1. We have 105 data sets from the four Primes.
2. More data is being gathered, up to the end of ADDOPT.

Initial data summary – broad spread of data



Ring shear cell:

FFC values range from less than 1 to more than 10

Data analysis and model building

Utilising size and shape information from MG3

Each powder samples is divided into 40 volume fractions based on particle volume.

For each fraction, the mean particle aspect ratio is calculated.

This results in a size and shape “signature”† for each powder sample and …

… forms the basis for comparing size and shape information from every sample to all others using the earth mover’s distance metric† (EMD).

† Y. Rubner et al. “The earth mover’s distance as a metric for image retrieval”, 2000

G3 size and shape descriptors

Modelling – Support vector regression

Support vector regression† was performed, utilising the particle size and shape signatures to predict flowability.

Models were built using:

- size information only, and
- size and shape information.

Considering that flowability is typically different at different consolidation pressures, the models above were replicated for seven different summaries of flowability (min(ffc), max(ffc), mean(ffc), etc.).

In total, fourteen models were built.

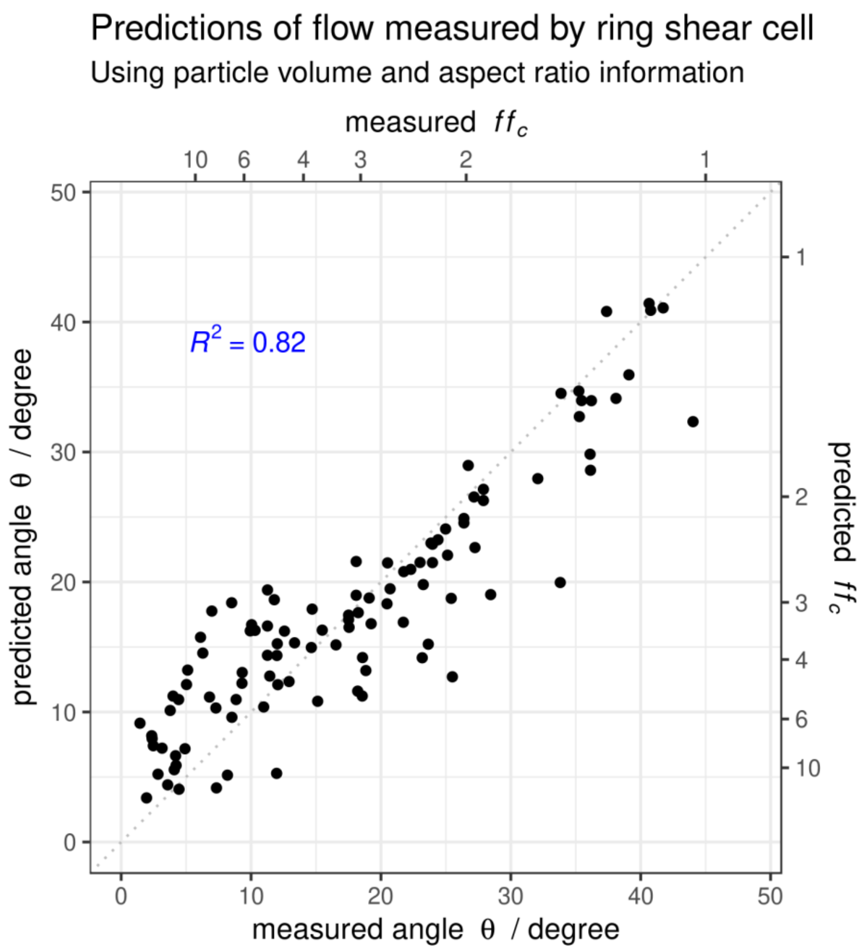
† V. Vapnik. "Statistical learning theory", Wiley, 1998

Modelling outcome

A range of models were produced.

Examples: models built using max(ffc).

Models using size and shape, and their distribution, meet targets



Other model outcomes

1. Subsets of the data could provide greater predictive capability, in terms of r^2, for that data set
2. However use of the whole data set strengthens predictive capability for the whole data set.
3. For a given data set the model can predict whether the material will meet the broad criterium of FFC ±3 with considerable accuracy
    1. Always remembering that this is not an absolute

Adding Additional Terms

1. Surface area correlated with flow but did not add anything additional to the model, presumably as the information provided by surface area was already captured in the G3 data
2. No terms from SEA correlated with flow or provided additional precision in the model.

Broad Conclusions

1. A working model for likely flow behaviour of a wide range of materials likely to be used in LIW feeders
2. Particle size and shape (and relevant distributions) are sufficient to provide such a model
   - From Morphologi G3
3. Presence of wider particle size distribution and/or agglomerates are key determinants of flow
   - Not captured by other particle size techniques
   - May have limited previous modelling efforts
4. Other data points (surface area, surface energy) do not add much specificity or knowledge

Predictive capability of model

flow measure settings	number of samples with $ff_c \leq 3$ (out of 101)	performance	true negative	false negative	false positive	true positive
low σ_{pre}	40	0.80	34	4	10	57
low σ_1	40	0.79	53	9	5	38
mid σ_{pre}	40	0.84	37	6	49	53
mid σ_1	40	0.83	53	10	10	33
high σ_{pre}	40	0.83	53	11	4	37

Next steps

Continue to develop data set

Publish model for others to use

- Github etc

Incorporate into gPROMS software –

- Use G3 data to predict flow at an early stage of development

Further publicity

- Paper

Questions?

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