Near-Infrared Spectroscopy for Nondestructive Evaluation of Tablets

Javed Ali, Pramod K, SH Ansari

Departments of Pharmaceutics and ¹Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, New Delhi, India

Introduction

Evaluations of a pharmaceutical product are an essential and mandatory criterion to assess and confirm the quality of a product to be used by the patients. Nondestructive evaluation techniques are always considered to be advantageous to destructive analytical techniques. A rapid and simple nondestructive technique can be used for the in-process evaluation of a pharmaceutical product. This can be helpful in achieving the goals of process analytical technology (PAT). Chemical and physical information of virtually any matrix can be extracted using near-infrared (NIR) spectroscopy and imaging. Multivariate data analysis combined with these methods can be used for exploring both qualitative and quantitative data. NIR spectroscopy has been a very interesting area of research for the development, optimization, and monitoring of the process being studied. The possible pharmaceutical applications of NIR spectroscopy include identification, determination of composition, moisture content determination, detection of impurities, checking of homogeneity of blending, etc. For NIR spectroscopy, data calibration is required using the measurement of the property being studied. The calibration models developed should be robust enough.

Near-infrared spectroscopy

The near-IR region of the electromagnetic spectrum comprises the wavelength range of about 800-2500 nm. Molecular overtone and combination vibrations form the basis for this method. The molar absorptivity in the near-IR region is very small as these transitions are forbidden. But the near-IR has a good penetration power than mid-infrared radiation. Thus though it is not a sensitive technique, it can be used for the evaluation of bulk materials. Another advantage is that this technique requires no sample preparation in most cases. The broad nature of the molecular overtone and combination bands in the near-IR results in complex spectra. This makes it difficult to assign specific features to specific chemical components. Principal component analysis or partial least squares are mainly used as a multiple wavelength (multivariate) calibration technique. This helps in understanding the chemical details. The application of near-IR analytical method is mainly dependent upon two key factors - the calibration samples and calibration technique.

Instrumentation

The instrumentation mainly consists of a source, a detector, and a dispersive element. Incandescent, quartz halogen light bulbs, light-emitting diodes, etc. are also used as a source of near-IR radiation. Silicon-based charge-coupled devices, indium gallium arsenide devices, and lead sulfide devices are mostly used as detectors. A 2D array detector with an acousto-optic tunable filter is used in instruments used for chemical imaging. Diffracting gratings are
mainly used for the purpose of dispersion of the radiation though prism is also used.\[3\]

**Measurement and data analysis**

Transmission mode and reflectance mode measurements are possible with NIR spectroscopy depending upon the positioning of the sample and the detector.\[4\] The ratio of the intensity of radiation that passes through the sample to the intensity of radiation falling on it is called as transmission whereas the ratio of the intensity of radiation reflected by the sample to the intensity of radiation falling on it is called as reflectance. The process of diffuse reflectance involves the re-emergence radiation after penetration into the bulk of the sample and undergoing multiple reflections within the sample substance. For the evaluation of solid samples like tablets, mainly reflectance spectroscopy is used. NIR spectra are complex with multiple broad overlapping peaks. This necessitated the use of chemometric data processing to gather sample properties from spectral information.\[5\] Iyer et al. have carried out comparative studies of the reflectance and transmittance methodologies for the evaluation of tablets. The study results showed that both methods might be sensitive to sample inhomogeneity and that transmittance measurements are sensitive to path length variations.\[6\] Typically to correct collinearity and the typically poor selectivity of NIR spectra, multivariate models are used though some researchers were able to develop a univariate calibration model for pharmaceutical analysis based on NIR spectra.\[7\]

**Near-infrared imaging**

Digital imaging with the attributes of spectroscopic measurements is possible with chemical imaging techniques. The measurement of the photon interacting with a molecule or matter is involved in vibrational spectroscopy as in NIR spectroscopy. A pattern of absorption of photons of specific energy is obtained as a result of absorption or scattering of these photons by the interacting molecules. This obtained pattern in chemical imaging provides spatial or chemical information about the sample. An illumination source, an imaging optic, a spectral encoder selecting the wavelengths and a focal plane array are the basic instrumental requirements for this technique. The resulting data are recorded as a series of images. Even coating layers on a tablet can be visualized by this technique.\[8\]

