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Modelling and understanding powder flow properties and compactability of selected active pharmaceutical ingredients, excipients and physical mixtures from critical material properties

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ABSTRACT

The development of solid dosage forms and manufacturing processes are governed by complex physical properties of the powder and the type of pharmaceutical unit operation the manufacturing processes employs. Suitable powder flow properties and compactability are crucial bulk level properties for tablet manufacturing by direct compression. It is also generally agreed that small scale powder flow measurements can be useful to predict large scale production failure. In this study, predictive multilinear regression models were effectively developed from critical material properties to estimate static powder flow parameters from particle size distribution data for a single component and for binary systems. A multilinear regression model, which was successfully developed for ibuprofen, also efficiently predicted the powder flow properties for a range of batches of two other active pharmaceutical ingredients processed by the same manufacturing route. The particle size distribution also affected the compactability of ibuprofen, and the scope of this work will be extended to the development of predictive multivariate models for compactability, in a similar manner to the approach successfully applied to flow properties.

1. Introduction

Robust manufacturing processes and consistent quality of pharmaceutical products is crucial in terms of ensuring uninterrupted manufacturing with minimal failures, and may be achieved by controlling and identifying critical material properties (CMPs) of active pharmaceutical ingredients (APIs) and functional excipients (Fonteyne et al., 2014). However, a lack of precise understanding of the relationship between critical quality attributes (CQAs) of a drug product, CMPs and critical process parameters (CPP) precludes the implementation of a Quality by Design (QbD) approach (Mohammed et al., 2015). Molecular level and fundamental powder properties of pharmaceutical materials, such as solid form, particle size, surface area, porosity, moisture or solvent content and surface properties can affect derived powder properties such as powder flow and compactability, which ultimately affect processability of formulations and the CQAs of the final drug product (Hlinak et al., 2006).

Acceptable powder flow is one of the measures of processability which can be affected by particle size, particle shape distribution, and moisture content (Staniforth, 2002; Yu et al., 2011). Many powder flow characterisation techniques have been implemented to evaluate diverse types of "*static*" and "*dynamic*" powder flow properties, where measures of the former involve shear cell and wall friction analyses of a consolidated state of the powder, and the latter involves flow studies using a rotating helical blade in a less consolidated state of the powder sample. However, a single technique or testing protocol has been shown to be insufficient to properly characterise powder flow properties (Krantz et al., 2009).

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Tablets are the most common type of solid dosage form, where powder flow is a critical bulk level property governing the direct compression method of tablet manufacturing. It is generally accepted that small particles have poor flow properties and tend to agglomerate to reduce their high surface energy. Garekani et al. previously evaluated the flow and compaction properties of ibuprofen crystallised from ethanol, methanol, isopropanol and hexane. Ibuprofen crystallised from hexane showed a poor flow rate, as measured by a flow meter, and poor compression properties, which were attributed to the particular crystal morphology, i.e. needle-like crystal habit (Garekani et al., 2001a). However, in trying to establish correlations between such fundamental powder properties (e.g. particle shape) and flow, a challenge exists in generating powders with diverse morphology and the "same particle size", or *vice versa*. In addition, the progress of a science-based approach for solid dosage form product development has been limited due to lack of standardized methods to characterise particulate and bulk level properties of APIs and excipients. Hlinak et al. pointed out that the lack of a database and predictive relationships among CMPs, CPPs and CQAs hinders a precise understanding of the influence of physical properties of materials on manufacturing processes (Hlinak et al., 2006).

