Near Infrared Spectroscopy: Basic principles and use in tablet evaluation
Hiren Patel
Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, PA 19104, USA

Abstract: The continuous preference of the oral route for the delivery of the drugs has led the ongoing research in the field of oral delivery. With emergence of Near-infrared spectroscopy (NIRS) as a fast and non-destructive analytical method, researchers have used NIRS for non-destructive evaluation of tablets. This review looks at the basics, theoretical aspects of NIRS, qualitative and quantitative treatment of sample spectra for better understanding of NIRS in tablet evaluation. Use of NIRS in tablet evaluation is discussed in detail with focus on evaluation of tablet hardness, content uniformity and dissolution with use of NIRS. In addition to advantages and limitation of use of NIRS, the current regulatory status and exploration of NIRS as a PAT tool is discussed in the later part of the review.

Key words: Near infrared spectroscopy; pharmaceuticals; tablet evaluation; chemometrics; Process analytical tool; mathematical data treatment

Introduction

Though in recent past many studies are performed for topical/transdermal drug delivery (Patel et al., 2015; Soroushnia et al., 2016), oral route still is the most popular route for drug administration. Among various oral dosage forms, tablet form is most widespread used to deliver drug, particularly due to cost effectiveness and convenience for both manufacturer (e.g., simplicity, economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (e.g., accuracy of dosage, compactness, portability, blandness of taste, and ease of administration). Now tablets are available in various types including film coated, enteric coated, efervescent and fast dissolving tablets satisfying different needs.

After manufacturing of tablets, they have to be characterized or described by various parameters in order to assure the integrity of the manufacturing process and to meet up the regulatory requirements. Official standards for the evaluation of tablets are given by the U.S. Pharmacopeia (USP) and other compendia and include uniformity of dosage units (weight variation, content uniformity) and disintegration testing. Unofficial tests include those for mechanical strength (hardness or crushing strength) and resistance to abrasion (friability).

A major disadvantage of current method of tablet evaluation is that they are time-consuming, destructive in nature and often highly variable. Once a test is performed on a sample, the integrity of that sample is usually lost (with the exception of weight testing) and no additional testing may be done on it. That leads manufactures and researchers to look for the better option for tablet evaluation. Furthermore, with FDA initiative to follow Quality by design (QbD) rather than quality by testing, emphasis is given to find real time alternatives that can evaluate tablet properties accurately. The QbD approach emphasizes the understanding of various components and properties of the system for improved control over desired output (Jain, 2014) and widely used recently for studying various delivery in detail (Dangre et al., 2016; Jain et al., 2015b; Patel et al., 2016; Shah et al., 2014).

Near-infrared spectroscopy (NIRS) continues to grow in importance as a useful analytical technique for pharmaceutical analysis. It offers unique potential as a rapid, non-destructive method of quantitative and qualitative evaluation. Recent technological advances in instrumentation and software have increased use of NIRS for pharmaceutical applications. In the following discussion, basics of NIR spectroscopy, various mathematical and statistical treatment will be discussed in detail to understand the role of NIRS in pharmaceutical tablet evaluation.

Basics of near infrared spectroscopy

Near infrared region: Spectroscopy is a scientific discipline studying interactions of light with the matter. Light can be of different wavelengths, which are represented by the electromagnetic spectrum applied. Conventional infrared instruments usually operate in the near-, mid-, or far infrared regions, depending on the energy source and the detectors used (Moes et al., 2008a).

The NIR region of the electromagnetic spectrum is from 800 to 2500 nm. The region mainly used in the analysis of pharmaceutical products is 1100 nm to 2500; also, known as Herschel region. In terms of wave numbers, the near-infrared region is...
14,300– 4000 cm⁻¹, the mid infrared range is 4000– 200 cm⁻¹, and the far infrared is from 200–10 cm⁻¹. Absorption of light in the IR region causes molecules to vibrate and rotate. Absorption of light in the matter is usually not uniform and depends on molecular arrangement. At certain intervals, more intense absorption can be observed indicated by wide of absorption bands.

The NIR region mainly contains overtones and combination bands that are due to hydrogen (CH, OH, NH) vibrations (Dyrby et al., 2002). These overtones and combination bands are called secondary vibrations and are weaker than the fundamental vibrations. Therefore, the molar absorptivities are much smaller than those of the corresponding infrared bands. That was the reason for the limited acceptability of NIRS in pharmaceutical industry. But smaller molar absorptivities allow the use of undiluted samples and penetration of solid samples with good results. NIR spectra have only a few significant peaks, but they are exceptionally information-rich due to the number of overlapping absorption bands (Blanco and Villarroya, 2002). Thus, interpretation of NIR spectra is usually combined with mathematical and statistical methods such as chemometric methods in order to extract the necessary information.

