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Quality assessment of pharmaceutical tablet samples using Fourier transform near infrared spectroscopy and multivariate analysis

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HIGHLIGHTS

- FT-NIR technique was used for investigation of content uniformity and hardness of pharmaceutical tablet samples.
- Multivariate analysis predicted API and hardness of tablets with higher accuracy.
- FT-NIR demonstrated a great potential tool for detection of chemical and physical properties of the pharmaceutical samples.

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ABSTRACT

Determination of the content uniformity, assessed by the amount of an active pharmaceutical ingredient (API), and hardness of pharmaceutical materials is important for achieving a high-quality formulation and to ensure the intended therapeutic effects of the end-product. In this work, Fourier transform near infrared (FT-NIR) spectroscopy was used to determine the content uniformity and hardness of a pharmaceutical mini-tablet and standard tablet samples. Tablet samples were scanned using an FT-NIR instrument and tablet spectra were collected at wavelengths of 1000–2500 nm. Furthermore, multivariate analysis was applied to extract the relationship between the FT-NIR spectra and the measured parameters. The results of FT-NIR spectroscopy for API and hardness prediction were as precise as the reference high-performance liquid chromatography and mechanical hardness tests. For the prediction of mini-tablet API content, the highest coefficient of determination for the prediction (R^2p) was found to be 0.99 with a standard error of prediction (SEP) of 0.72 mg. Moreover, the standard tablet hardness measurement had a R^2p value of 0.91 with an SEP of 0.25 kg. These results suggest that FT-NIR spectroscopy is an alternative and accurate nondestructive measurement tool for the detection of the chemical and physical properties of pharmaceutical samples.

1. Introduction

A pharmaceutical tablet is the solid unit dosage form produced by combining the active pharmaceutical ingredient (API) and excipient substances. An API is the central, chemically active substance producing desired effects in the human body, while excipients are the inactive or inert components of the finished drug product that are added during formulation to bind the APIs [1]. A key factor in pharmaceutical manufacturing is the monitoring of API content uniformity in the finished drug product [2], which is required to deliver the correct amount of API per unit dose. If not, the complete batch will be rejected by the United States Food and Drug Administration (FDA) [3]. API uniformity is a critical quality attribute because it is linked to the safety and efficacy of the finished drug product. Poor uniformity of API content results in miscalculated doses and mistakes in prescriptions and may influence the dissolution properties and performance of the product [4]. Therefore, quality control of the API content in different steps (e.g., blending, drying, granulation, tableting, and coating) of the pharmaceutical production process is essential to determine whether the given production batch is fit for release or not [5].

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In addition to content uniformity, the product hardness (especially for tablets) is also important because, hardness is associated with the dissolution and friability of the tablet. Tablets are subjected to mechanical shocks and aberrations during manufacturing, packaging, storage, transportation, and handling processes, which may lead to capping, aberration, or breakage of the tablets [6]. Therefore, a tablet requires a certain degree of hardness to withstand mechanical shocks inflicted during these processes. Hence, a sufficient mechanical strength of tablet samples is essential throughout the manufacturing process [7].

Common procedures used to detect API content and tablet hardness usually rely on offline techniques such as high-performance liquid chromatography (HPLC) and mechanical hardness testing methods, respectively [7,8]. These methods require lengthy calibration runs and preparation of buffers and are often destructive techniques. Therefore, it is essential to apply non-destructive and rapid analytical techniques to scale up the pharmaceutical manufacturing process [9]. Integration of rapid controls such as spectroscopic measurements or other process analytical technologies (PATs) into manufacturing operations provides a significant opportunity to improve both the understanding and control of the process while decreasing the safety risks associated with sampling and testing [10]. Since the mid-1980s, infrared (IR) spectroscopy has been widely reported as a technique well suited as a PAT tool for the simultaneous determination of physical and chemical properties of samples [11]. Previously, a wide range of IR applications are reported for non-destructive quality monitoring of pharmaceutical products [12]. Most recently, advancement in spectroscopy have also lead to the development of NIR imaging monitoring technique that enables both spectral and spatial features of the pharmaceutical materials [13,14].

