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Spectroscopic Techniques for Nondestructive Quality Inspection of Pharmaceutical Products: A Review

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Abstract

Spectroscopy is an emerging technology for the quality assessment of pharmaceutical samples, from tablet manufacturing to final quality assurance. The traditional methods for the quality management of pharmaceutical tablets are time consuming and destructive, while spectroscopic techniques allow rapid analysis in a non-destructive manner. The advantage of spectroscopy is that it collects both spatial and spectral information (called hyperspectral imaging), which is useful for the chemical imaging of pharmaceutical samples. These chemical images provide both qualitative and quantitative information on tablet samples. In the pharmaceutics, spectroscopic techniques are used for a variety of applications, such as analysis of the homogeneity of powder samples as well as determination of particle size, product composition, and the concentration, uniformity, and distribution of the active pharmaceutical ingredient in solid tablets. This review paper presents an introduction to the applications of various spectroscopic techniques such as hyperspectroscopy and vibrational spectroscopies (Raman spectroscopy, FT-NIR, and IR spectroscopy) for the quality and safety assessment of pharmaceutical solid dosage forms. In addition, various chemometric techniques that are highly essential for analyzing the spectroscopic data of pharmaceutical samples are also reviewed.

Keywords: Applications, Chemometrics, Hyperspectroscopy, Pharmaceutical, Vibrational spectroscopy

Introduction

The pharmaceutical manufacturing process has to undergo a number of operational checks from tablet manufacturing to the final packaging of chemical materials, so that the tablets can be used as medications for humans and animals (WHO, 2007; Pharmaceutical production policy). Pharmaceutical drugs are manufactured in two major stages, primary and secondary. The primary stage is the extraction and production of the active pharmaceutical ingredient (API) from its sources (organic synthesis, biological processing, and inorganic chemicals) and the secondary stage includes the conversion of the API into the product e.g., tablets, powders, capsules, liquids, creams, ointments, aerosols, and injectables. Thus, characterization of the drug and drug intermediates is necessary during the drug development process in the pharmaceutical industry. Various instrumental and analytical techniques are widely employed for this purpose. The classical chemical-based technique, high performance liquid chromatography (HPLC), has been successfully used for drug quality determination; however, the use of HPLC for the quality control of the material and the finished drug product is time-consuming and labor-intensive (Freitas, et al., 2005). To overcome these complications, various non-destructive techniques are being frequently used to replace the conventional methods in the pharmaceutical field.

Non-destructive spectroscopic techniques play an important

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role in the pharmaceutical industry for improving the drug product and manufacturing process. Spectroscopic techniques, especially hyperspectroscopy and vibrational spectroscopy (e.g., Raman and near-infrared (NIR) spectroscopy), have various applications in pharmaceutical industries, from tablet manufacturing to final product quality assurance. Quality tests are conducted to analyze the active content (Amigo et al., 2008; Cruz, et al., 2009), blend homogeneity (Lyon et al., 2002; Amigo et al., 2009), coating level (Palou et al., 2012), moisture content (Grohganz et al., 2010), tablet hardness (Blanco et al., 2006), film thickness (Romer et al., 2008), dissolution profiles (Freitas et al., 2005), and tablet defects (Cairos et al., 2009). The primary advantages of spectroscopic methods are that they are rapid, non-destructive, easy to use, and require less sample preparation. Hyperspectral imaging techniques, combined with NIR and Raman spectroscopy, offer significant advantages as they collect large amounts of both spectral and spatial data simultaneously. The collected data contribute to qualitative and quantitative information (also known as chemical imaging, CI) about pharmaceutical tablets, enabling the collection of high fidelity, spatially resolved pictures of the chemistry of the sample. A variety of NIR chemical imaging (NIR-CI) applications are documented in the pharmaceutical field, including the study of homogeneity of powder samples (Ma et al., 2007), particle size determination (Li et al., 2008), determination of concentrations, and distribution of components in solid tablets and content uniformity (Cruz et al., 2011). NIR hyperspectral CI is the most widely used qualitative analysis method that provides information about the chemical distribution in the drug samples, such as the API and excipient ingredients (Palou et al., 2012). IR spectroscopy also plays an important role in both industrial and research applications for evaluating drug quality and provides knowledge about various chemical functional groups of the drug ingredients, including –CH, –OH, –SH, and –NH bonds.

However, the major problem observed with spectroscopy is the interpretation and evaluation of spectral data due to their complexity. Therefore, the use of chemometric techniques is highly essential for spectral pretreatment and interpretation purposes. These chemometric techniques comprise various mathematical, statistical, and computer science methods for data treatment to allow the extraction of meaningful information. Furthermore, this information is used for prediction or classification purposes, in addition to testing the assumptions. The mathematical pretreatments are mainly used for data normalization methods, while the statistical techniques comprise various models used for classification and prediction purposes (Otsuka et al., 2005; Dowell et al., 2008).

This review paper presents an overview of the various applications of the hyperspectroscopy and vibrational spectroscopy techniques used for process control in drug product development. In addition, numerous chemometric techniques that have been applied by various researchers for analysis of pharmaceutical data have been discussed in this article.