**Basic NIRS (NIR spectroscopic) device set up for analysis:** Various instrumentations are available for NIRS analysis has various statistical software in built with basic spectroscopic design. Basic NIR spectrometer contains light source, monochromator and detector to get the spectrum of sample (Dyrby et al., 2002).

1) **Light source:** A single polychromatic thermal source is generally used for NIR spectroscopy. An inert solid mainly tungsten (a tungsten halogen lamp small and rugged) electrically heated to 1500–2200K irradiates uniformly in the IR spectral range. The choice of wavelength will depend on the solid-state properties of the sample for the analysis and its fluorescence.

2) **Monochromator:** Monochromators is used to spill the radiation before it reaches to the sample. FT, tunable filter, and diffraction grating spectrometers are mainly used monochromators. A diffraction grating has a large number of parallel lines or slits separated by a distance comparable to the wavelength of light. When a polychromatic ray of light hits the grating, it is dispersed in several directions and the angle of diffraction is dependent on the wavelength of light. High detector sensitivity and high source intensity in the NIR range make it suitable for NIRS.

3) **Detector:** Detectors are used to record the signal after wavelength separation. Photon detectors are the most widely used in NIRS. Detector types include silicon, lead sulfide (PbS) and indium gallium arsenide (InGaAs).

Silicon detectors are fast, low noise, small and highly sensitive from the visible region to 1100 nm. PbS detectors are slower, but very popular since they are sensitive from 1100 to 2500 nm and provide good signal-to-noise properties. The most expensive InGaAs detector combines the speed and size characteristics of the silicon detector with the wavelength range of the PbS detector.

**Near infrared measuring modes used in pharmaceutical analysis:** Basic components of NIR spectrometer was discussed above. Different arrangements of light source and detectors are followed in order to get different NIR spectra for different types of pharmaceutical products.

**Transmission:** In transmission measurement, the light source, the sample and the detector is placed behind the sample in line to acquire the fraction of light transmitted through the sample. Transmission analysis requires the sample to be partly transparent. The basic principle of transmission spectroscopy is that light passes through a clear or transparent sample and energy is absorbed by the chemical components. In most cases, in the NIR range, samples must be diluted in non-absorbing matrix otherwise no light might be transmitted to the detector. Liquid can thus be prepared as a dilute solution in a cell. It is not possible with thick samples such as tablets so cannot be used for tablet evaluation.

**Reflection:** In reflection measurement, the detector is placed on the same side of the sample as the source to record the signal reflected by the sample. The sample is presumed infinitely thick and incapable of transmission of light that reflect back the light to detector.

**Diffuse reflection:** Incoming radiation interacts with the sample and is scattered by interaction with the particles. A fraction of this light is reflected by the sample and recorded by the detector. Samples require dilution for diffuse reflection in NIRS, it is not commonly used in NIRS. In NIRS, samples can be used without dilution as the bands are weak. Diffuse reflection is the method of choice for tablet evaluation in NIRS.

The difference between the two instrument configurations lies in the positioning of the sample and the detector(s). In transmittance mode, the sample is placed between the monochromator and the detector so that the entire path length of the sample is integrated into the measurement. Transmittance measurements require higher
frequency energy (800–1400 nm) because of the greater depth of penetration into the sample. In reflectance mode, the monochromatic light is illuminated directly onto the sample, and the reflected light is collected by detectors positioned at 45° angles to the sample.

The appropriate NIR measuring mode will be dictated by the optical properties of the samples. Transparent materials are usually measured in transmittance. Turbid liquids or semi-solids and solids may be measured in diffuse transmittance, diffuse reflectance or transfectance, depending on their absorption and scattering characteristics.

Sample arrangement and getting NIR spectra using NIRS
Basic design of NIR spectroscope was described above. The process of scanning a sample with NIR spectrometer is quite simple and very rapid. The sample holder and surface must first be gently cleaned of debris and a reference scan is taken. The sample may then be placed in the sample holder, which may hold one or more of a specific type of sample.

The sample is positioned, the lid closed, and the scan taken. Scan times differ with the type of analyte used but are usually approximately 40 s. For multiple scans of the same sample, the sample may be removed and rescanned. Instrument software facilitates the process and spectra can be stored in the data files. Various mathematical and statistical treatments may be applied to extract the information required.

Theoretical basis of NIRS in tablet evaluation
The basis of use of NIRS in content uniformity determination is having different spectrum with different API at different concentration. The key issues that determine the spectral properties such as frequency and intensity of NIR absorption bands are anharmonicity and Fermi resonance. Since the energy curve of an oscillating molecule is affected by intramolecular interactions, vibrations around the equilibrium position are non-symmetric and the spacing between energy levels that the molecule can attain is not identical, but rather decreases with increasing energy.