Among the different modalities of NIR measurement, Fourier transform near-infrared (FT-NIR) spectroscopy offers increased spectral resolution, greater sample specificity, and robust calibration with significantly fewer calibration standards. Taking into account its non-destructive analysis, FT-NIR can easily replace the conventional methods. Pharmaceutical compounds typically have unique spectral signatures in the region of 4000–10,000 cm^{1} that can be measured using FT-NIR with minimal or no sample preparation, which is ideal for rapid process control. The broad spectral range of FT-NIR allows access information in the combination of first, second, and third overtone vibrational regions permitting the composition and discrimination of the drug product [15]. However, the major problem observed when using spectroscopic devices is the need to interpret and evaluate large amounts of data consisting of several variables [9,16]. Furthermore, the complexity of the spectra makes correlation with quantitative properties difficult without pre-processing and subsequent chemometric analysis. Hence, the use of multivariate analysis and pre-processing techniques is crucial for the identification of the relationship between spectral characteristics and the material properties of interest [17]. For this purpose, several chemometric methods have been tested in order to obtain quantitative and qualitative information about pharmaceutical materials [9]. Chemometric analysis yields predictive models that enable the at-line or online rapid analysis of materials that were traditionally analyzed using time-consuming analytical techniques such as HPLC.

In this study, two physically different types of tablet samples (standard and mini-tablets) were chosen for physio-chemical quality analysis. The selection of tablet samples was made to fit the need of the pharmaceutical industry as well as to provide comparisons with previously published work. With regard to hardness and API content, standard tablets easily undergo API detection owing to their large size (>5 mm), but are highly susceptible to mechanical shock and, therefore, difficult to manufacture. On the other hand, mini-tablets, which are new to the market, have a high mechanical strength [18], but their relatively small size make API detection challenging [19,20]. As a result, most of the previous work has particularly focused on the API detection in standard tablets [21,22]. To date, no work has been published in which the API content of mini-tablets was predicted.

Therefore, the goal of this study was to investigate the feasibility of Fourier transform near-infrared (FT-NIR) spectroscopic techniques in detecting the API content of mini-tablet samples and the hardness of standard tablet samples. In addition, multivariate analysis models such as principal component analysis (PCA) and partial least square regression (PLSR) were developed to enable analysis of the pharmaceutical tablet spectra.

2. Materials and methods

2.1. Tablet samples

Tablet samples used in this study were manufactured by Biogen Idec (Cambridge, USA). For FT-NIR measurements, mini-tablets were used for API detection and standard tablet samples were used for hardness detection. The tablet samples were produced by compressing powders of the API and the excipients. In accordance with company regulations on confidentiality, the API used in this study is simply referred to here as API and is not identified. A detailed description of sample preparation is provided below.

Eight batches of mini-tablets (diameter: 2 mm, height: 2.25 mm, mass: 0.005 g) with an API concentration of 60–130% (w/w) were produced by adding the corresponding amounts of API (with 10% w/w intervals) and excipient compounds. The formulations (API and excipients) were prepared by mixing in a blender with a speed of 10 RPM for 25 min to achieve a good uniformity, and similar particle size. The common excipients ingredients were microcrystalline cellulose (MCC), magnesium stearate (MgSt), and mannitol. These aforementioned excipients are selected for achieving a good stability with the drug, therefore MCC, MgSt, and mannitol normally has good stability and compatibility which binds to this particular API perfectly. The tablets were weighed after preparation and there was no suspected errors in weighting. Standard tablet samples (diameter 5 mm, height: 3.94 mm, mass: 0.1 g) were produced using 1 mg and 30 mg API blended with excipient powder and compressed by an eccentric press (AC27, GEA-Courtoy, Belgium). Fig. 1 shows the tablet samples used during the study.

2.2. Acquisition of Fourier transform near-infrared (FT-NIR) spectra

The NIR spectra for standard tablet and mini-tablet samples were recorded using an FT-NIR spectrometer (Antaris II FT-NIR analyzer, Thermo Scientific Co., Waltham, MA, USA). The FT-NIR instrument comprises an InGaAs detector module, a halogen NIR light source, a beam splitter, a laser diode, a moving mirror, and a sample holder. A single standard tablet sample was manually placed in the sample holder (20 mm thickness × 20 mm diameter) that contain a hole in the center (Fig. 2a) and scanned over the wavelength range of 1000–2500 nm (4000–10,000 cm^{1}) at a spectral resolution of 4 cm^{1}. The sample holder allows all radiation to reflect back form the tablet surface (Fig. 2b).

The mini-tablets are very tiny in size therefore, a single tablet was unable to fit in the sample holder area. If the holder is not filled properly the light was transmitted through the gaps between mini-tablets and thus effect the spectra collection as a result noisy (atmospheric background) spectra. For this region, six mini-tablet from the same concentration group was placed in the sample