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Raman spectral imaging technique for API detection in pharmaceutical microtablets

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ABSTRACT

In pharmaceutical manufacturing, quality monitoring of end products is essential to gain regulatory approval. In particular, monitoring the quantity of an active pharmaceutical ingredient (API) in the administered dosage is key to ensuring the content uniformity of the product. Thus, we herein aim to demonstrate the ability of the newly developed line-scan Raman hyperspectral imaging (RHSI) technique for the quantitative analysis of APIs in microtablet samples. Microtablets containing the API of interest and appropriate excipients of varying concentrations (i.e., 60–130% (w/w) API) were prepared by direct compression. The microtablet RHSI spectra were obtained over a wavelength range of 400–1800 cm^{-1}. High-performance liquid chromatography was also employed as a reference method for the API assay. Multivariate analysis methods, including partial least squares and least-squares support vector machines, were employed to predict the API concentrations using the spectral and reference values of the microtablets. The developed models exhibited excellent prediction abilities for the API concentration, with a coefficient of correlation (R^2) >0.95, which was associated with an error of <5% (w/w) API. Furthermore, visualization of the API concentrations and distributions in the microtablets was achieved through chemical imaging. These results confirmed that line-scan RHSI is a powerful tool for the characterization of pharmaceutical products. In addition, this approach is suitable for application in the pharmaceutical production line for the online inspection of bulk products and would be expected to easily replace conventional measurement techniques.

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1. Introduction

Tablet manufacturing is a complex process in the pharmaceutical industry, as it relies on numerous unit processes, including blending, granulation, drying, milling, compression, and coating [1,2], with the content uniformity, bioavailability, and stability of the product being potentially affected throughout these stages. In the pharmaceutical industry, active pharmaceutical ingredients (APIs) and excipients are combined to formulate the desired products, which can take the form of a tablet, capsule, syrup, or injection [3]. However, to produce a uniform dosage, monitoring of the component at different stages of the manufacturing process is essential, and such monitoring also ensures the safety, effectivity, and quality of the medicine [4]. Although a good tablet batch is composed of an adequate amount of the API, a poor batch results in the production of non-homogeneous products which lack the desired therapeutic effect, and ultimately influence the performance of the end product. Indeed, in the pharmaceutical industry, the most time-consuming and challenging task is assessment of the API content uniformity in a final product, as the various production parameters, including raw material characteristics, rotation speed of the blending

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; API, active pharmaceutical ingredient; CCD, charge-coupled device; HPLC, high performance liquid chromatography; LS-SVM, least-squares support vector machines; MCC, microcrystalline cellulose; MIR, mid-infrared; NIR, near-infrared; PAT, process analytical technology; PLS, partial least squares; PLSR, partial least squares regression; RBF, radial basis function; RHSI, Raman hyperspectral imaging; RMSEC, root mean square error of calibration; RMSECV, root mean square error of cross validation; RMSEP, root mean square errors of prediction; SEC, standard error of calibration; SEP, standard error of prediction; SG, Savitzky-Golay; SNV, standard normal variate; SWIR, short-wave infrared.

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equipment, processing conditions, and tablet compression, require simultaneous regulation throughout the process [5].

Currently, API detection in tablets relies mainly on offline strategies, such as high-performance liquid chromatography (HPLC) with UV detection, which is an expensive, often destructive, and lengthy process for the simple examination and confirmation of the content uniformity [6]. To address these issues, the process analytical technology (PAT) mechanism proposed by the U.S. Food and Drug Administration is an alternative strategy for conducting non-destructive quality control evaluation of drug materials [7]. For example, spectroscopy has emerged as a promising PAT tool, as it allows the non-destructive and rapid quality verification of pharmaceutical products [8]. Indeed, over the past few years, different spectroscopic modalities have been applied for the quality monitoring of drug samples, including near-infrared (NIR), mid-infrared (MIR), and Raman spectroscopy [9–12]. However, these techniques tend to detect only a small, and often non-representative, area of the sample region and provide the output as a single spectrum, thereby failing to represent the entire sample characteristics. Thus, to address such issues, recent spectroscopic advancements have led to the development of line-scan hyperspectral imaging (HSI). The main advantage of line-scan HSI over traditional techniques is that it holds vast amounts of information on the spectral and spatial (pixel-based) characteristics of samples [13]. In addition, hyperspectral chemical imaging provides both qualitative and quantitative information regarding the chemical components present in drug samples. Furthermore, near-infrared HSI has recently been applied in the pharmaceutical industry to assess the content uniformity [14], tablet coatings [9], and contamination [15] in standard tablet samples.