Combination bands that appear between 1900 nm and 2500 nm are the result of vibrational interactions, i.e. their frequencies are the sums of multiples of each interacting frequency (Dyrby et al., 2002). A special type of configuration interaction, called Fermi resonance, leads to the feature that two NIR absorption bands of a polyatomic molecule with the same frequency do not simply overlay and sum up, but split in two peaks of somewhat higher and lower frequencies than the expected unperturbed position (Pasquini, 2003).

Furthermore, intermolecular hydrogen bonding and dipole interactions have to be considered, since they alter vibrational energy states, thus shifting existing absorption bands and/or giving rise to new ones. This effect allows crystal forms, for instance, to be determined by NIR spectroscopy.

Quantitative and qualitative analysis of NIR spectra of sample
NIR Spectroscopy covers the wavelength range adjacent to the mid infrared and extends up to the visible region. Near-infrared spectroscopy (NIRS) continues to grow in importance as a useful analytical technique. It offers unique potential as a rapid, non-destructive method of quantitative and qualitative evaluation. NIRS has been used extensively in the food and agricultural industries for many years to determine moisture, protein, and starch content in grains. NIRS mainly works with secondary bands; absence of the primary bands might be the reason for slower acceptance of NIRS by the pharmaceutical industry.

In the beginning NIRS was mainly used for the qualitative and identification purpose for the pharmaceutical preparations. With advancements in chemometrics and statistics, now it is possible to correlate NIR spectra with quantitative parameters of the pharmaceutical products. That has changed the whole perspective of pharmaceutical industry towards NIRS. In recent years, NIRS has been successful to get the attention from the academia and research is carried out on the theory behind NIR spectroscopy. NIR spectroscopy has gained widespread acceptance within the pharmaceutical industry from raw material testing, product quality control to process monitoring. Technological advancements in instrumentation and software and urge of on line monitoring of pharmaceutical products have increased the use of NIRS for pharmaceutical applications.

As it has been noted that NIRS can be used for various purposes in pharmaceutical industry nowadays but still not widely accepted. The primary reason behind that is the complexity of the whole process. NIRS involves the multidisciplinary approaches of the analytical chemist, statistician, and computer programmer simultaneously.

Chemometrics - A tool for data processing in near infrared Spectroscopy
Chemometrics means use of mathematics to get information from the chemical data. Chemometrics is defined as the chemical discipline that uses mathematical, statistical, and other methods that apply formal logic to design or select optimal measurement procedures and experiments, and to provide maximum relevant chemical information by analyzing chemical data. Chemometrics has found widespread use in the interpretation of analytical data and is relied on for the development of NIRS.
methods that can relate spectrum to the quantitative and quality active parameters of pharmaceutical products (Dyrby et al., 2002). For tablet evaluation, when NIRS is applied to the tablet a spectrum is achieved. Chemometrics relates obtained spectra to the quantitative measure of the various properties of the tablets such as tablet hardness, amount of active ingredient and thickness of the coating.

Chemometric data processing
As we have discussed earlier, NIR spectra are typically composed of broad overlapping and, thus, chemical and physical information of all sample components are in ill-defined absorption bands. The analytical information of sample is hardly selective as it is multivariate in nature. To relate this absorption band information to properties of analyte involve use of chemometrics. To perform qualitative or quantitative NIR analysis, mathematical and statistical methods are required that extract relevant information and reduce irrelevant information. The analytical information of pharmaceutical products can be obtained with NIRS but it is a multi-step process involving use of chemometrics and statistics.

The process of extracting information regarding analyte can be generally described as below:

- Some mathematical data pretreatment is given to the analyte spectra.
- Reduction of variables (as spectra is multivariate) with principal component analysis.
- Quantitative analysis is carried out with multivariate calibration methods.
- Qualitative analysis is carried out with multivariate classification techniques.

 Mathematical data pretreatment (pre-processing)
Variable physical sample properties or instrumental effects cause interference in NIR spectrum. Interfering spectral parameters involves light scattering, path length variations, optic effects and random detector noise. Most commonly used methods are discussed below with respect to the effect on the interference parameters.

First treatment NIR spectra required are correction in the base line to reduce the background effect of uncontrolled spectral variation. Derivative preprocessing is one solution but it increases the noise. Other techniques use polynomial curves. Mathematical treatments used to compensate for scatter-induced baseline offsets include multiplicative scatter correction (MSC) and standard normal variate (SNV) (Roggo et al., 2007). Both methods can be applied to process reflectance spectra as well as transmittance spectra. MSC and SNV are algorithm helps in normalizing baseline on NIR spectra (Dyrby et al., 2002). Baseline shifts and intensity differences resulting from variable positioning or path length variations may be reduced or eliminated by these two methods.