Fundamental Concepts of Spectroscopy

Vibrational spectroscopy

Briefly, vibrational spectroscopy comprises NIR (780-2595 nm), mid-infrared (MIR; 400-4000 cm^{-1}), and Raman spectroscopy (Raman shift; 200-4000 cm^{-1}) (Gendrin et al., 2008). The phenomenon of IR spectroscopy (NIR and MIR) is based on the absorption, reflection, and emission of the light from the sample, while Raman spectroscopy is based on the scattering phenomenon. However, both techniques deliver information about the fundamental vibrational and rotational modes of the molecules. The IR bands result from a change in the dipole moment of a molecule, while Raman bands arise due to change in the polarizability of the molecules. Therefore, the IR spectroscopy provides knowledge about the dipole vibrations (e.g., –CH, –OH, –NH) whereas the Raman technique provides knowledge about polarizable vibrations (e.g., C=C, C=N, C≡N) of the sample. During IR spectroscopy, the sample spectrum is acquired by passing infrared radiation through the sample, which excites the molecular vibrations. The transmitted or reflected incident radiation from the sample is then analyzed by the detector. To obtain a Raman spectrum, the sample is illuminated by a monochromatic laser beam that interacts with the molecular vibrations. The scattered light from the sample is detected by the spectrometer. For a more thorough understanding of the principles of vibrational spectroscopy, refer to the work of Das et al. (2011) and Ozaki et al. (2012).

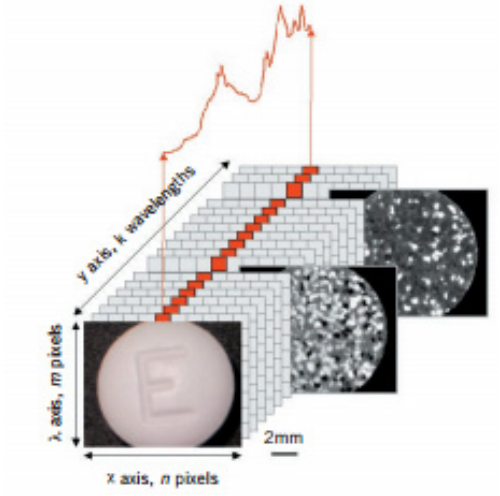
Hyperspectral chemical imaging

In recent years, hyperspectral imaging (HSI) technique has been demonstrated as an accurate and robust tool in the quality control of the pharmaceutical development and manufacturing process. HSI provides information about the quantitative composition and chemical distribution on the sample surface. An HSI image of the sample consists of a three-dimensional data cube (also known as a 3D hypercube), that holds two spatial (pixel) coordinates and one spectral (wavelength) dimension (Figure 1(a), Lewis et al., 2005). Furthermore, each pixel in the hypercube is composed of a particular spectrum that provides a chemical fingerprint to characterize the object (Amigo et al., 2009). In addition, the HSI technique is faster than point-based spectroscopic techniques because many samples can be analyzed simultaneously. HSI can be used to obtain spatial and spectral information about an object, using visible or NIR and Raman spectroscopy. HSI sensors have the flexibility to collect hyperspectral data for specimens of different sizes and shapes. Recently, the HSI technique has been used as a potential alternative to the point-based spectroscopic techniques used in a wide range of applications within the pharmaceutical sector. These applications include API detection (Ravn et al., 2008; Amigo et al., 2009; Vajna et al., 2012), content uniformity (Cruz et al., 2011), dissolution (Roggo et al., 2005), contamination (Roggo et al., 2005), and blend homogeneity of the pharmaceutical products (Amigo et al., 2008). Figure 1(b) shows an example about the potential of NIR hyperspectral imaging for determining the chemical distribution of API, lactose, and cellulose compounds in the tablet sample.

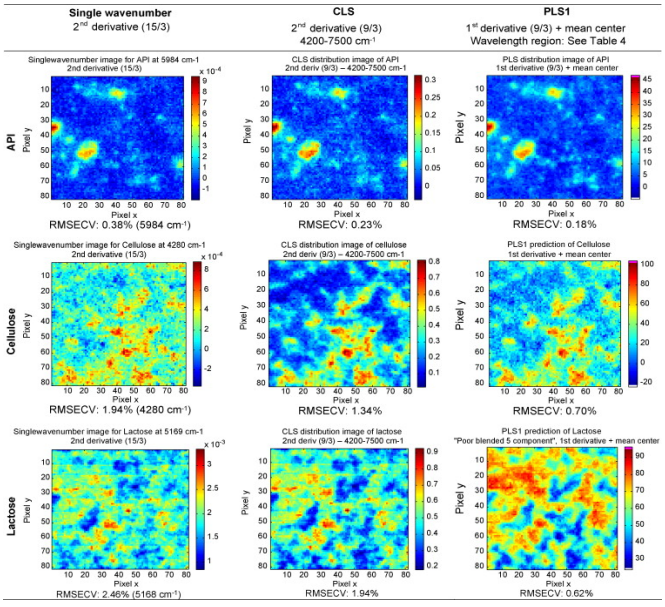
Spectral Data Processing

Mathematical pretreatments

The raw data obtained from spectroscopy can contain scattering noise, generated from uncontrolled physical variations during spectral acquisition. Therefore, pretreatment of spectral data by appropriate mathematical analysis is highly crucial to enhance the essential information from the sample and to remove the unwanted variations from spectral data. Pre-processing of spectral data allows for spectral correction by increasing the signal and minimizing undesired information including baseline drifts, scatter variation, path-length variation, and background noise. The most common pretreatment techniques (Table 1) used in pharmaceutical data processing include multiplicative scatter correction (MSC) (Virtanen et al., 2008; Lee et al., 2009; Cairos et al., 2009; Puchert et al. 2010; Neves et al., 2010), standard normal variate (SNV) (Virtanen et al., 2008; Cairos et al., 2009; Cruz et al., 2011), and Savitzky-Golay filtering (Virtanen



(a)



(b)

Figure 1. (a) Schematic of a hyperspectral image structure of a tablet; spatial axes x and y and spectral axis λ (Lewis et al., 2005); (b) His chemical image of a tablet showing the distribution of three components API, cellulose & lactose (Ravn et al., 2008).