Yu et al. successfully developed a partial least square model to predict powder flow function (FF) from particle size and morphology distributions of excipients and binary blends (Yu et al., 2011). However, a single powder flow characteristic is often insufficient to set a suitable flow specification for drug product manufacturing due to the complexity of manufacturing processes and material properties. The flow behavior of a powder is a multi-faceted problem, originating from both material properties (particulate and bulk level) and the equipment used for handling, storing, and/or processing the material (Krantz et al., 2009). Various powder flow classification systems and indices have been suggested, where Geldart (Geldart, 1973); Carr (Carr, 1965); Taylor (Taylor et al., 2000); Tomas and Schubert (Tomas and Schubert, 1979) introduced flow parameters as a screening technique during early stage drug product development. However, these classifications and flow indices are inadequate to predict the powder flow properties for different manufacturing processes and process parameters, since these powder flow tests hardly reflect manufacturing equipment used in practice for handling and processing the material (Krantz et al., 2009). Nevertheless, single powder flow indices, such as FF (Yu et al., 2011) or basic flow energy (BFE) have been used to assess the processability of powders. Inconsistencies between different powder flow characterization techniques have also been reported, indicating that a single powder flow property can be unreliable to predict powder flow properties (Navaneethan et al., 2005). Hence, process specific and rational selection of powder flow characterisation techniques and the use of more than one powder flow parameter should be essential components of drug product development.

As well as impacting powder flow, fundamental powder properties, such as particle size, can also affect compression and compactability or "tabletability" of powders and powder blends (Patel et al., 2007). Patel et al. showed that particle size and compression pressure can affect derived mathematical parameters of compressibility (Patel et al., 2007). Optimum material properties of APIs should create a balance between processability and CQAs like tensile strength and appearance of the tablet.

The objective of the current work was to identify the critical particle size distribution descriptors from measured and derived particle size distribution data for APIs and binary mixtures of APIs and excipients which can affect (1) the powder flow parameters measured under a "dynamic state" and "*static* state" and (2) the tabletability of powders, as reflected by the tensile strength and ejection force of compacts/tablets. The critical material properties from particle size data, identified using multivariate analysis, were used to develop multilinear regression models (MLR) to predict multiple powder flow parameters for APIs manufactured by a similar route and API/excipient binary mixtures comprising either the free flowing functional excipient, microcrystalline cellulose (MCC), or the relatively cohesive lubricant, magnesium stearate.

2. Material and methods

2.1. Materials

RS-Ibuprofen (IBU) and cilostazol (CLZ) were purchased from Kemprotec Limited (UK). Paracetamol (PCM), magnesium stearate, diiodomethane and ethylene glycol were purchased from Sigma-Aldrich (United Kingdom). Microcrystalline cellulose (Avicel PH-102) was a generous gift from FMC Health and Nutrition (Ireland). Analytical grade ethanol, methanol and hexane were purchased from Fisher Scientific (UK) and used without further purification. Purified water was used as the anti-solvent during crystallisation.

2.2. Sample preparation

Various batches of APIs were prepared by cooling or ultrasound assisted crystallisation from a saturated solution of IBU, CLZ or PCM in an organic solvent (ethanol, methanol and hexane) or mixture of solvents (ethanol-water, hexane-water and methanol-water) (Reactor-Ready^{TM} Lab Reactor, Radleys, UK). Two batches of PCM were also prepared by dry (PCM D) and wet milling (PCM W) (Quadro comill, Ytron-Quadro, UK) of crystallised materials. The physical mixtures of IBU (all three batches were needle shaped crystals) with MCC or magnesium stearate with various compositions (% w/w) were prepared in a Turbula mixer (Glen Creston Limited, Switzerland) using 60 rpm for 20 min mixing time (Table 1).

Table 1
Summary of APIs and binary mixtures.

Sample used in the Multilinear Regression (MLR) models	Composition of excipients (% w/w)	Number of batches	Method of preparation
IBU	0	13	Cooling crystallisation
IBU and MCC	100, 90[3], 85, 80, 70[2], 50[3], 30[2], 10[3] and 0[3,a]	19	Blended using a Turbula mixer
IBU and Magnesium stearate	5[2], 2[2], 1, 0.25[2] and 0[2,a]	9	Blended using a Turbula mixer
CLZ	0	2	Cooling crystallisation
PCM	0	4	Milling (2 batches), Sonocrystallization (1 batch) and purchased (1 batch)

[2] and [3] are the number of batches for each composition of the binary systems with variable physical properties of ibuprofen.
[a] Selected ibuprofen batches included in developing the MLR models of binary systems.