Extraction of distribution maps obtained after pretreatment
The information from the mathematical pretreatment is in the form of distribution maps. Extraction of these maps is carries out for localization of chemical compounds in the sample as shown in the figure. Extraction has to be as accurate as possible to avoid pixel misclassification. Many methods have been developed mainly based on classic spectroscopy or image processing. Choice of the most appropriate method is based on the information available, the spectral signatures of the pure compounds in sample and experimental noise. Method mainly involves univariate and multivariate analysis.

Post processing and extraction of quantitative parameters
After reducing the data cube and extracting the distribution maps using the either univariate or multivariate analysis, the next task is to develop methods for interpreting those images. The application of image-processing techniques is used to enhance an object of interest that can extract user-independent information. Such techniques mainly include color and contrast enhancement, segmentation into homogenous areas, edge detection, and texture classification.

Multivariate calibration for quantitative analysis
After achieving the distribution maps, NIR spectrometer has to be trained and then data can be used for any further quantitative analysis (Roggo et al., 2007). The data should be calibrated using various multivariate methods. Calibration models are developed to determine the relationship between calibrated set of spectra and the constituent value of interest for those samples. Calibration involves taking spectra from many samples varying over the measurement range from lower to higher value and measuring the desired parameters. A rugged chemometric model for a complex sample may require hundreds to thousands of samples taken from all possible situations, in and out of specification, that it may encounter in order to set a calibration model.

Samples selected for calibration must contain all of the variables affecting the chemical and physical properties of the samples to be analyzed. To characterize each source of variation, 15 to 20 samples to be run for each variable is recommended. Application of a mathematical treatment as discussed above, prepares the raw spectral data for use in a regression and subsequent development of a calibration equation. This type of mathematical treatment results in a data file that
yield more information more easily than a raw data file.

As NIR bands are mixtures of overtones and combinations, the intensity of the absorbance at particular wavelengths do not necessarily respond linearly to a change in concentration of analyte in pharmaceutical products (Roggo et al., 2007). In the case of a mixture, band mixing results in further disruption of any linear relationship between the intensity and the concentration and that is the reason behind not applying Beer’s law.

The calibration process basically involves the following steps:
- Selection of a representative sample set for calibration.
- Acquisition of spectra and determination of reference values.
- Multivariate modeling to relate the spectral variations to the reference values of the analytical target property.
- Validation of the model by cross validation, set validation or external validation.

Methodology to carry out tablet evaluation using NIR spectroscopy
NIR instruments are rapid scanning devices. Total time varies from 1 min to 5 min. The same sample scan can be used for further sequential qualitative and quantitative analysis, and simultaneous multicomponent determinations may be included in the quantitation. Multivariate calibration is a process for creating a model that correlates component concentrations or properties to the absorbance of a set of known reference samples. The reference method is the analytical method that is used to determine the reference component concentration or property values that are used in the calibration. The mathematical expression relating component properties to absorbance is known as a calibration model. Using spectral software, the analyst can acquire spectra, correlate them to laboratory data, develop a calibration equation and apply that equation to similar new samples to predict constituent concentrations or properties (Otsuka and Yamane, 2009).

Qualitative analysis of NIR spectra involves the comparison of the sample spectrum with spectral libraries set up previously for known samples of known products. Sophisticated software assists in spectral matching of sample and followed by stringent identification and discrimination criteria. For quantitative analysis, the NIR response first is calibrated against reference analytical data generated by a standard technique (e.g. HPLC/UV) on a calibration set of samples providing a necessary range of compositions). This calibration set must comprehensively cover all possible variations in analyte and matrix components likely to be encountered in real samples. Inclusion of higher number of samples makes the calibration equation robust and reliable. The equation itself is generated by software application of linear regression or more complex chemometric approaches like Partial Least Squares (PLS) regression.

Due to several reasons, tablets give different NIR spectrum with different amount of the component, different hardness and coating thickness. Tablet dissolution rate changes with the tablet hardness and tablet spectrum can be correlated to dissolution results to give calibration equation.

Use of NIR spectroscopy in evaluation of tablet properties
As we have discussed earlier evaluation of various parameters of tablets are very essential and NIRs provides a tool to determine various evaluation parameters of tablets. NIR applications for intact dosage forms focus on tablets, ranging from identification, assay and content uniformity to physical and biopharmaceutical parameters, such as hardness, coating thickness and dissolution rate. Selecting the measuring mode (transmission or reflectance) for NIR analysis is highly dependent on tablet thickness, composition and target parameter (Otsuka and Yamane, 2009).

Considering quantitative analysis of active ingredients in tablets, the reflectance mode, mainly used in early work, may have some limitations, since it covers only a certain part of the tablet. Current methods of hardness testing involve use of Erweka hardness tester, Strong-kobb testers, are destructive in nature and often subject to operator error (Elzoghby et al., 2015). NIR spectroscopy, on the other hand, offers the opportunity for fast and nondestructive hardness measurements, and provides additional information on structural features of the tablet matrix.