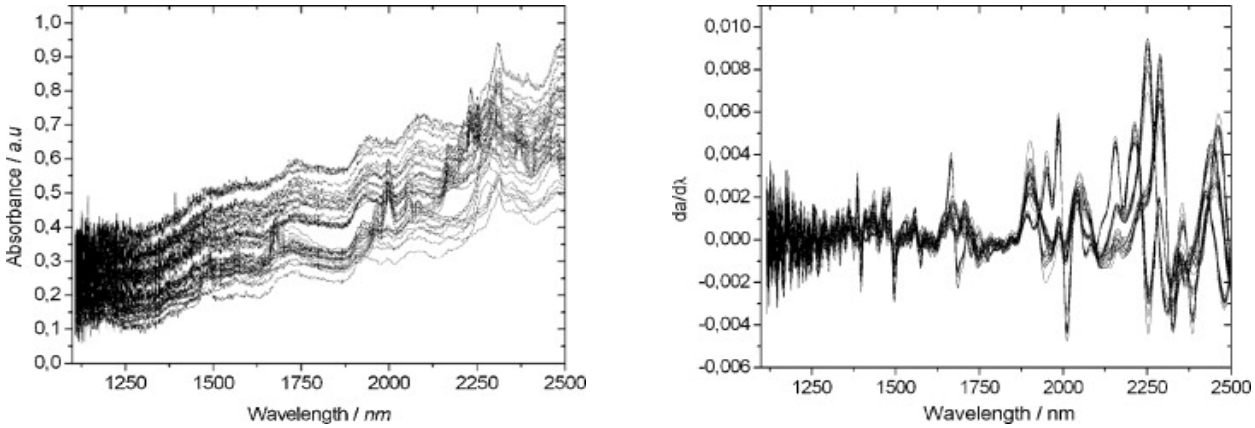


Figure 2. Tablet samples: (a) preprocessed spectra (b) Savitzky-Golay processed spectra (Neves et al., 2012).

Table 1. Application of chemometrics in pharmaceutical analysis

Sample	Application	Instrument	Pretreatment & chemometrics	Reference
Aspirin tablet	Content uniformity	NIR-HSI	Savitzky-Golay, MCR-ALS, CI	Cruz et al. (2009)
Tablet	API prediction	NIR-HSI	PLS-DA, CLS, CI	Amigo et al. (2009)
Tablet	Counterfeit	NIR	PLS-DA	Dowell et al. (2008)
Tablet	Counterfeit	NIR	MSC, Savitzky-Golay, PCA, PLS, CI	Puchert et al. (2010)
Viagra tablet	Counterfeit	Raman	PCA, HCA	Veij et al. (2008)
Placebo tablet	Hardness	NIR	MLR, PLS	Morisseau et al. (1997)
Powder	Hardness	NIR	PCA, PCR	Otsuka et al. (2005)
Theophylline tablet	Crushing strength	Raman	SNV, MSC, Savitzky-Golay, PLS	Virtanen et al. (2008)
Isoniazid Tablets	Dissolution profile	NIR	MSC, Savitzky-Golay, PLS	Neves et al. (2012)
Clonazepam tablets	Dissolution profile	NIR	PLS	Freitas et al. (2005)
Hydrophilic tablets	Drug release	NIR	SNV, Savitzky-Golay, PLS	Gendre et al. (2011)
Placebo tablets	Coating uniformity	Raman	PLS	Hagrasy et al.(2006)
Tablet	Film thickness	NIR	MSC, PCA, PLS	Lee et al. (2009)
Tablet	Moisture content	FT-NIR	Savitzky-Golay, PLS	Corredor et al. (2011)
Ibuprofen tablet	Coating defects	FT-NIR	Savitzky-Golay, SNV, MSC, PCA, CI	Cairos et al. (2009)
Tablets	Coating distribution, excipients	NIR	Savitzky-Golay, SNV, PLS, CI	Palou et al. (2012)

et al., 2008; Cairos et al., 2009; Puchert et al., 2010; Gendre et al., 2011; Corredor et al., 2011; Cruz et al., 2011; Neves et al., 2012). Briefly, the purpose of MSC is to correct the scatter level of the spectra by elimination of the spectral difference of the data (Puchert et al., 2010). SNV is applied to remove the additive baseline and slope variation (Virtanen et al., 2008); the Savitzky-Golay polynomial derivative filters (first- and second-degree polynomial) are used to smoothen the spectra by removing baseline variations and resolving overlapping peaks (Romer et al., 2008). Figure 2 shows the performance of Savitzky-Golay pretreatment for the correction of tablet data (Neves et al., 2012).

Chemometrics (Multivariate data analysis)

The spectral data consist of enormous amounts of variables, which can be difficult to interpret without the help of the multivariate analytical methods of chemometrics. The analysis of complex spectra, such as those containing relatively weak or greatly overlapping spectral bands, poses a challenge. Multivariate analysis is used for the analysis of large amounts of data and assessing chemical and physical information involved in the pharmaceutical manufacturing process (Pawar et al., 2014). Several studies, shown in Table 1, have implemented various kinds of chemometric techniques for data dimension

reduction, optimum waveband selection, pattern recognition, prediction, and classification of pharmaceutical products (Singh et al., 2013). Table 1 demonstrates that partial least squares (PLS) regression is the most frequently applied chemometric technique for predicting or characterizing the quality parameters of pharmaceutical products. Principal component analysis (PCA), multivariate curve resolution-alternating least squares (MCR-ALS), multiple linear regression (MLR), hierarchical cluster analysis (HCA), and CI methods are also widely implemented for product identification and quantification.

