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High-throughput NIR-chemometric methods for determination of drug content and pharmaceutical properties of indapamide powder blends for tabletting

Alina Porfire[a], Lucia Rus[b], Andreea Loredana Vonica[c], Ioan Tomuta[a,*]

[a] Iuliu Hatieganu University of Medicine and Pharmacy, Department of Pharmaceutical Technology and Biopharmaceutics, 41 Victor Babes Street, 400023 Cluj-Napoca, Romania
[b] Iuliu Hatieganu University of Medicine and Pharmacy, Department of Drug Analysis, 6 L. Pasteur Street, 400023 Cluj-Napoca, Romania
[c] S.C. Polipharma Industries, 550052 Sibiu, Romania

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ABSTRACT

This paper describes the development and application of NIR-chemometric methods for active content assay and pharmaceutical characterization (granulometric analysis and flowability assessment) of indapamide powder blends for tabletting. Indapamide powder blends were prepared and their NIR spectra were recorded in reflectance mode. Partial least-squares (PLS) regression followed by leave-one-out cross-validation was used to develop calibration models for predicting the indapamide content and pharmaceutical properties. The method for indapamide assay was validated in terms of trueness, precision, accuracy. The near infrared based property predictions were compared with the reference method results and no significant differences were found between the reference and predicted characteristics. The developed NIR-chemometric methods can be useful tools for prediction of active content, granulometric properties and parameters related to flowability of pharmaceutical powders.

1. Introduction

Powders are encountered in pharmaceutical industry and practice as a pharmaceutical dosage form as well as in the manufacture of tablets, capsules and suspensions. Their properties and behavior of finely divided solid materials are of considerable importance, being determined by the chemical and physical properties of their components and by the manner in which their components interact [1]. As a result, the knowledge of chemical composition and physical behavior of powder blends is essential in the development of solid dosage forms.

In the manufacture process of solid dosage forms, the uniform mixing of drug and excipients is an essential step before proceeding to other operations, since it is well known that inert excipients can affect the characteristics, quality, stability, and even the performance of the final product. Thus, blend homogeneity is crucial to ensure uniformity of dosage units of the end product. Uniformity of dosage units warrants that each unit in a batch has active substance content within a narrow range around the label claim [2]. Problems concerning the assurance of content uniformity of tablet dosage units are due to three main effects: loss of powder homogeneity, variability of tablet weight (either by changing the flow properties of powder or by changing the weight of the die volume) and lack of powder homogeneity. The uniformity of a powder blend is determined in practice by estimating the distribution of the drug, based on its assay in representative samples from the blenders [3]. The assay of active content is usually done through conventional HPLC and UV spectrophotometry. Because particle segregation can occur during the tabletting process, a tool able to detect particle segregation on line (in the hopper of the compression machine) would be very useful to ensure uniformity of dosage units of the final product. Besides assuring the uniformity, an accurate pharmaceutical characterization of powder blends in terms of particle size, size distribution and flow properties is of equal importance. The methods currently used for granulometric analysis are sieving, microscopy or indirect measurements related to particle size such as sedimentation rates, permeability and optical properties [1]. The powder flow properties are evaluated by employing parameters such as angle of repose, Carr's index, Hausner ratio, and time of flow. In conclusion, a complete evaluation of powder characteristics requires a variety of labor-intensive and time-consuming techniques [4].

Near-infrared (NIR) spectroscopy is an interesting alternative for powder characterization regarding both chemical composition and various physical or pharmaceutical properties. This technique is offering rapid, non-invasive and non-destructive sample analysis, requiring little or no sample preparation, and has gained wide acceptance in pharmaceutical industry [5,6]. NIR spectrum of powder contains both chemical and physical properties and the

* Corresponding author at: Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, 41 Victor Babes Street, 400012 Cluj-Napoca, Romania. Tel.: +40 264595770; fax: +40 264595770.
E-mail address: tomutaioan@umfcluj.ro (I. Tomuta).

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response is quick, so NIR spectroscopic technique can be used for on-line monitoring of powder from point of view of powder homogeneity, powder flow properties and particle size distribution, in order to assure consistent uniformity of dosage units. Moreover, because the information provided is very complete, this technique can detect the source for lack of uniformity of dosage units. A lot of papers are reporting the determination of chemical composition of powders by NIR methods [7,8], but few applications have been performed on low dosage forms, due to low sensitivity of NIR techniques [9–11]. Other papers are focusing on prediction of pharmaceutical properties of powders based on their NIR spectra. Sarraguça and co-workers [12] reported the prediction of particle size distribution of pharmaceutical powder blends having paracetamol as active ingredient by the use of NIR spectra of powder blends and other two data blocks (their flowability properties and the mass fraction of the components present in the samples) taken separately or together, in a multi-block strategy. Alcala et al. [13] monitored both physical (particle size distribution and bulk density) and chemical (moisture content) properties during a wet granulation process at a production plant by the use of a portable NIR spectrometer for on-line spectral acquiring on a noninvasive approach, and used chemometric algorithms to characterize the formulation and obtain a better knowledge of the granulation process. Other authors [14] used NIR spectra of flowing powders to evaluate the consistency of powder flow, based on the plots of 1/noise versus time as well as PCA score plots, and to evaluate drug concentration in powder mixtures using the same NIR spectra. The same group quantified the powder flow by recording the in-line spectra of powder being discharged from a container and the results are further utilized as a tool for distinguishing the difference in flow behavior between the cohesive and surface modified or dry coated powders [15].