Since the approaches are different with respect to the measuring mode, and tablet hardness data can be used in prediction of drug dissolution rates from whole tablet NIR spectra. The moisture content present in the sample can also affect the NIR spectra, so prediction of moisture content can also be helpful in determining dissolution rate of the tablet with NIRS. Quantitative modeling of drug dissolution rates of commercialized tablets is certainly a greater challenge and requires exhaustive calibration work based on a priori knowledge of the formulation- and process-dependent tablet variables and their effect on both drug dissolution and the spectra.

Evaluation of tablet harness using NIR Spectroscopy
Tablet hardness shows mechanical strength of tablet to withstand the shock of handling during various phases of shelf life. Tablet strength also affects the...
other more important properties of tablet such as disintegration and dissolution. It is also known as ‘tablet crushing strength’. Too ‘soft’ tablets can disintegrate during transportation and too ‘hard’ tablets would not disintegrate at all. Thus, an acceptable ‘hardness’ is required and tablet strength testing is very important. Current methods for evaluation of tablet involve use of various hardness tests such as the Erwoka tester, the Strong-Kobb tester and the Pfizer tester (Moes et al., 2008b; Morisseau and Rhodes, 1997). Current advancements in tablet harness testing include the much more automated instrumentation based on the same working principle.

NIR spectroscopy is a rapid, nondestructive and potential way to analyze the tablet hardness. Tablet hardness could then be monitored nondestructively via NIR method throughout the production run, avoiding destruction of tablets that had been ruined by the destructive test (Moes et al., 2008b). The economic benefits of such an approach are obvious. The primary advantage, however, is the possibility of analyzing a larger number of tablets from each lot, providing more statistical significance to decisions regarding adherence to product specifications. As higher compression pressure is applied for tablet manufacturing, tablet hardness increases. Compression pressure brings some changes in the NIR spectra itself and quantitative analysis can be done with those changes (Otsuka et al., 2007).

Since there is a larger air/solid boundary surface area in high porosity tablets manufactured with lower compression pressure, the intensity of scattered light is greater than that of transmitted light in the tablet (Moes et al., 2008b). Conversely, since there is a larger solid/solid boundary surface area in tightly packed tablets, the intensity of scattered light is less than that of transmitted light.

With the transmittance method, the intensity of scattered light decreases, and the transmittance increases as the tablet’s porosity decreases. In the diffused reflectance spectra, the light penetrates deeply into the tightly packed tablet, and gets absorbed between the matrices. In contrast, the light scatters at air/solid boundary faces in the high porosity tablets, it does not penetrate deeply into the powder bed, and so the intensity of scattered light was higher than that in tightly packed tablets. This indicates that the intensities of scattered and transmittance NIR spectra reflects changes in the microporous structure of the tablet due to compression pressure.

**Evaluation of dissolution testing of tablets using NIR spectroscopy**

Tablet Dissolution is a standardized method for measuring the rate of drug release from tablets. The samples containing active ingredient is removed at predetermined time intervals and is analyzed for determination of active concentration. UV spectroscopy and HPLC are the widely-used method for determination of active quantity in the samples. They both methods are time-consuming as analysis of active should be carried out for each tablet. In addition, they are destructive methods of analysis. Use of NIR spectroscopy provides rapid and nondestructive means of analysis for determination of dissolution property of tablets.

Theoretical basis for NIR application for dissolution testing remains same as described in the tablet hardness. Application of different compression pressure brings some changes the NIR spectra and can be related to tablet hardness. Dissolution time is moreover dependent on the disintegration time of tablets; which is primarily a function of tablet hardness (Moes et al., 2008b). Thus, dissolution profile can be related to the compression pressure used for tablet manufacturing. In the same way, variations in NIR spectra due to compression pressure can be related to dissolution property of the tablets (Blanco et al., 2006).

**Evaluation of content uniformity testing of tablets using NIR Spectroscopy**

Tablet analysis is a crucial component of the manufacturing process ensuring quality and integrity across batches. Tablets are evaluated for various parameters such as tablet hardness, friability, weight variation and so on the single most critical and commonly analyzed parameter for QA and QC of tablets, however, is the concentration of API from tablet to tablet across an entire batch called as content uniformity. The content uniformity test is carried to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets (Parashar et al., 2012). Tablet monographs with a content uniformity requirement do not have weight variation requirements. The USP includes a permanent chapter dedicated to content uniformity measurements in tablets. Although the USP is not a regulatory body, their recommendations for testing protocols are readily adopted by pharmaceutical companies.

In the case of content uniformity in compressed tablets, the criteria for acceptance testing are:

1. The actual % API in 10 tablets tested must be between 85.0% and 115.0% of label claim.
2. The Relative Standard Deviation (RSD) is no greater than 6.0%.