Applications of Spectroscopy in Pharmaceutical Analysis

API and excipient identification

A drug is composed of two main components, the API and excipients. The APIs mostly used in the manufacturing of pharmaceutical drugs are synthesized from natural sources (Jones et al., 2011). They are the central ingredients that are chemically active substances meant to produce desired effects in the human body, while excipients are the inactive or inert components of a finished drug product that are added during formulation for a specific purpose such as improvement of esthetics, function, appearance, or retention of quality of drug (Fathima et al., 2011). Therefore, uniform distribution of the API and excipient content is essential to improve the tablet quality. The determination of API content is generally performed by standard techniques such as HPLC, which is destructive and time consuming, and non-destructive spectroscopic methods combined with CI, which reveal physical and chemical information about the tablet and powder components (Roggo et al., 2005). A number of articles have described the applications of NIR-CI for the detection of API content in pharmaceutical testing (Li et al., 2003; Amigo et al., 2008; Alvarenga et al., 2008; Cruz et al., 2009; Cruz et al., 2011). Most of these measurements are based on CI methodology because NIR-CI is a promising approach for visualization of the chemical distribution in the tablet surface.

NIR-CI has been successfully applied for content uniformity studies in tablets. Cruz et al. (2011) used a CI method for investigating acetylsalicylic acid (ASA) and microcrystalline cellulose (MCC) content in aspirin tablets from different brands. This group applied NIR spectroscopy in the range 1200-1400 nm; further, an MCR-ALS algorithm was applied to quantify each pixel in the tablet images to obtain a concentration map of ASA and MCC substances. The chemical images demonstrated that both components were equally distributed throughout the image, as no API or excipient clustering zones were observed. In addition, the histogram of both components showed a very narrow range of concentration values. This suggested that both components were uniformly distributed in the tablets, showing appropriate homogenization of API in the samples. In another research (Amigo et al., 2009), the NIR-CI technique (4000-7800 cm^{-1}) was used for the quantification of various ingredients in tablet samples including API, MCC, lactose magnesium stearate, and talc components. This study applied MCR-ALS and classical least square (CLS) analysis and developed chemical images for the quantification of ingredients. The obtained results were robust and reliable for the quantification of given ingredients by using MCR-ALS analysis.

Palou et al. (2012) developed an NIR-CI method for assessing the distribution of API and excipients in coated and uncoated tablets. The chemical images generated from the PLS model gave a good indication about the homogeneity of the coating. NIR-CI was also able to characterize the blending process of pharmaceutical powder samples (Ma et al., 2007). In this study, the powder sample was formed by mixing acetaminophen (the API), MCC, and lactose monohydrate in a mini-blender, and the spectral data from different blends were collected by NIR spectroscopy (1400-1675 nm). The chemical images generated with PCA and PLS showed a good correlation with the UV-Vis monitoring method (reference method) for blending homogeneity. Li et al. (2003) also used the NIR-CI technique (1850-2200 nm) for investigating the blending behavior in powder blends prepared by mixing two excipients (hydroxypropyl methylcellulose and MCC) during a rotating mixer process. The study showed that NIR-CI is feasible for quantifying agglomeration in powder blends, and suggested that blends prepared with $\leq$ 325 mesh showed randomized mixing of API particles.

In contrast to previous researchers, Firkala et al. (2013) proposed surface enhanced Raman spectroscopy (SERS) for the determination of API in dry and wet tablets over the range of 500-1750 cm^{-1}. The chemical images generated with Raman mapping could easily differentiate between the dry and wet technologies and highlight the number of API pixels present in the mixture. Apart from this, various

other publications have also utilized Raman CI (Clark et al., 2006; Doub et al., 2007; Sasic et al., 2008; Kuriyana et al., 2014).

Drug counterfeit

As reported by the World Health Organization (WHO), the term "drug counterfeit" is used to describe a drug that is manufactured without authorization by someone other than the genuine manufacturer, fraudulently mislabeled and may contain no, or an inappropriate quantity of an API. These counterfeit drugs are unsafe, because they may not be effective or may result in serious harmful consequences for public health including side effects such as kidney failure, liver damage, heart failure, or allergic reactions [U.S. Food and Drug Administration, WHO]. The primary intention behind drug counterfeiting is to earn quick money by replacing the active ingredient with other chemicals (or an absence of an active ingredient), fake packaging, or by mislabeling the product (Rodionova et al., 2005). The WHO states that one million malaria deaths occur each year in Southeast Asia and Africa, with 200,000 resulting from counterfeit anti-malarial drugs [WHO]. In addition, numerous instances of drug counterfeiting have been encountered all over the world, especially in the developing countries: In Haiti and Nigeria (1995), dozens of children died after taking counterfeit syrups containing a poisonous solvent; counterfeits have been identified in cancer drugs in Europe and the United States; the API was adulterated with baking powder in Turkey (1993); in China (2001), more than 100,000 people died after taking fake drugs; fake meningitis vaccines were available in Nigeria (1995); bogus polio vaccines were available in India; and counterfeit yellow tablets were available in Colombia (Deisingh et al., 2005). Apart from this, drug counterfeiting has been reported in many other countries, and the most frequent counterfeits were noted in the drugs used for the treatment of asthma, malaria, cancer, HIV/AIDS, tuberculosis, blood pressure, diabetes, and severe diarrhea (Amigo et al., 2009).