**Applications**

Near-IR finds its major applications in food and drug industry, combustion products, medicine, and astronomical spectroscopy. It is used in studying the atmospheres of cool stars. It can be used for remote monitoring of plants and soils. Its medical uses include noninvasive measurement of the amount and oxygen content of hemoglobin, noninvasive assessment of brain function, NIR imaging or functional NIR imaging, oximetry (determination of blood flow, volume, and oxygenation), etc. Particle size measurement can also be carried out by NIR spectroscopy. The application of near-IR, though established, is still in its infancy for its utility in the pharmaceutical industry. Near-IR has been proposed as an in-process real time test for tablets by FDA.\[9\] Major pharmaceutical applications include identification of actives/exciipients, moisture determination in samples, determination of blend uniformity, determination of particle size, quantification of actives/exciipients, etc. The following sections describe in detail about the application of near-IR for the nondestructive evaluation of tablets.

**Evaluation of tablets**

**Tablet hardness**

The use of near-IR as a nondestructive method of tablet hardness has been reported first in 1991.\[10\] Later on so many studies were reported for the quantitative and qualitative evaluation of tablet hardness. NIR spectrum can be obtained by the determination of absorbance (inversely proportional to reflectance, R) as a function of wavelength or wave number. A change in the slope of the best fit line of the spectrum can be used for the determination of tablet hardness. This approach is based on the established fact that changes in tablet hardness cause a variation in the slope of the baseline of the NIR spectra. Figure 1 displays a schematic representation of NIR spectra of tablet samples with the same composition but with different hardness. The straight lines represent the regression line of the corresponding spectrum. Sample positioning also affects the baseline of the spectrum. So it is of importance to take due care to maintain same sample positioning during the analysis of all samples.

The calibration of the method involves the laboratory determination of tablet hardness and fitting each spectrum with a regression line. Then a plot is prepared using the slopes of the regression lines versus the corresponding hardness of the tablets using a mechanical hardness tester by a destructive technique. Using this calibration plot the tablet hardness is predicted from the slope of the NIR spectra of the tablet sample. Figure 2 displays a schematic representation of a typical calibration curve for the determination of tablet hardness using NIR spectroscopy. The standard error of calibration and standard error of prediction should be small and almost same for a robust calibration model.

Kirsch et al. proposed a new algorithm for testing tablet hardness using near-IR spectroscopy. They carried out their study in cimetidine-containing tablets. Different tablets having 1-20% w/w of cimetidine were used. Both tablet hardness and sample positioning were found to affect the spectral baseline. A destructive diametral crushing test was carried out on each tablet using a calibrated

![Figure 1: Schematic NIR spectra of tablets of same composition but with different hardness values (Hardness: ......Highest _____Medium _____Lowest)](image-url)
hardness tester, after recording the spectra from the unscored face of the tablets. The study was carried out using excipients showing plastic deformation (sodium chloride and microcrystalline cellulose) and brittle fracture (dibasic calcium phosphate dihydrate and lactose). After compression of the blends, one punch was removed and a fiber-optic probe was inserted into the die and the NIR spectra were recorded. Principal component analysis/principal component regression and spectral best-fit method were compared using two different approaches. In one approach, the data from the group of a particular potency of cimetidine were used to predict the hardness of the tablets in the other potency groups. In the second approach, the data from half of the group of a particular potency of cimetidine were used to predict the hardness of the rest of the tablets in that particular potency group. The standard error of calibration and the standard error of prediction were used for the comparison and evaluation of the data. The spectral best-fit method was compared to the established multivariate principal component analysis/principal component regression method. The results showed that the spectral best-fit method was easier to develop and can be used for the determination of tablet hardness using NIR spectroscopy. The spectral best-fit method was also found to be applicable for a wide range of drug concentration.

Donoso et al. determined tablet hardness using NIR diffuse reflectance method. Seven theophylline tablets with different hardness values were used in their study for developing a model equation, validating the model and testing the model predictive ability. Placebo tablets with different hardness values were also prepared for the study for evaluation. The relationship between tablet hardness and the NIR spectra were evaluated using linear regression, and quadratic, cubic, and partial least-squares methods. The study results suggested that NIR absorbance was increased as the tablet hardness increased. The predicted values using the models were found to be in agreement with the experimental values using destructive evaluation of the tablets by a hardness tester. They concluded that the NIR diffuse reflectance method could be an alternative for the destructive testing of tablet hardness.

