Understanding Powder Flow for Continuous Processing

Earlier and better decision making about how to formulate APIs successfully

Working together to understand how to use particle fundamentals to inform an earlier choice of formulation platform for new materials

Drivers

The manufacture of solid oral dose pharmaceutical forms is underpinned by the need for good powder flow. Most Active Pharmaceutical Ingredients (APIs) are formed as very fine solids and do not inherently flow freely, and so additional treatment by wet or dry granulation is frequently needed to render freely flowing blends.

Industry trends towards more complex APIs and continuous processing further increase the need for a better grasp of the links between measurable particle properties and resultant flow behaviour, and the means to predict one by the other as early as possible in the development workflow.

Approach

This work has taken place in parallel with and in the context of the development of a Manufacturing Classification System[1], modelled on the FDA Biopharmaceutics Classification System. This will allow materials to be classified for processability according to the API powder properties and the level of drug loading. A material's position in the classification then informs the choice of processing route, or whether further particle engineering is required.

Key Features

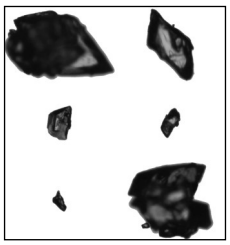
- A cross-industry collaboration to measure fundamental API properties and use the links to resultant powder flow along with drug loading in a Manufacturing Classification System
- More informed and productive dialogue between formulators and material developers
- More effective use of resources in drug product and process development

Using an agreed and standardised best practice approach to measure powder properties which elucidates flow behaviour, the partners have undertaken a study of around one hundred real APIs. The resultant data set is an order of magnitude larger than anything similar to date and uniquely, it represent the full range of performance characteristics encountered in practice: FFCs from 10—1 encompassing free down to badly flowing APIs.

An ADDoPT Case Study featuring collaboration between BMS, AZ, GSK, Pfizer, and the STFC Hartree Centre

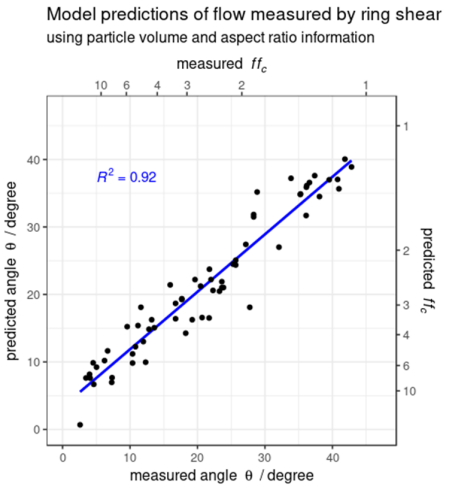
1. MCS Working Group (2018): *Manufacturing classification system in the real world*, Pharmaceutical Development and Technology, DOI: 10.1080/10837450.2018.1534863

Building a common language of key parameters



After initial discussions to share ideas on which particle properties had the most potential to shed light upon flow, the partners agreed to standardize measurements upon the Malvern Morphologi G3 particle size analyzer. This provides rapid, automated particle imaging for thousands of individual particles, enabling visual and statistical data acquisition and interpretation. The result is a rich, multiparameter-based data set describing both particle size and shape distributions for a representative sample of the powder, rather than a single point D50 average particle size.

With the resultant models it has been possible to predict, for the first time across a range of pharmaceutically relevant materials, which systems would be likely to have the necessary flow characteristics to deliver the required performance in a loss in weight feeder. Importantly, this could be applied not only to pre-existing materials but also used to create material profiles, the properties of which (*e.g.* size, shape) could realistically be made, allowing the formulator to direct manufacturing colleagues to make, procure and specify suitable materials capable of performing in continuous direct compression.



Identifying the "parameters that matter" and measuring them in a concerted way for maximum information richness and insight

Results and Benefits

The rich, multiparameter based data set generated, which describes both particle size and shape distributions for the range of materials studied, can be broken down by multi-variate analysis into a set of key descriptors. From this a material "fingerprint" may be constructed, to provide a better understanding of the links between the fundamental characteristics of the particles and their resultant flow properties measured in a shear cell.

Ultimately, with as little as 50mg being enough to provide the crucial material property fingerprint, the MCS enabled by this work will allow

- formulators to give meaningful feedback to those producing materials and specifications for right-first-time manufacture of particles
- choice of manufacturing technology platforms to be based on science rather than preconceptions or assumptions
- developers to identify the degree of fit of new materials with a given technology platform early in the development cycle.

Further Steps

The MCS is at its heart a means of facilitating a meaningful, actionable conversation between API development and drug product formulation functions in an organisation. The lower are the boundary walls between these two key functions and the closer they work together the better.

A modelling tool will be implemented in gPROMS FormulatedProducts to facilitate specification of the critical powder parameters for flow performance.

Transforming pharmaceutical development and manufacture

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