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Determination of flow properties of pharmaceutical powders by near infrared spectroscopy

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ABSTRACT

The physical properties of pharmaceutical powders are of upmost importance in the pharmaceutical industry. The knowledge of their flow properties is of critical significance in operations such as blending, tablet compression, capsule filling, transportation, and in scale-up operations. Powders flow properties are measured using a number of parameters such as, angle of repose, compressibility index (Carr's index) and Hausner ratio. To estimate these properties, specific and expensive equipment with time-consuming analysis is required. Near infrared spectroscopy is a fast and low-cost analytical technique thoroughly used in the pharmaceutical industry in the quantification and qualification of products. To establish the potential of this technique to determine the parameters associated with the flow properties of pharmaceutical powders, blended powders based on paracetamol as the active pharmaceutical ingredient were constructed in pilot scale. Spectra were recorded on a Fourier-transform near infrared spectrometer in reflectance mode. The parameters studied were the angle of repose, aerated and tapped bulk density. The correlation between the reference method values and the near infrared spectrum was performed by partial least squares and optimized in terms of latent variables using cross-validation. The near infrared based properties predictions were compared with the reference methods results. Prediction errors, which varied between 2.35% for the angle of repose, 2.51% for the tapped density and 3.18% for the aerated density, show the potential of NIR spectroscopy in the determination of physical properties affecting the flowability of pharmaceutical powders.

1. Introduction

Pharmaceutical powders are described as heterogeneous systems with different physical and/or chemical compositions with a range of particle sizes between a few micrometers to about a millimeter. In a typical pharmaceutical industry, in average, more than 80% of its production is based on powders in tablet form [1,2]. For those reasons, the knowledge and subsequent control of the powders physical behavior is crucial in the development and processing of solid dosage forms. The powders flow behavior is a key factor in a series of unit processes such as blending, compression, filling, transportation and in scale-up operations [1,3]. In tablets compression and capsules filling, an optimal powder flow must be achieved in order to produce final products with an acceptable uniformity content, weight variation and physical consistence. In the drug development stage, an accurate assessment of the flow properties is essential in order to identify the optimum formulation [1,4–6].

To evaluate the powder flow properties, parameters such as, angle of repose, compressibility index or Carr's index, and the Hausner ratio, are generally employed. These methods are recommended by the pharmacopeia's to evaluate powders flowability, they are easy to handle and their application is widely used in industrial applications and in scale-up operations [3,4]. However, they are indirect methods and its relation with the powders flow true behavior is not straightforward. Moreover, to have a complete evaluation of the powders flowability, various labor intensive and time-consuming techniques must be used [7].

Near infrared spectroscopy (NIRS) is a fast non-destructive and low-cost technique, vastly used in the pharmaceutical industry in quality and process control [8–12]. NIR spectra carry significant information not only on the chemical composition but also on the morphological structures of the sample due to light scattering [13]. Applications such as, determination of water content, control of polymorphisms and optical isomers, identification of raw materials, homogeneity analysis, active principle and excipients determination, are frequently used in the pharmaceutical industry

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[9,14]. However, the use of NIRS to determine physical parameters is still under exploration. Some work has been done in relating the near infrared (NIR) spectrum with tablet hardness, drug stability, tablet coating and particle size of powders [15–18]. Otsuka et al. [19] used NIRS to predict the angle of repose of granules obtained after the granulation process using various amounts of added water using principal component regression (PCR). In the cited work, the authors discuss that the angle of repose is an index to powder flowability and that can be easily predicted by NIRS. However, no extensive work has been done to explore the potential of this spectroscopic technique to determine parameters associated with the flow properties of pharmaceutical powders in a systematic approach.

In this work, the possibility to use NIRS to predict the flow properties of pharmaceutical powders, angle of repose and bulk densities (aerated and tapped), during the scale-up operation was assessed. For that purpose, blended powder samples based on paracetamol as the active pharmaceutical ingredient (API), with three excipients were constructed. NIR spectra were recorded on Fourier-transform near infrared spectrometer in reflectance mode. The tests to determine the angle of repose, and the bulk densities were performed according to what is stipulated by the European Pharmacopeia. The experimental results obtained were correlated with the NIR spectrum by partial least squares (PLS) optimized in terms of latent variables using cross-validation.

2. Theory

2.1. Flow properties of powders

The angle of repose can be defined as the constant three-dimensional angle measured relatively to the horizontal base, assumed by a cone-like pile of material formed when the powder is passed through a funnel-like container [20]. An angle of repose lower then 40°, indicates good flowability, conversely an angle of repose superior to 40° is an indication of cohesiveness [21,22]. This method is very simple but has some disadvantages. The powder experiences segregation, consolidation or aeration, which influence the cone formation [20]. The angle of repose is not considered for many a good method to measure powder flow, because is highly dependent on experimental factors, since it is not an intrinsic property of the powder [4]. However, it is still considered useful since it is a simple method that gives the powder tendency to flow, and has an associated general scale of flowability consistence with the classification reported by Carr [22].