Morisseau et al. evaluated and quantified the effect of compression force on tablet hardness using NIR spectroscopy. They used drug-containing formulations and one placebo formulation for their study. Two formulations each were of hydrochlorothiazide (15% and 20%) and chlorpheniramine maleate (2% and 6%). The placebo was prepared out of microcrystalline cellulose and magnesium stearate.

The NIR reflectance data were compared to the destructive hardness test data using multiple linear regression and partial least-squares regression methods. They correlated these data and showed that the increased tablet hardness caused by the increased compression force resulted in an increased absorbance of NIR radiation. The study results revealed that the NIR spectroscopic evaluation was as precise as the hardness tester in determining the tablet hardness.

Ebube et al. investigated the application of diffuse reflectance NIR spectroscopy for the determination of hardness of three different grades of microcrystalline cellulose. Tablets of different hardnesses have been prepared by varying the compression force from 0.2 to 1.2 tons. The partial least-squares technique was employed for the prediction of tablet hardness. The error of prediction was found to be 8.8%, 5.3%, and 4.6% for MCC PH 101, MCC PH 102, and MCC PH 200, respectively.

Otsuka et al. used NIR chemometrics to study the effect of lubricant mixing on tablet hardness. Two formulations were prepared for the evaluation. The first formulation contained sulpyrine, microcrystalline cellulose, and magnesium stearate whereas the second formulation contained sulpyrine, spray-dried lactose, corn starch, and magnesium stearate. Blends of the above two formulations without a lubricant (magnesium stearate) were prepared. Finally the blends were lubricated by mixing with magnesium stearate for various mixing times. A reflection-type Fourier transform NIR (FT-NIR) spectrum spectrometer was used for recording the spectra of the blend samples. A principal component regression technique was employed for evaluation. All the NIR spectra showed change with the lubricant mixing time. The evaluated blends were compressed and hardness was checked. Their study results showed that the tablet hardness decreased with the increasing mixing time. They concluded that the evaluation of tablet blends using NIR spectroscopy prior to compression can be used for predicting the hardness of the tablets after compression which in turn helps in assuring the product quality.

Chen et al. evaluated the possibility of predicting hardness of tablets using artificial neural networks and NIR spectroscopy. The tablet formulation contained microcrystalline cellulose and magnesium stearate. Different tablet hardness values were obtained by varying the compression force from 0.4 to 1 ton. Two sets of tablets were prepared for each hardness value and one set was used for generating the models whereas the other set was used as a test sample for the evaluation of prediction of tablet hardness. Artificial neural network and partial least-squares models were used to predict the hardness of tablets. They found that artificial neural network calibration models can be used as a powerful tool for the analysis of NIR data.

Otsuka et al. evaluated the effect of the scale-up factor of blending and tableting processes using NIR spectroscopy. They prepared tablets containing sulpyrine, microcrystalline cellulose, and 1% magnesium stearate both in lab-scale and plot-scale. Principal component regression was used for data evaluation. They observed that in both the cases, tablet hardness decreased as the mixing time increased.

Otsuka et al. evaluated the effect of the amount of water used for granulation on tablet hardness. They prepared granules using antipyrine, hydroxypropylcellulose, lactose, and potato starch. Granulation was done with water in varying quantities from 11% to 19% w/w. The calibration model was prepared using principal component regression using the data obtained from tablet hardness and NIR spectra. The hardness of tablets was found to decrease as the quantity of added water increased. The correlation coefficient
for the prediction of tablet hardness was observed to be 0.8064. Thus from their study they concluded that that the chemometric evaluation of tablet granules by NIR spectroscopy can be used for predicting resultant tablet hardness.[16]

Tanabe et al. evaluated the use of NIR spectroscopy to predict tablet hardness by principal component regression analysis. The study was conducted on tablets formulated from berberine chloride, lactose, and potato starch. The tablet weight was 800 mg and the diameter was 8 mm. Tablets of different hardnesses were obtained by varying the compression pressure from 59 to 195 MPa. The reflectance NIR data and the corresponding tablet hardness data were used for preparing a calibration for further predicting the hardness of test samples. Principal component regression analysis was carried out for the study. The Pearson product moment correlation coefficient was found to be 0.925 between the actual and predicted tablet hardness values.[16]