Over the past decades, several methods have been described and employed for the detection of counterfeits in pharmaceutical products, including thin layer chromatography (TLC), HPLC, and mass spectrometry. However, these techniques are destructive and slow during sample measurement. Therefore, a more sophisticated technique, NIR spectroscopy has become popular owing to its nondestructive and rapid approach (Puchert et al., 2010). Many efforts to assess the counterfeiting in tablets using NIR spectroscopy have been undertaken. Recently, Fernandes et al. (2010) used NIR (1250-2500 nm) and a fluorescence spectroscopic technique (excitation/emission: 300-400nm/405-600nm) for the detection of adulteration in glibenclamide tablets (anti-diabetic tablets). Soft independent modeling of class analogy (SIMCA) and PLS discriminant analysis (PLS-DA) was performed for the classification of different classes of glibenclamide contents. The results demonstrated that NIR performs well in discriminating between adulterated and non-adulterated glibenclamide tablets with a classification accuracy of 100%. In another study, counterfeit artesunate tablets (antimalarial tablets) were investigated using the NIR technique over the range 350-2500 nm (Dowell et al., 2008). In this study, the author showed that NIR resulted in an increased ability to differentiate between genuine and counterfeit artesunate tablets with 98% accuracy. In addition, an important NIR peak was noticed in counterfeit tablets at around 1940 nm, and corresponded to the chemical present in the tablet instead of artesunate. Rodionova et al. (2005) used NIR hyperspectral imaging technique for the detection of counterfeit antimicrobial coated tablets and antispasmodic uncoated tablets. The study showed that the genuine tablet (antispasmodic uncoated) spectra presented a peak in the region of 1351-1428 nm while these peaks were absent in counterfeit tablets (antispasmodic uncoated), perhaps owing to the difference in the chemical components of genuine and counterfeit tablets since PCA analysis was able to determine clusters between both groups. In another approach, an NIR chemical based method (800-2500 nm) was successfully applied for counterfeit drug detection (Puchert et al., 2010). This group studied drug products that are used to treat hypertension, arrhythmias, coronary heart disease, glaucoma, and heart failure. As identified from the NIR chemical image, the chemical components such as the API and excipients are well distributed throughout the genuine tablet but not in the counterfeit tablet. The high concentration regions of the image indicated a lack of mixing of chemical components in the counterfeit tablets. Additionally, the PCA score plot also showed differences between both tablet batches. Apart from NIR spectroscopy, Veij et al. (2008) used Raman spectroscopy (700-1800 cm^{-1}) for the detection of counterfeit and genuine Viagra® tablets. In this study, Raman spectroscopy detected 9 tablets as counterfeit from a total of 15 tablets. Furthermore, Raman bands of

counterfeit materials such as barium sulfate, calcium sulfate, calcium carbonate, mannitol, and sucrose were found in counterfeit tablets, while the rest of the Raman spectra were similar to those of genuine Viagra tablets.

Tablet hardness

Tablet hardness is also known as the "crushing strength" or "breaking force," which is an indication of the mechanical strength of a tablet. It is the force (load) required to crush a tablet along its diameter by applying compression loading [US & European Pharmacopeia]. Tablet hardness is directly associated with other physical parameters including disintegration, density, porosity, dissolution, and friability, and plays a vital role in tablet development and subsequent quality control. Tablets are subjected to mechanical shocks and aberrations during manufacturing, packaging, storage, transportation, and handling processes (May et al., 2013). These processes lead to capping, aberration or breakage of the tablets, and therefore a tablet requires a certain amount of hardness to withstand the mechanical shocks inflicted during these processes. Previously, it has been mentioned that a tablet should not be harder than necessary for adequate handling and shipping. If it is too hard, it may not disintegrate in the required amount of time; if it is too soft, it may not withstand the rigors of shipping and handling (Morisseau et al., 1997). Hence, sufficient amount of mechanical strength is essential during the manufacturing process of tablet samples (Tanabe et al., 2007).

Traditionally, tablet hardness is determined by a "mechanical hardness tester" instrument, which is a laborious and destructive method for hardness determination and does not always produce accurate results (Morisseau et al., 1997). However, a spectroscopic technique (especially the NIR technique) is a rapid, non-contact, non-destructive tool, and provides real-time quantitative and qualitative measurement for tablet hardness. Tanabe et al. (2007) proposed an NIR spectroscopic technique for the prediction of hardness of tablet formulations. They carried out their study on tablets prepared from berberine chloride, lactose, and potato starch with different compression pressures (59, 78, 98, 127, and 195 MPa). The reflectance NIR spectra of various compressed tablets were obtained, and furthermore, a principle component regression (PCR) model was developed to predict the tablet hardness. The study found that the NIR absorbance increased in response to an increase in the compression pressure. In addition, the PCR showed a good prediction performance for tablet hardness with a correlation coefficient of 0.977. In another study, placebo formulated tablets were used for hardness detection using NIR spectroscopy in the range 1100 to 2500 nm (Morisseau et al., 1997). In this study, tablets were directly compressed with a tablet press instrument with hardness levels of 2, 4, 6, 8, 10, and 12 respectively. Furthermore, PLS and MLR models were used to compare NIR reflectance data with the destructive hardness test data. Similar to the research of Tanabe et al. (2007), this study also suggested that NIR absorbance increased as tablet hardness increased, but a higher correlation coefficient of 0.99 for hardness prediction was obtained from this study.

