PREDICTION OF POWDER FLOW OF PHARMACEUTICAL MATERIALS FROM PHYSICAL PARTICLE PROPERTIES USING MACHINE LEARNING

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ABSTRACT

Understanding powder flow and how it affects pharmaceutical manufacturing process performance remains a significant challenge for industry. This work aims to improve decision making for manufacturing route selection, achieving the key goal of digital design within Industry 4.0 of being able to better predict properties whilst minimizing the amount of material required and time to inform process selection during early-stage development. A Machine Learning model approach is proposed to predict the flow properties of new materials from their physical properties. The model's implementation will enhance manufacturing quality by taking advantage of the data generated throughout the manufacturing process.

Keywords: pharmaceutical manufacturing, pharmaceutical materials, particle characterization, Machine Learning, digital design.

INTRODUCTION

Understanding powder flow and how it affects pharmaceutical manufacturing process performance remains a significant challenge for industry, adding cost and time to the development of robust production routes. It is therefore crucial improve our understanding of powder flow and how this relates to both tableting and capsule filling. Tablet formation can be addressed by several techniques; however, direct compression (DC) and wet granulation (WG) are the most widely used in industrial operations. DC offers lower-cost manufacturing due to it provides streamlined process with fewer steps compared with other techniques. However, to achieve the full potential benefits of DC for tablet manufacture, this places strict demands on material flow properties, blend uniformity, compactability, and lubrication, that need to be satisfied. On the other hand, WG improves flowability and compactability while preventing segregation through the use of binding agents and secondary process steps although it is not suitable for materials which are sensitive to heat or moisture. WG is, therefore, more expensive and time consuming. Due to these economic advantages, DC is increasingly the preferred technique for pharmaceutical companies for oral solid dose manufacture, consequently making the flow prediction of pharmaceutical materials of increasing importance (Schaller et al., 2019; Trementozzi et al., 2017). Flow properties are influenced by the particle size and shape, which are defined upstream during crystallization and/or milling processes. Currently suitability of raw materials and/or formulated blends for DC requires detailed characterization of the bulk properties. A key goal of digital design within Industry 4.0 is to be able to better predict properties whilst minimizing the amount of material required and time to inform process selection during early-stage development.

Traditionally, powder flow has been measured by experimental methods, such as angle of repose, bulk density, Carr's compressibility index, Hausner ratio, and FT4 powder rheometer. However, they are time and material consuming, which is inefficient at the beginning of the material development.

There have been several publications of different approaches to estimate powder flow, such as the study of packing efficiency based on measuring particle size of granular intermediates using Principal Component Analysis (PCA) (Sandler & Wilson, 2010), a big-data approach using shear cell test (Megarry, Swainson, Roberts, & Reynolds, 2019), the study of granular Bond number, which correlates to the flow function coefficient (Ghadiri et al., 2020); or using statistical modelling techniques (Barjat et al., 2021), which is focused on the prediction of flowability for loss in weight feeders.

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RESEARCH CONCEPT

This work aims to improve decision making for manufacturing route selection in the early stages of the drug product manufacturing process development when time and amount and cost of available material are at a premium. A Machine Learning (ML) model approach is proposed to predict the flow properties, specifically the flow function coefficient (FFc) of a new material from its physical particle properties. The aim is that the model produced as an outcome can help decide whether a new material is suited for DC.

Initially, unsupervised learning algorithms were used; however, these were not useful to classify the data. Consequently, supervised learning algorithms were selected for classification, where FFc was defined as the target property (dependent variable), and the independent variables were particle size and shape distribution, and bulk density. The training data was experimentally generated using the Powder Rheometer – FT4 and a dynamic image analysis (QIC/PIC). Furthermore, a testing data set was generated to validate the model.

RESULTS

The data set used to build the ML model included 115 fully characterised materials. Regarding particle size distribution, 42 of the materials had a D50 smaller than 100 µm, 56 had a D50 between 100 µm and 250 µm, and 17 had a value of D50 greater than 250 µm. Concerning particle shape, most of the materials' aspect ratio falls between 0.6 and 0.8, which corresponds with a cubic shape (Yu, Liao, Bharadwaj, & Hancock, 2017). Based on the FFc, the 27 materials were classified into class 1 (cohesive materials with FFc < 4), 34 were classified into class 2 (easy-flowing materials, 4 < FFc < 10), and 54 materials were classified into class 3 (free-flowing materials, FFc > 10). The physical particle properties were ranked according to their correlation with the target variable, resulting particle size distribution (D10 and D50) and aspect ratio distribution (a90) the variables that provided more information.

Table 1: Number of Instances per class regarding their flow function coefficient and powder behaviour.

FFc	Behaviour	Number of materials
< 4	Cohesive	27
4 < FFc < 10	Easy flowing	34
>10	Free flowing	54

The supervised learning algorithms selected were compared between each other to analyse their performance; and the model was thereafter validated using the external data set, for which 6 of the 8 materials included were correctly classified.

DISCUSSION

A wide range of materials were included in the training dataset. Among the algorithms selected, Random Forest (RF) exhibited the best performance (0.802), which means that there is a probability of 80.2 % for the algorithm to correctly classify the powder flow class of a new material. The other algorithms included in this study exhibited a performance higher than 70 %. Regarding the validation set, 75 % of the materials were correctly classified.

CONCLUSIONS

The ML model's implementation enables the prediction of the material flow properties from their physical properties, enabling rapid decision-making regarding manufacturing route selection, achieving a key goal of digital design of being able to better predict properties whilst minimizing the amount of material and time required to inform process selection during early-stage development. This work suggests that particle size and shape distribution are sufficient to enable accurate prediction of flow properties, and hence, the application of this model will enhance manufacturing quality by taking advantage of the data generated throughout the manufacturing process.

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