**Disintegration time**

From the results of the studies on the effect of tablet hardness, it is clear that as the tablet hardness increases the NIR absorbance of the samples also increases. As increased tablet hardness is indicative of the increased tablet disintegration time, NIR spectroscopy can provide useful information on tablet disintegration by measuring the NIR spectrum. A calibration model has to be generated for this purpose. Donoso et al. evaluated the application of NIR reflectance spectroscopy for the determination of the disintegration time. Seven theophylline tablets of different disintegration times were prepared by varying the compression force while keeping the tablet composition same. Five placebo formulations with different disintegration times were also prepared for the study. They used linear regression, and quadratic, cubic, and partial least-squares methods for establishing a relationship between the laboratory tablet disintegration time and the NIR absorbance and found that an increased NIR absorbance caused an increased disintegration time.[17]

**Dissolution**

The dissolution profiles of tablets are found to be inversely proportional to their NIR absorbance. NIR diffuse reflectance spectroscopy can be used for the prediction of drug dissolution. Donoso et al. established this in their study using theophylline tablets. Seven different release rates were obtained by varying the compression force. The compositions of all the tablets were kept same. They calibrated the NIR data with the results of laboratory dissolution tests. They developed model equations and the results revealed that the increased absorbance of NIR radiation of a sample is indicative of a reduced tablet dissolution.[16]

Freitas et al. evaluated 10 different formulations of clonazepam tablets varying in excipient content. Three dissolution media were employed for the study. Seven dissolution times were chosen in the study using conventional dissolution apparatus and HPLC analysis of the dissolution samples. Multivariate analysis using the partial least-squares regression was used for the correlation between the dissolution data and NIR spectra. The study results revealed that this nondestructive method using NIR can be used for the dissolution study of tablets.[19]

The above study results can be assumed due to the increased hardness as a result of increased compression force. Thus the samples show increased NIR absorbance due to close packing of the particles.

**Identification and quantification of actives and excipients**

Pharmaceutical actives and excipients can be identified with the help of an NIR spectrum. The NIR spectrum consisting of a plot of absorbance versus wave number or wavelength will be unique for a compound with definite absorption peaks. The particle size of pharmaceutical excipients and thus their grades accordingly can be determined by checking the spectral reflectance baseline and the absorbance peaks. A reduction in particle size causes decreased absorbance resulting from increased light scattering. Figure 3 shows the schematic NIR spectra of three different concentrations of an active/excipient in a tablet formulation. A significant change in the absorbance values is observed in the characteristic region of the particular compound.

A second-derivative spectrum is also useful in the identification and quantification of a compound. The intensity of the band at specific wavelengths characteristic to the compound could be observed to have been changed as its quantity changes in the sample being analyzed. This forms the basis for the quantification of actives and excipients using NIR spectroscopy. A calibration curve can be prepared using these derivative spectra and can be used for the prediction of drug content in tablet samples.

A simultaneous determination of the identification and composition of tablets was carried out by Malik et al. using NIR spectrometry. Aspirin tablets were taken for their study. The tablets were packed in a blister package. A hole was punched through the foil backing. Through this hole the tablets were exposed to water vapor or a pH 9.0 ammonium hydroxide solution. The salicylic acid content and water absorption were determined in the study using NIR spectrometry. The salicylic acid content and water absorption were also determined by HPLC analysis and weighing, respectively. They prepared a calibration curve for the water absorption and salicylic acid content from the obtained data. They used an IRC-160 InSb focal plane array video camera with a NIR bandpass cold filter for the 0.5-m multispectral imaging of the tablet samples. Imaging with the bootstrap error-adjusted single-sample technique (BEST) was carried out in their study. The study results showed

![Figure 3: Schematic NIR spectra of three different concentrations of an active/excipient in a tablet formulation (Drug content: ...Highest — Medium — Lowest)](image)
the technique to be very fast (approximately 1000 times) and the precision to be very close to that obtained by spectrometric analysis of single tablets. Multispectral imaging enabled simultaneous analysis of a large number of samples.\textsuperscript{[89]}

The application of a combination of chemometrics with NIR spectroscopy has been demonstrated by Jedvert et al. They compared the results with those obtained with liquid chromatography. The NIR spectroscopic method was found to be equally good as liquid chromatography and demonstrated a good stability. They could analyze the sample even after 1.5 years after applying baseline correction.\textsuperscript{[90]} Bhowmik et al. have demonstrated the suitability of reflectance NIR spectroscopy for pharmaceutical process monitoring by carrying out quantitative analysis of an active ingredient in different production steps of tablet formulation.\textsuperscript{[91]}