Otsuka et al. (2003) successfully predicted both porosity and hardness (compression force: 73.5 MPa) of the tablets using FT-NIR spectroscopy. The tablets were prepared using a formulation of antipyrine, hydroxypropylcellulose, lactose, and potato starch. The PCR model predicted maximum R^2 values of 0.74 and 0.80 for tablet porosity and hardness, respectively. The same group (Otsuka et al., 2005) used the same FT-NIR technique (1000-2222 nm) to investigate the effect of lubricant mixing on tablet hardness. In this study, samples were prepared with two kinds of formulation: a cellulose-based formulation (F-C) and lactose/starch based formulation (F-L). The F-C is composed of sulpyrine, MCC, and magnesium stearate and the F-L is composed of sulpyrine, spray-dried lactose, cornstarch, and magnesium stearate. The tablets prepared using these formulations were compressed at 5 mm/min by a hardness tester and spectra were recorded with an FT-NIR spectrometer. The results indicated that tablet hardness decreased with increase in mixing time. In addition, the spectra changed with the lubricant mixing time. Finally, the PCR model predicted that the R^2 values for hardness were 0.98 (F-L) and 0.92 (F-C). NIR spectroscopy in the range 1100-2498 nm for detection of both chemical and physical parameters of tablet samples was developed by Blanco et al., 2006. The physical parameters studied included tablet hardness (range 74-880 MPa), while the chemical parameters were API and content uniformity. The tablets were prepared by mixing the API (mirtazapine) and excipients (lactose, maize starch, and hydroxypropylcellulose) and pressing the mixture into tablets. The compaction pressure predicted by the PLS model was 0.98 (calibration) and 0.96 (validation) within a range of 148 to 813 MPa. The predicted API and content

uniformity results were also excellent.

Apart from NIR spectroscopy, Raman spectroscopy has also been used for measuring tablet hardness (Shah et al., 2006; Virtanen et al., 2008; Heigl et al., 2012). Virtanen et al. (2008) examined the application of Raman spectroscopy within the range 100-2200 cm^{-1} for the determination of the crushing strength in theophylline (TP) tablets. A PLS model was established to define the correlation between the spectra and the crushing strength of the tablets, and it predicted a crushing strength of 0.99 for TP of 100-M and 200-M respectively. The authors noticed from the Raman spectra that the spectral intensity decreased with increasing compression force because when the pressure increases, the space between the tablet particles decreases and leads to an increase in density, which affects spectral intensity. A combined method including Raman (100-3700 cm^{-1}) and NIR spectroscopy (1100-2500 nm) was also demonstrated for hardness and porosity determination in metoprolol tablet samples prepared by direct compression and wet granulation methods (Shah et al., 2006). This study applied PLS analysis coupled with a CI method to predict the hardness and porosity of the tablet, and to visualize the physical changes due to the compression differences of the tablet. The results suggested that both techniques are able to predict the tablet hardness and porosity, which led to the high correlation coefficient of > 0.90 and low RMSC value of 0.005 respectively.

Drug dissolution

Dissolution is an important attribute, which is essential to know the drug release characteristics of solid oral products. In this process, the API contents of the drug samples (e.g. tablets or capsules) are released from the product, dissolve within the gastrointestinal (GI) tract fluid and are absorbed by the blood stream to reach their desired target (Palmieri et al., 2007). The rate of drug dissolution is strongly dependent on numerous factors namely API type, excipient type, coating, hardness, instrumentation, and media buffer (Tabasi et al., 2008; Nissankararao et al., 2013). Hence, verification of the drug quality with a dissolution test is crucial for quality and safety concerns. The dissolution testing methods also involve a series of time-consuming and labor-intensive tasks (e.g. HPLC); therefore, new powerful and non-destructive techniques for dissolution measurement are in great demand (Neves et al., 2012). Recently, for such a purpose, a NIR spectroscopic technique in combination with multivariate statistical methods has been successfully evaluated by various investigators to assess the dissolution profile of drugs.

The ability to predict the drug dissolution profile has been evaluated in several studies (Donoso et al., 2004; Blanco et al., 2006; Otsuka et al., 2007; Tabasi et al., 2008, 2009;). Some of the recent studies are presented here. Freitas (2005) carried out the investigation of the drug dissolution profile of clonazepam-containing tablets by using NIR diffuse reflectance spectroscopy (1000-2500 nm). They evaluated the dissolution profile using a conventional HPLC method and obtained samples seven times at three different pH values. The reflectance spectra of the tablet samples were measured using a NIR spectrophotometer. A PLS model was used to determine the relationship between the measured dissolution profiles and the NIR spectra. The results demonstrated high correlation coefficient values of 0.99 (calibration) and 0.92 (validation) at pH 6.8 and the standard error varied from 2.75 to 4.96. Neves et al. (2012) evaluated the NIR based technique over the range of 1100-2500 nm to monitor the dissolution profile of four APIs in pulmonary tuberculosis treatment: isoniazid, rifampicin, pyrazinamide, and ethambutol. Similar to the previous study, this study also used HPLC and a NIR diffuse reflectance technique for reference analysis and spectral collection of tablet samples. The results demonstrated a good correlation coefficient value of 0.98 with root mean square error of prediction (RMSEP) of 8.63% for the prediction of the rifampicin component, while the prediction accuracy of the other three components was lower.

Tabasi et al. (2008) predicted the drug release for theophylline tablets at different time periods (2, 4, 8, 24, and 48 h) by using NIR spectroscopy, with a curing temperature of 40°C. The obtained R^2 values were 0.90 and 0.96 for calibration and validation sets with standard error (SE) of 1.12 % and 0.94%, respectively. Different from the above studies, Gendre (2011) described a new approach of NIR spectroscopy for real-time monitoring of drug release from coated hydrophilic matrix tablets by inserting an NIR probe inside the pan coater. In this work, a PLS model was established with different time periods (4, 8, and 12 h) for predicting the dissolution profile of the coated tablets. The obtained R^2 values from both the calibration and validation sets were 0.98, with predictive errors of 1.7%, 1.9%, and 1.5% respectively, across all time periods of drug release.