If 1 in 10 tablets do not meet the specification for % label claim (outside 85.0% to 115.0% but not
outside 75.0% to 125.0% or RSD, then an additional twenty (20) tablets must be tested. If the RSD for the set of now 30 tablets is less than or equal to 7-8% with not more than 1 unit outside the range of 85.0% to 115.0% label claim (but still not outside 75.0% to 125.0%), then the criteria are met.

Currently used methods for determining concentration of active involves use of UV spectroscopy and HPLC. Laboratory methods for tablet assay and content uniformity are usually time-consuming because they routinely are done by high-performance liquid chromatography (HPLC), which requires lengthy calibration runs, the mixing of buffers, and the procurement and disposal of volatile solvents. Analyzing 10 tablets for content uniformity may take hours, and the results may not be available to tablet-press operators or for batch release for many days or even weeks after the tablets are compressed.

NIR is preferred technique for carrying out content uniformity of tablets as it is rapid. Statistical process control (SPC) techniques can be applied while measuring the tablets with NIR in real time during tableting so that assay and content-uniformity problems can be detected before they go beyond acceptable limits (Moes et al., 2008b). Each of these techniques carries the risks of operator error and poor reproducibility. In addition, both methodologies use solvents and require a significant amount of training.

Advantages of NIR Spectroscopy over conventional methods used for tablet evaluation

Near-infrared (NIR) spectroscopy has become one of the most powerful techniques in analytical chemistry and particularly in the pharmaceutical industry, because of the following important advantages.

- A non-destructive analysis of samples.
- However, contrary to mid-IR radiations, the energy of NIR radiations is high enough to allow longer path, lengths through the sample without the radiation being completely absorbed. Therefore, NIR spectroscopy enables the analysis of a wider variety of samples, including for instance strongly absorbing samples and opaque solid materials.
- NIR radiations allow the use of long fiber optics, which can be useful for separating the sample measurement position, e.g., for the online analysis of homogeneity pharmaceutical blends.
- NIR spectroscopy requires minimum sample preparation.
- NIR spectroscopy can be used for the on-line monitoring of industrial processes which makes it more acceptable.

- NIR spectroscopy enables the determination of several physico-chemical properties and/or concentrations of chemical compounds from a single spectrum. This is particularly important for quality control applications, where a lot of different properties and/or concentrations must be determined for a high number of routine samples.
- NIR analyses do not require organic solvents.
- Samples may be retained for further analysis by NIR or other methods, allowing a direct correlation between tests. Economic benefits are obvious for manufacturers, who may increase profits per batch because of the need for fewer retained samples.
- A single spectrum can be obtained and compared with several different calibrations sets at the same time, allowing the measurement of several constituents at one time. This saves considerable time and labor.

Limitation of NIR Spectroscopy used for tablet evaluation

Though NIRS possesses several advantages over conventional methods for tablet evaluation, there are some limitations in performing analysis with NIRS.

- The initial calibration process for a substance or a product should be quite detailed. A calibration equation is needed for each constituent in the sample. NIR calibrations must be formulation specific and varies with formulations and even with devices.
- The accuracy of the NIRS method cannot be better than the reference method (HPLC/UV) from which it was validated.
- Ruggedness of the models improves when all expected types of variation are included in the model.
- Another issue is that of transferability of the calibration model among instruments. This has been a significant obstacle to more widespread use of NIR methods. Transferability is especially important to multisite facilities, because it is needed to avoid time consuming recalibration procedures.
- Calibration errors may occur among instruments because of slight differences in instrument response.
- Physical attributes of the tablets can affect the calibration process. For example, scored tablets and those of during geometries may produce more variability in NIR spectra than flat, un-scored tablets.
- Homogeneity of the sample affects the NIR spectra and mixed calibration models composed of flat and concave tablets gave variable hardness prediction results, supporting the assertion that calibration models should contain samples of homogeneous composition.
Current Regulatory Status of NIR Spectroscopy in Pharmaceutical Industry

NIR spectroscopy has a large number of advantages over other analytical techniques and thus, offers many interesting perspectives in pharmaceutical analysis. The scientific rationale of this technology has been established for many different applications and justified by a huge number of publications from both academia and industry (Reich, 2005). However, in the highly regulated pharmaceutical world, an analytical method is only valuable for routine implementation if it is approved by regulatory authorities. Increasing use of NIRS for evaluation of tablets and testing of pharmaceutical products calls for the regulatory steps from the regulatory authorities around the world. Involvement of mathematical treatment and statistical procedures makes it difficult for the standardization of method for NIRS.