In recent decades, Raman hyperspectral imaging (RHSI) has also gained growing interest in the food and agricultural sectors due to its production of high resolution spectra and superior information regarding molecular bonding, in addition to its limited sample preparation requirements [16]. In addition, RHSI is a rapid and non-destructive analytical technique that offers numerous advantages over existing methods. However, to date the utilization of RHSI in the line-scan configuration has been limited to the food and agricultural sectors [17]. Although the application of Raman spectroscopy is not new to the pharmaceutical industry, no studies into the use of line-scan RHSI technology have been reported, thereby encouraging us to examine this technique for the simultaneous prediction and visualization of API concentrations in microtablet samples. In terms of its operation, line-scan RHSI devices inspect the object through continuous movement and record a whole line of spatial and spectral information for each point in the object [18]. It can therefore be performed easily on the pharmaceutical production line for the rapid and high-throughput screening of bulk ingredients over a short acquisition time. In contrast, the point scan Raman device collects only a single spectrum for one point in the fixed element, and requires a long acquisition time in addition to a time-consuming positioning procedure. The use of vibrational spectroscopy for API determination in large tablets (i.e., >5 mm diameter) has also been investigated [4,19], and HSI techniques for the determination of API concentrations in microtablet samples have been reported [14]. However, no study have reported the use of RHSI technique for determination of API concentration in micortablet samples. In the context of microtablets, which are relatively new to the market and have diameters $\leq$3 mm, a number of advantages are presented over larger tablets, including their facile manufacture, convenience, immediate release, lower risk of dose dumping, improved size uniformity, and high mechanical strength.

Thus, we herein report our study into the evaluation of microtablet samples containing different API concentrations based on the following objectives: (a) Demonstration of the feasibility of line-scan Raman HSI techniques for monitoring API concentrations in pharmaceutical microtablet samples; (b) the development of partial least squares regression (PLSR) and least-squares support vector machine (LS-SVM) algorithms for predicting API concentrations in microtablet samples; and (c) the establishment of an image processing technique combined with chemometrics for visualization of the API materials in microtablet samples.

2. Material and methods

2.1. Microtablets

The microtablets used for API detection were supplied by Biogen (Cambridge, MA, USA). The formulation used for tablet production contains the API as the major component, microcrystalline cellulose (MCC) as the major excipient, and magnesium stearate as the minor excipient. Tablet manufacturing involved several common operations, including weighing, mixing, drying, and compression. In this study, the API name is assigned as API to protect the company law. A detailed description of tablet preparation is provided below.

A total of eight batches of tablets (2 mm diameter, 2.25 mm height, and 0.005 g weight) were produced by direct compression. More specifically, various quantities of API and excipient compounds were mixed to give API concentrations ranging from 60 to 130% (w/w), as indicated in Table 1. The concentration of the minor excipient was maintained constant, and 30 microtablets were prepared at each concentration for API detection. Table 1 provides detailed information regarding the nominal concentrations of the API and excipients used for tablet preparation.

2.2. Reference method for API determination

HPLC (Waters Alliance 2690 equipped with a photodiode array detector, Milford, MA, USA) was initially employed to assay the API contents of the individual tablet samples. The procedure was used as a reference method to confirm the content uniformity of tablet samples. Each weighted portions of microtablet sample were transferred into a 500 mL volumetric flask, to which methanol (300 mL) was added to each volumetric flask. The samples for analysis were then prepared in 50/50 (v/v) phosphate buffer/methanol with 0.1% trifluoroacetic acid sonicated, and filtered using 0.7 μm nylon syringe filters. Chromatographic separation was performed at a column temperature of 30 °C, an autosampler temperature of 5 °C, and a flow rate of 1.2 mL/min on a 2.6 μm, Kinetex C18 column (4.6 × 150 mm; Phenomenex, Torrance, CA, USA). An injection volume of 5 μL was employed, and analysis was completed within 8 min. The UV absorption of each sample was measured at 223 nm and Empower Pro was used to analyze the chromatograms.

2.3. The Raman hyperspectral imaging system

Raman spectral measurements of the microtablet samples were carried out using a line-scan RHSI system built in-house, which is presented in Fig. 1. This system uses a line laser excitation source (OptiGrate Corp. FL, USA) operated at 785 nm and with a laser power of ~400 mW. The laser light from 19 emitters mounted inside the laser box was focused onto a 785 nm bandpass filter to generate a strong Raman signal. A reflection mirror to reflect the laser beam out from the box and a cylindrical lens (f = 200 mm) to expand the laser beam were also employed. This system also employs an Engineer diffuser (ED1-L4100, ThorLabs, USA) to avoid the generation of a non-uniform laser intensity from the cylindrical lens. The laser light was projected on the sample surface via a 45° dichroic beam splitter (Semrock, Rochester, NY, USA). A 35 mm focal length objective lens was mounted on the spectrograph for collection of the Raman signals.

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