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The effects of material attributes on capsule fill weight and weight variability in dosator nozzle machines

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ABSTRACT

The goal of this work is to identify and understand the complex relationship between the material attributes, capsule fill weight and weight variability of capsules filled with a dosator nozzle machine. Six powders were characterized and filled into size-3 capsules in three volumes of dosing chambers and at two filling speeds. Subsequent multivariate data analysis was used to identify the influence of the material attributes on the capsule fill weight and weight variability. We observed a clear correlation between the capsule fill weight and the particle size, the air permeability and the compressibility. As the fill weight decreases, more factors affect capsule fill weight. For example, the wall friction angle, the tapped density, and the particle shape proved to be important factors. Larger fill weights were more affected by density while lower fill weights by flow and friction characteristics. No correlation was found between the material attributes and the weight variability. Rather, we could also see the major effect of process parameters on capsule fill weight and weight variability.

1. Introduction

Hard-gelatin capsules are one of the most common pharmaceutical dosage forms. Compared to tablets, capsules are relatively easier to formulate and manufacture, which results in shorter development times (Augsburger, 2009). However, the quality of filled capsules is affected by a large number of powder and processing parameters and several researchers have undertaken the task of identifying and assessing these effects (Podczeck and Newton, 1990, 2000; Patel and Podczeck, 1995; Tan and Newton, 1990a). Numerous material and process parameters affect the quality attributes of filled capsules, such as the weight variability. Due to the large number of parameters to consider, a design of experiments (DOE) and multivariate data analysis (MVDA) (Hogan et al., 1996) in framework of quality by design (QBD) is the best approach to obtain a deep process understanding.

The aim of this study was to identify and quantify the effect of critical material attributes (CMA) on the critical quality attributes (CQA), which in our work were the (1) fill weight and (2) weight variability (RSD) of capsules filled with a dosator nozzle (Labby, MG2, Bologna, Italy). Capsules were filled with six different microcrystalline cellulose (MCC) powders, and their material attributes were amply characterized. The MCC grades represent a wide range in terms of particle sizes, density, flow and several other material attributes. A dosator filling mechanism is the most conventional principle used in capsule-filling machines. It consists of a nozzle that dips into a powder bed, collects powder and transfers into an open capsule (Tan and Newton, 1990e; Podczeck and Jones, 2004).

A DOE was developed using process parameters of the capsule filling machine as controllable variables (dosator size, dosing chamber length, powder layer height and filling speed). The material attributes of the six types of MCC powders were the "uncontrollable" variables. Finally, a multivariate data analysis (MVDA) using the entire data set was performed. The data set contained the average value (of three measurements) for each material attribute and the average values of capsule fill weight and weight variability (of the contents of 100 capsules) for each experimental condition. A partial least square (PLS) method was applied to study the correlations between the CMAs and CQAs.

In summary, material attributes were assessed and their correlations to capsule fill weight and weight variability were investigated. Subsequently, these attributes were ranked according

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Nomenclature

AIF	Angle of internal friction
AOR	Angle of repose
AR	Aspect ratio of 50% particle population of powder
BD	Bulk density
BFE	Basic flowability energy
C	Cohesion
CI	Carr's compressibility index
CMA	Critical material attribute
CPH	Capsules per hour (filling speed)
CPL	Compressibility
CQA	Critical quality attribute (capsule fill weight and weight variability)
DC	Volume of the dosing chamber
DOE	Design of experiments
FFC	Flow function
MCC	Multi crystalline cellulose
MVDA	Multivariate data analysis
PD	Pressure drop
PLS	Partial least squares
QBD	Quality by design
RSD	Relative standard deviation (weight variability)
TD	Tapped density
VMD	Volumetric mean diameter
WFA	Wall friction angle

to their effect on the capsule fill weight. These results can help scientists design formulations with the CMAs in order to obtain products amenable to capsule filling and with the desired weight variability.

2. Materials and methods

2.1. Materials

We selected six common pharmaceutical microcrystalline cellulose (MCC), which have been extensively characterized (Amidon and Houghton, 1995; Patel and Podczeck, 1996). We used Avicel® PH102, PH200, PH301, PH302 (FMC BioPolymer), Vivapur®12 (JRS Pharma GmbH) and Prosolv®_SMCC 90 (JRS Pharma GmbH), which is a silicified material. All materials were used as received and each test was carried out in triplicates. In order to minimize the number of material attributes to be investigated and to simplify our research, we only used MCC.