Actually, the major pharmacopoeias have generally adopted NIR techniques. The European and United States Pharmacopoeia both contain a general chapter on near-infrared spectrometry and spectrophotometry, respectively. These chapters address the suitability of NIR instrumentation for use in pharmaceutical analysis focusing mainly on operational qualification and performance verification comprising wavelength scale and repeatability, response repeatability, photometric linearity, and photometric noise. The general legal requirements for instrumentation qualification procedures, namely design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), are described in the cGMP guideline title 21 CFR part 211 (Reich, 2005). The American Society for Testing and Materials (ASTM) recently published an official document providing a guide to spectroscopists for the multivariate calibration of infrared spectrometers. Publication includes standard practices for infrared multivariate quantitative analysis includes a description of multivariate calibration methods for the determination of physical or chemical characteristics of materials.

Many pharmaceutical companies have successfully implemented NIR spectrometers in their quality control laboratories for routine use in raw material identification and qualification. This is based on the fact that major pharmacopoeias allow manufacturers to use analytical methods other than compendial ones for compliance testing, provided they are validated according to parameters, such as specificity, linearity, range, accuracy, precision, repeatability, reproducibility, detection limit, quantification limit, and robustness. Interestingly, only few quantitative NIR methods have gained regulatory approval as yet. Regulatory bodies around the world have given approval for NIR methods for a variety of purposes (None in USA).

In June 1995, the Medicines Control Agency (MCA) in United Kingdom granted approval for a NIR method for the identification and assay of Zovirax® (acyclovir) tablets, which believed to be the first official approval for NIR granted by the MCA as an assay method for tablets. The use of NIR as an alternative method for identification, assay, and determination of moisture content of paracetamol (acetaminophen) tablets was approved in Norway.

NIR spectroscopy as analytical tool in view of the USFDA – Initiative on PAT

The production of pharmaceutical dosage forms is usually a multistage operation, consisting of several validated processes. Quality assurance, including decisions concerning the satisfactory completion of each unit operation, is actually based on off-line testing to document quality of a small, nominally random product sample. Final parameters of pharmaceutical products are also carried out using off-line analytical techniques. This approach is often very time consuming and significantly lengthens the manufacturing cycle, since it requires the process to be stopped during sample removal, data generation and documentation.

In addition, off-line testing does not assure zero defect product quality, since risk assessment and risk management are not included for example, critical process parameters and material performance attributes may not be identified (Reich, 2005). In view of this undesirable situation for pharmaceutical industry and public health, it has been recognized that new testing paradigms are required to succeed in both, an increase in manufacturing efficiency and product safety.

The Process Analytical Technology (PAT) initiative, driven by the United States Food and Drug Administration (USFDA) and major pharmaceutical companies, might be a solution for current situation (Reich, 2005). PAT is a challenging approach intended to assist the progression of real-time or parametric release and quality-by-design concepts by providing an opportunity to move from the laboratory-based off-line testing to a continuous quality assurance paradigm. According to recently published USFDA-guidance for industry, PATs are defined as systems for real-time monitoring and control of critical process parameters and material performance attributes. PAT helps to improve process understanding, manufacturing cycle time, and final product quality (Cogdill et al., 2004).

NIR spectroscopy and imaging may be one of the major PAT tools, since these techniques are well-suited for at-line, in-line and on-line measurements. They can provide a wealth of chemical and physical information important for measuring process performance and open up opportunities to move forward from conventional quality control concepts to process qualification and product conformity.
testing (Reich, 2005). Although a number of challenges concerning hardware design and regulatory approval must be overcome to realize the full potential of NIR spectroscopy and imaging as PAT tools, it may be expected that parametric or even real-time release concepts may be well assisted by the use of NIR techniques.

**Summary**

Oral route is still a most preferred route with majority of oral drug product available in form of tablets (Jain *et al.*, 2015a; Singh and Kim, 2002). The NIR technology has several benefits that can be effectively utilized for pharmaceutical drug product evaluation. However, it is still not widely used in tablet evaluation. However, considering that regulatory authorities require more accurate data for tablet properties, NIR technology can be of great benefit.

**References**

1. Blanco, M., M. Alcalá, J.M. González, and E. Torras. “A process analytical technology approach based on near infrared spectroscopy: tablet hardness, content uniformity, and dissolution test measurements of intact tablets.” Journal of pharmaceutical sciences 95 (2006): 2137-2144. Print.

2. Blanco, M. and I. Villarroya. “NIR spectroscopy: a rapid-response analytical tool.” TrAC Trends in Analytical Chemistry 21 (2002): 240-250. Print.

3. Cogdill, R.P., C. A. Anderson, and J. Drennen. “Using NIR spectroscopy as an integrated PAT tool.” Spectroscopy 19 (2004): 104-109. Print.

4. Dangere, P., R. Gilhotra, and S. Dhole. “Formulation and statistical optimization of self-microemulsifying drug delivery system of eprosartan mesylate for improvement of oral bioavailability.” Drug delivery and translational research 6 (2016): 610-621. Print.