Polymorphism

Polymorphism is the ability of a compound (here, a drug compound) to exist in more than one crystalline form that possesses the same physicochemical properties and biological activities (Park et al., 2009; Thiruvengadam et al., 2014). It is an important process in the development of pharmaceutical ingredients and affects different aspects of the manufacturing of the drug substance and the drug product. Different polymorphic forms of the drug substance have different physiochemical properties in terms of melting point, bioavailability, solubility, chemical reactivity, dissolution rate, stability, and density (Blanco et al., 2000, 2003). Therefore, it is important to investigate the polymorphic behavior of drug materials and to monitor it during drug formulation, production processes, and storage (Gombas et al., 2003). Presently, various techniques are available for the investigation of polymorphic substances including x-ray diffraction (XRD), differential scanning calorimetry (DSC), thermo-gravimetric analysis, dissolution kinetics, IR spectroscopy and Raman spectroscopy. In contrast, NIR spectroscopic techniques are widely suited for the polymorphic analysis of pharmaceutical substances because this technique offers fundamental information on molecular vibrations of the polymorphs affected by differences in the crystal lattice (Blanco et al., 2000). Moreover, these techniques are simple and allow non-destructive sample preparation (Otsuka et al., 2003).

Blanco et al. (2003) demonstrated the use of an NIR technique in the range of 1100-2500 nm for the determination of total miokamycin (the antibiotic that occurs in both amorphous and crystalline form), and its crystalline form in solid dosage. The content was accurately determined with absolute errors of less than 1% for total miokamycin and 1.5% for the crystalline content, which is comparable to the detection limit of the XRD method used as a reference. Buckton et al. (1998) examined an NIR technique to investigate the change in the form of amorphous and crystalline lactose at room temperature. From this study, the authors demonstrated that with NIR, it is possible to differentiate between the crystalline and amorphous states of lactose by a change in the first overtone frequencies of the water, which is found in the NIR region. NIR spectroscopy and XRD were also performed for quantitative determination of crystallinity in crystalline/amorphous powder mixtures of alpha-lactose (Gombas et al., 2003). MLR predicted a crystallinity R^2 of 0.99 for the mixtures of crystalline and amorphous lactose, which indicated that NIR can determine the crystallinity of materials during pharmaceutical manufacturing. Seyer et al. (2000) conducted a study on the identification of the degree of crystallinity in powder mixtures of sucrose and indomethacin using diffuse reflectance NIR spectroscopy (1100-2500 nm). This study also used XRD and DSC methods for parallel studies of the mixtures. The PLS models showed accurate quantification with a high correlation coefficient (0.99) and lower standard errors (1.73%) for crystallinity determination. In addition, several works have been reported for the detection of crystallinity in various pharmaceutical substances such as polymorph A, glycine, paracetamol, miokamycin, and indomethacin using NIR spectroscopy (Aldridge et al., 1996; Blanco et al., 2003; Bai et al., 2004; Otsuka et al., 2007; Wang et al., 2011;).

Moisture content

Moisture has a significant impact on chemical and physical properties of pharmaceutical products. It influences the chemical stability, crystal structure, powder flow, compaction lubricity, hardness, and dissolution of powder or solid dosage forms. In pharmaceutical processing, various stages require water including wet granulation, particle or film coating, spray drying, lyophilization, and crystallization. Therefore, methods to control the moisture content during processing are important to maintain product quality. These include shelf life and ease of transport. The traditional wet chemistry method of water content determination is Karl Fischer (KF) titration, which is time consuming, destructive, and laborious (Mainali et al., 2014). Therefore, various spectroscopic techniques have been widely developed to extract information concerning the moisture content of pharmaceutical samples in a non-destructive manner. Recently, Mainali (2014) studied the potential of NIR spectroscopy for the measurement of moisture content in tablets. The KF method was used as the reference method for water content determination and FT-NIR (1000-2500 nm) was used for spectral collection of tablet samples prepared with different APIs and excipients. The PLS model developed for KF data (water content) and NIR spectra demonstrated a strong correlation with R^2 of 0.99 and Root mean square error (RMSE) of 2.55% and 2.03%, respectively. Corredor et al. (2011) developed a new approach for determining the moisture content in powders and tablet samples. In this work, they applied NIR (1000-2500

nm) and microwave resonance (MR) sensors for in-line moisture measurement of the samples, while the KF method was carried out for reference measurement of water content. The predicted water content from the PLS model showed the highest R^2 of 0.99 and SEP of 0.18 (water content ranging from 1-5%) and R^2 of 0.96 and SEP of 0.052 (water content ranging from 0.2-1%) respectively. Moreover, the comparison of prediction results for the three methods (KF, MR, and NIR) also showed strong correlation between each other. In a different study, Zhang (2008) determined the moisture content of beta-lactam powder injections by NIR spectroscopy and obtained low RMSECV and RMSEP values of 0.283 and 0.261, respectively. Recently, Uppaluri et al. (2014) described the use of NIR and attenuated total reflectance Fourier transform IR (ATR-FTIR) technique for the determination of moisture contents of different superdisintegrants (used in tablet formulations). In this study, a thermogravimetric method was used for a reference moisture analysis, and a PLS analysis was performed to evaluate the relationship between the measured moisture contents and the spectra. The output results predicted the highest R^2 of 0.99 with NIR, for Kollidon® CL-SF, Kollidon® CL (superdisintegrants) and 0.99 of highest R^2 with ATR-FTIR for Kollidon® CL-SF, Ac-Di-Sol (superdisintegrants).