2.2. Methods

2.2.1. Particle size characterization

QICPIC (OASIS/L dry dispersing system Sympatec, Germany) was used to measure the size (volumetric mean diameter, VMD, and median particle size) and shape of millions of particles in each sample via dynamic image analysis. The two-dimensional images of a particle were described in terms of the minimum and maximum Feret diameters (F_{min}, F_{max}).

The aspect ratio (AR) is the ratio between F_{min} and F_{max} and describes the shape of particles. Its value can be between 0 and 1, which reflects the elongation of a particle and deviation from a sphere. The higher the value, the more spherical the shape.

Since the particle size and shape are known to affect the bulk behavior of powders (Fu et al., 2012), they are critical to capsule filling. For example, the particle size of a powder significantly influences the flow properties and cohesion of bulk powder. Typically, the smaller the particle size, the more cohesive the powder (Jolliffe and Newton, 1982; Fu et al., 2012). Moreover, the particle shape affects the particle packing and therefore their flowability and internal friction (Podczeck and Miah, 1996; Yu et al., 2011). In addition, they influence how powders interact with walls and hence it has an impact on the wall friction coefficient (Jolliffe and Newton, 1982). Furthermore, particle size and shape have a considerable impact on the powder compressibility and permeability (Fu et al., 2012).

2.2.2. Bulk density, tap density and true density

The bulk (BD) and tapped densities (TD) were analyzed (Pharmatest PT-TD200) via a standardized method described in the United States Pharmacopeia (USP 2011,). A certain mass of powder was filled into the cylinder and the level was recorded. The tapped density was attained after mechanically tapping the powder sample. These numbers were used to estimate the flow index (Carr's compressibility index).

To obtain the true density, a helium pycnometer (AccuPyc II 1340, Micromeritics, Norcross, USA) was used after drying the powders.

2.2.3. Compressibility (CPL)

Compressibility is a measure of the volume change in a conditioned sample when it is slowly compressed under a specific normal force. Compressibility of a powder is important for dosator filling because powder is compacted by the piston to enhance powder retention inside the nozzle and to reduce its volume in order to accommodate the powder inside a capsule. Further, the powder undergoes pre-compression as the nozzle dips into the powder bed and in this study the powder bed height was higher than the dosing chamber length (see Section 2.2.7). In our study, compressibility was measured with the FT4 powder rheometer (Freeman Technology, Malvern, United Kingdom). The test starts at 0.5 kPa, increases pressure stepwise until 15 kPa and calculates the ratio between the density and bulk density for each compaction step.

2.2.4. Air permeability

Air permeability is a measure of how easily material can transmit air through its bulk and it is measured by the air pressure drop (PD) across a powder bed. A high pressure drop indicates low air permeability. Moreover, high air permeability is obtained for large particles as inter-particular spaces are large as well, reducing the pressure drop. It is expected to affect capsule filling because during powder pre-compression and piston compaction the entrained air must escape the powder bulk (Freeman and Fu, 2008). The permeability test was performed with pressured dry air (2 mm/s air velocity) with the FT4 powder rheometer. Details of these methodologies can be found in the literature (Freeman, 2007; Freeman and Fu, 2008).

2.2.5. Powder flow properties

The flowability of powders affects various capsule quality attributes, such as fill weight and content uniformity (Prescott and Barnum, 2000). Powder flow affects the weight variability of capsules e.g., in tamp-filling machines (Tan and Newton, 1990c; Podczeck and Miah, 1996; Schulze, 2011). In this study, we measured the following flow indexes:

- Carr's compressibility index (CI) (Carr, 1965) is a density-based index assessed according to Pharmacopoeia 2011 (Method <616>). The CI indicates how a powder changes its density upon tapping. Large changes indicate poor flowability.
- Flow function coefficient (FFC): A shear-cell based flow index determined in a 1 ml shear cell module with the FT4 powder rheometer. FFC is the ratio of consolidation stress, σ_1, to unconfined yield strength, σ_c. A high FFC value (>4, or more