5. Dyrbø, M., S.B. Engelsen, L. Norgaard, M. Bruhn, and L. Landsberg-Nielsen. 2002. “Chemometric quantitation of the active substance (containing C≡ N) in a pharmaceutical tablet using near-infrared (NIR) transmittance and NIR FT-Raman spectra.” Applied Spectroscopy 56 (2002): 579-585. Print.

6. Elzoghby, A.O., B.Z. Vranic, W.M. Samy, N. A. Elgindy. “Swellable floating tablet based on spray-dried casein nanoparticles: Near-infrared spectral characterization and floating matrix evaluation”. International journal of pharmaceutics 491 (2015): 113-122. Print.

7. Jain, S. “Quality by design (QBD): a comprehensive understanding of implementation and challenges in pharmaceuticals development.” Int. J. Pharm. Pharm. Sci. 6 (2014): 29-35. Print.

8. Jain, S., N. Patel, and S. Lin, “Solubility and dissolution enhancement strategies: current understanding and recent trends.” Drug development and industrial pharmacy 41 (2015a): 875-887. Print.

9. Jain, S., N. Patel, P. Madan, and S. Lin. “Quality by design approach for formulation, evaluation and statistical optimization of diclofenac-loaded ethosomes via transdermal route.” Pharmaceutical development and technology 20 (2015b): 473-489. Print.

10. Moes, J.J., M.M. Ruijken, E. Gout, H. W. Frijlink, and M. I. Ugwoke. “Application of process analytical technology in tablet process development using NIR spectroscopy: blend uniformity, content uniformity and coating thickness measurements.” International journal of pharmaceutics 357 (2008a): 108-118. Print.

11. Moes, J.J., Ruijken, M.M., Gout, E., Frijlink, H.W., and Ugwoke, M.I. “Application of process analytical technology in tablet process development using NIR spectroscopy: Blend uniformity, content uniformity and coating thickness measurements.” International journal of pharmaceutics 357 (2008b): 108-118. Print.

12. Morisseau, K.M. and C. T. Rhodes. “Near-infrared spectroscopy as a nondestructive alternative to conventional tablet hardness testing.” Pharmaceutical research 14 (1997): 108-111. Print.

13. Otsuka, M., H. Tanabe, K. Osaki, K. Otsuka, and Y. Ozaki. 2007. “Chemoinformetrical evaluation of dissolution property of indomethacin tablets by near-infrared spectroscopy.” Journal of pharmaceutical sciences 96 (2007): 788-801. Print.

14. Otsuka, M., and I. Yamane. “Prediction of tablet properties based on near infrared spectra of raw mixed powders by chemometrics: Scale-up factor of blending and tableting processes.” Journal of pharmaceutical sciences 98 (2009): 4296-4305. Print.
15. Parashar, B., A. Chauhan, D. Prashar, A. Chandel, H. Kumar, and R. Purohit. “Formulation and evaluation aspects of tablets-An overview.” Am J PharmTech Res 2 (2012): 2249-3387. Print.

16. Pasquini, C. “Near infrared spectroscopy: fundamentals, practical aspects and analytical applications.” Journal of the Brazilian Chemical Society 14 (2003): 198-219. Print.

17. Patel, N., S. Jain, P. Madan, and S. Lin. “Influence of electronic and formulation variables on transdermal iontophoresis of tacrine hydrochloride. Pharmaceutical development and technology” 20 (2015): 442-457. Print.

18. Patel, N., S. Jain, P. Madan, S. Lin. “Application of design of experiments for formulation development and mechanistic evaluation of iontophoretic tacrine hydrochloride delivery.” Drug development and industrial pharmacy 42 (2016): 1894-1902. Print.

19. Reich, G. “Near-infrared spectroscopy and imaging: basic principles and pharmaceutical applications.” Advanced drug delivery reviews 57 (2005): 1109-1143. Print.

20. Roggo, Y., P. Chalus, L. Maurer, C. Lema-Martinez, A. Edmond, and N. Jent. “A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies.” Journal of pharmaceutical and biomedical analysis 44 (2007): 683-700. Print.

21. Shah, M.K., P. Madan, and S. Lin. “Preparation, in vitro evaluation and statistical optimization of carvedilol-loaded solid lipid nanoparticles for lymphatic absorption via oral administration.” Pharmaceutical development and technology 19 (2014): 475-485. Print.

22. Singh, B.N., and K.H. Kim. Drug delivery-oral route. Encyclopedia of pharmaceutical technology 1 (2002). Print.

23. Soroushnia, A., F. Ganji, and S.M. Taghizadeh. “Transdermal Delivery of Desmopressin Acetate from Water-in-Oil Nano/submicron Emulsion Systems.” Iranian Journal of Chemical Engineering 13 (2016): 1-13. Print.

Source of support: Nil
Conflict of interest: None Declared