Freeze-drying is an important process typically used in the pharmaceutical industry to stabilize, preserve, or increase the shelf life of drug products. In this process, the water in the samples is removed by sublimation under vacuum; hence, monitoring the correct moisture content is important during the drying process. Grohganz et al. (2009) investigated water content (determined by the KF titration method) of freeze-dried mannitol-sucrose excipients using NIR spectroscopy (1250-2500 nm). The PLS provided satisfactory results of linear regression between the NIR and the KF method with R^2 of 0.98 and RMSECV of 0.15 % appropriately. Similarly, Grohganz et al. (2009) also demonstrated a NIR technique for quantification of water in freeze-dried lyophilized mixtures and showed good model accuracy with a low error. Muzzio et al. (2011) used NIR combined with PCR and PLS analysis for the prediction of water contents in lyophilized mannitol (mannitol was used as an excipient in lyophilized pharmaceutical products). The obtained results suggested that both PCR and PLS models are able to predict moisture content, with R^2 of 0.99 (calibration) and 0.96 with RMSEP of 0.233% respectively.

Coating process

Coating is the final step of the drug manufacturing process, in which a layer of coating material (sugar or film layer) is applied to the outer surface of the drug to achieve specific benefits. Coatings have a number of advantages and are often used to improve product characteristics such as controlled release of the APIs from the core of a tablet, maintain the shape of the tablet, protect the tablet from environmental influences, lubricate the tablet to ease swallowing, disguise unpleasant tastes, and control the release of drug into the body (Romer et al., 2008). Therefore, the determination of coating parameters, such as layer thickness, uniformity, and reproducibility, are crucial in the quality assurance of controlled release dosage forms (Romer et al., 2008; Sovany et al., 2009;). Traditionally, the coating process is determined offline via HPLC, or by measuring weight gain (Hagrasy et al., 2006). However, these methods are time-consuming and require laboratory analysis. Alternatively, spectroscopic methods (NIR, FT-NIR, and Raman spectroscopy) provide non-destructive measurements and can be used for real-time monitoring of the tablet coatings (Sovany et al., 2009).

Sovany et al. (2009) implemented a Raman spectroscopic technique for the determination of thickness of polymer coating on pallets. In this study, the geometric parameters (film thicknesses) were determined by a stereomicroscope and image-analyzing system, and were 15.5, 23.5, 28.9, and 44.4 μm respectively. The Raman spectra were compared with the measured film thickness, which revealed the highest correlation coefficient of 0.99. Raman spectroscopy has been successfully applied for the determination of coating uniformity of a tablet prepared with a pan coater (Hagrasy et al., 2006). It was found that the Raman spectral data were correlated with the average weight gain of tablets during coating process. Lee et al. (2009) developed an in-line FT-NIR monitoring system (714-2500 nm) for film coating measurements. The fiber optic diffuse reflectance probe of this system was mounted onto the FB vessel, for real-time spectral acquisition of tablet samples. The tablets were produced using a rotary press and coated with hydroxypropyl methylcellulose by using an FB processor. The results of this study showed a good R^2 of 0.99 between the measured actual value and predicted value for coating thickness. NIR spectroscopy

was employed by Moes et al. (2008) for the evaluation of blending uniformity, content uniformity, and coating thickness in tablet samples. In this work, the coating was performed in a fluidized-bed coater and the average coating thicknesses were 0.0378, 0.0318, and 0.05044 mm for three different tablet batches. Furthermore, the spectra were collected over the range of 800-2777 nm. NIR exhibited good performance for prediction of coating thickness with an R^2 of 0.99. In addition, the blend uniformity and content uniformity have also been determined accurately. Cairos et al. (2009) and Palou et al. (2012) have shown an NIR-CI approach for determination of coating properties in tablets. The NIR-CI approach of Cairos et al. (2009) could help visualize any type of defects and contaminants in tablet coating. On the other hand, Palou et al. (2012) quantified coating thickness using PLS analysis, which accounted a total variance (Y-variance) of 99.3% with RMSEP and RSEP of 14.04 and 8.32%, respectively. Furthermore, they generated a concentration map using NIR-CI and concluded that the coating material is not homogenously distributed on all sides of tablets because of an improper spraying process.

Discussion and Conclusion

This review paper demonstrates the applications of spectroscopic techniques for the quality control of pharmaceutical compounds. Pharmaceutical processing is composed of critical operations from product manufacturing to final drug delivery process. Hence, quality assurance of the product is important during every stage. The NIR and Raman spectroscopic techniques play a key role in pharmaceutical production processes by troubleshooting the quality assurance tests of raw material, during off-line or online process monitoring. In contrast to the conventional methods, which are time consuming and destructive to the sample, these spectroscopic techniques are non-destructive, accurate, and rapid for quantitative and qualitative measurements of pharmaceutical products. The hyperspectral three-dimensional feature is more efficient and simultaneously provides spectral and spatial information about the samples (tablet and powder samples), which is essential to identify the homogeneity of distribution of chemicals in samples. In addition, vibrational spectroscopy delivers the information about the chemical bonds of the material or ingredients present in the sample. This information cannot be obtained using other kinds of conventional techniques. However, proper calibration of spectroscopic instruments is difficult during measurements, and the obtained data are composed of high dimensions. For this reason the different preprocessing and chemometric analysis tools are available to overcome these problems.

Finally, it can be concluded from this review that, in future, both NIR and Raman spectroscopic methods combined with hyperspectral imaging techniques will be an excellent, cost-effective alternative to the conventional methods for non-destructive quality control of pharmaceutical processing in industries.

Conflict of Interest

The authors have no conflicting financial or other interests.

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