Another parameter used to evaluate the flowability is the compressibility index (CI). This index measures the tendency of a powder to consolidate, and is calculated according to Eq. (1) [22,23]:

$$\mathrm{CI} = \frac{\mathrm{TD} - \mathrm{AD}}{\mathrm{TD}} \tag{1}$$

In Eq. (1), TD and AD represent the tapped (or packed) and aerated bulk densities, respectively. The aerated bulk density is defined as the mass divided by the volume occupied by the powder when the particles are not in direct contact with each other. However, a more realistic definition can be given by the density measured after the powder been aerated and left to settle gently. The tapped bulk density is obtained after tapping the container enclosing the aerated powder [21]. The compressibility index has an inverse relation with flowability, i.e. the more compressible is the material the less flowable it will be [22]. A powder with a compressibility index lower than 20% is considered to have a good flowability [5]. The Hausner ratio is defined as the ratio between the tapped bulk density and the aerated bulk density. This ratio is a useful measure of cohesion reflecting particle friction. With a Hausner ratio higher than 1.4, the powder is considered a cohesive difficult to fluidize powder. Ratios lower than 1.25 characterizes a free-flowing powder [21]. Hereafter, the aerated bulk density and the tapped bulk density will be designated by aerated and tapped density.

2.2. Experimental design

All developed models were calibrated and tested using different data sets. To construct the calibration and test sets an experimental D-optimal design [24] was developed and applied. The concentrations of each component present in the samples were varied in the experimental design in order to maximize the information in the selected set of experimental runs with respect to a stated model (e.g., a regression model). For a specific regression model in which $\mathbf{Y}$ is a $(N \times 1)$ vector containing the N experimental runs of observed responses, $\mathbf{X}$ is a $(N \times p)$ matrix, with p being the number of terms of the model, the D-optimal design maximizes the determinant of the $\mathbf{X}^t\mathbf{X}$ matrix, which is an overall measure of the information in $\mathbf{X}$. Geometrically, this corresponds to maximizing the volume of $\mathbf{X}$ in a p-dimensional space. In the case of a formulation, this design provides different physical properties to each sample, generating an ensemble of values that gives the necessary characteristics to the model.

2.3. Multivariate modeling

To assess the consistency between the calibration and test spectra, a principal component analysis (PCA) was used. This method reduces the data information originating new variables (principal components) that are linear combinations of the original variables [25]. The principal components are estimated to have maximum variance amongst all linear combinations. The usefulness of this method resides on the fact that multivariate data can be well described in a more workable set of variables that contain almost all the information, or variability of the original data.

The multivariate technique used to relate the experimental values of the parameters, angle of repose, aerated and tapped densities, obtained with the reference methods with the NIR spectra was partial least squares (PLS) with leave-one-out cross-validation [25]. This technique is commonly used in chemometrics analysis and is applied with the objective to establish a model for the analysis of unknown samples to determine physical or chemical properties [26,27]. To assess the PLS model accuracy (bias), the root mean square error of cross-validation (RMSECV) estimated according to Eq. (2) was used:

$$\mathrm{RMSECV} = \sqrt{\frac{(\mathbf{Y_C} - \hat{\mathbf{Y}}_\mathbf{C})^t \times (\mathbf{Y_C} - \hat{\mathbf{Y}}_\mathbf{C})}{N_\mathrm{C}}} \tag{2}$$

In Eq. (2), $\hat{\mathbf{Y}}_\mathrm{C}$ and $\mathbf{Y_C}$ are the PLS cross-validation estimate and the measured reference value for the ith sample, respectively. N_C is the number of calibration samples. The model robustness was evaluated in terms of the root mean square error of prediction (RMSEP):

$$\mathrm{RMSEP} = \sqrt{\frac{(\mathbf{Y_P} - \hat{\mathbf{Y}}_\mathbf{P})^t \times (\mathbf{Y_P} - \hat{\mathbf{Y}}_\mathbf{P})}{N_\mathrm{P}}} \tag{3}$$

In Eq. (3), $\hat{\mathbf{Y}}_\mathbf{P}$ is the PLS prediction value of sample i, and $\mathbf{Y_P}$ is the reference value for the same sample, N_P is the number of prediction samples. Model performance was assessed using the range error ratio (RER). This ratio is calculated by dividing the amplitude each parameter range by the RMSECV value. With a RER > 10 the model can be considered good for quality control purposes.

In a univariate analytical technique, uncertainty is assessed by the standard deviation of replicates. In multivariate techniques