Indapamide is an oral antihypertensive diuretic agent indicated for the treatment of hypertension and edema. A 2.5 mg formulation is used world-wide for the treatment of mild to moderate hypertension and low dose 1.5 mg formulation of indapamide in a sustained-release (SR) coated tablet was recently developed to maximize the efficacy/safety ratio following international recommendations favoring low dose antihypertensive therapy in hypertension [16,17].

This work describes the development of NIR-chemometric methods for chemical and pharmaceutical characterization of low-dosage indapamide powder-blends for tabletting. The chemical characterization consisted in determination of API content of the blends using a validated NIR-chemometric method. The pharmaceutical characterization was done through determination of particle size and dispersion, Carr's index, Hausner ratio and time of flow using NIR-chemometric methods. These proposed methods can be used as tools for detection of particle segregation of powder-blends during tablet manufacturing process.

2. Materials and methods

2.1. Materials

Indapamide (micronized powder, average particle size 15 μm) was purchased from PharmaZell, Germany. Lactose (Tablettose 80, average particle size 177 μm) was provided by Meggle, Germany. Microcrystalline cellulose (average particle size 100 μm) and sodium starch glycolate were obtained from JRS Pharma, Germany. Colloidal silicon dioxide (Aerosil) was supplied by Rohm-Pharma Polymers, Germany. Polyvinylpyrolidone was from BASF, Germany. Magnesium stearate was purchased from Union Derivan, Spain.

2.2. Sample preparation

For calibration purpose, powder blends for indapamide tablets were prepared. Briefly, indapamide, lactose (63.75%, w/w), microcrystalline cellulose (21.67%, w/w), sodium starch glycolate (5.00%, w/w), polyvinylpyrrolidone (6.00%, w/w) and colloidal silicon dioxide (0.75%, w/w) were mixed using a planetary mixer (PRS type, Erweka, Germany) for 5 min. Magnesium stearate (0.75%, w/w) was then added and the mixing was continued for 1 more minute. Subsequently, the powder blend was separated into three particle size classes: 0–100, 100–200 and 200–300 μm.

The mixture composition was designed for a tablet weight of approximately 120 mg and a usual amount of active ingredient inside each tablet of 2.5 mg (2.08%, w/w). This formulation will be further considered as the 100% active content formulation.

2.3. Calibration and validation protocol

2.3.1. Indapamide assay

For the calibration and validation of NIR method for indapamide assay, powder blends were prepared. The protocol included batches and days as sources of variability for calibration and validation steps.

The calibration set used included 5 different formulations containing 1.67, 1.88, 2.08, 2.29 and 2.5% (w/w) of indapamide (corresponding to 80, 90, 100, 110 and 120% indapamide content formulations). Three independent batches were manufactured per formulation type in three different days.

In order to validate the NIR method for indapamide assay, the same formulations as for the calibration set, corresponding to 80, 100 and 120% indapamide content, were manufactured. Four replicates were prepared for each concentration level, in three different days, resulting in a total of 36 validation samples.

2.3.2. Particle size and flow characteristics

In order to build calibration models for prediction of particle size and powder flow characteristics, blends consisting in particles belonging to known size classes were mixed according with a D-optimal experimental design with three factors and five levels developed in Modde 9.0 software (Umetrics, Sweden). In this experimental design, the input variables were granulometric classes and the levels were the mixing ratios. The matrix of experimental design is shown in Table 1.

2.4. NIR equipment and software

Near infrared spectra were recorded using a Fourier-transform NIRS analyzer (Antaris II, ThermoElectron Scientific, USA) in Reflectance Sampling configuration, equipped with an indium gallium arsenide (InGaAs) detector. Since the powder samples are not homogeneous, the device is equipped with a system for rotation of samples during the measurements so that obtained spectrum is representative for the sample and to ensure reproducibility of the measurements. Each reflectance spectrum was recorded using OMNIC software (Thermo Scientific, USA) by integrating 32 scans, over the range from 11,000 to 4000 cm^{-1}, with a resolution of 8 cm^{-1}.

2.5. Reference methods

Indapamide assay was performed on powder blends using a reference HPLC method. Accurately weighted samples were extracted with 5 ml methanol in an ultrasonic bath for 10 min and the obtained suspension was centrifuged for 5 min at 5000 rpm. Aliquots of the clear supernatants were diluted with the mobile