Meza et al. determined the drug content in a low-dosage formulation by transmission NIR spectroscopy. Ibuprofen concentrations of 0.5%, 0.7%, and 1.0% (m/m) were selected for the study. Microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate were used for the preparation of tablets. A multipurpose analyzer FT-NIR spectrometer was used for the recording of transmission spectra. The drug content was estimated by a validated UV method. A calibration model was developed using partial least-squares regression from the data obtained for 110 tablets. The accuracy, repeatability, intermediate precision, and linearity of the method were evaluated and found to be satisfactory. The results obtained indicated FT-NIR transmission spectroscopy to be industrially applicable to facilitate process development and optimization. They suggested that the method can be used for a large number of tablets during process development and detect drug agglomeration problems.\textsuperscript{[92]}

Ricci et al. developed a method for the identification of counterfeit medicines in blister packs by a combination of spatially offset Raman spectroscopy (SORS) and attenuated total reflection FTIR (ATR-FTIR) imaging. They carried out their study in genuine and fake artesunate antimalarial tablets. They also claimed the method to be useful for forensic investigation of counterfeit medicines.\textsuperscript{[93]}

Rapid infrared spectroscopic determinations of vitamin C in food and pharmaceutical products have been carried out by Yang and Irudayaraj. NIR, FT-NIR, and FTIR-ATR were studied for the quantification of vitamin C in powdered mixtures and solutions. Correlation coefficient ($r^2$) values 0.988, 0.992, and 0.999 were obtained for the developed methods using NIR, FT-NIR, and FTIR-ATR, respectively. The methods were found to be highly useful for the quantification of vitamin C.\textsuperscript{[94]}

Ebube et al. evaluated a method using NIR spectroscopy as a nondestructive technique to differentiate three microcrystalline cellulose forms in powdered form and in compressed tablets. Avicel\textsuperscript{®} grades PH-101, PH-102, and PH-200 were evaluated in their study. The developed technique was able to identify both in powdered form and in compressed tablets the three different Avicel\textsuperscript{®} grades. The result was not affected by the presence of a lubricant, magnesium stearate. They also successfully developed a method for the determination of magnesium stearate by a multiple linear regression method.\textsuperscript{[95]}

Chen et al. predicted theophylline content of intact tablets by NIR spectroscopy. Artificial neural network and partial least-squares models were used to predict the drug content. A better prediction of drug content was observed with a partial least-squares model than with an artificial neural network model for drug content greater than or equal to 5% w/w whereas the artificial neural network model showed good results than the partial least-squares model at less than or equal to 2% w/w theophylline content.\textsuperscript{[96]}

Rapid screening of counterfeit drugs is possible with a combination of qualitative and quantitative NIR analysis and was demonstrated by Lei et al. in their study with vitamin tablets. They identified NIRs as an excellent screening method for the detection of counterfeit drugs.\textsuperscript{[97]}

The application of a portable NIR spectrometer for the authentication of tablets and the detection of counterfeit samples has also been demonstrated by O’Neil et al.\textsuperscript{[98]}

**Tablet-coating process**

Romer et al. developed a calibration model using NIR spectroscopy for the in-line prediction of the coating layer thickness of tablets. The developed method was for a small-scale coating process using a side-vented drum coater. Flat-faced tablets of high-density polyethylene were used for the study and the coating was carried out using a suspension of Kollicoat IR and Kollicoat SR 30D. The film thickness was determined using a digital micrometer. A calibration model was developed using partial least-squares regression. It was observed that the model was able to predict the final coating thickness as accurate as a digital micrometer for biconvex high-density polyethylene tablets coated with the same suspension.\textsuperscript{[99]}

Maurer et al. evaluated the film coating process of a tablet by a nondestructive method using NIR. NIR was able distinguish inter- and intratablet differences by demonstrating different absorbance values. The method was also able to detect small coating defects. NIR spectroscopy obtained good results at thinner coating layers and displayed a higher spatial resolution.\textsuperscript{[100]}

The at-line determination of the amount of the polymer coat applied to tablet cores was carried out by Kirsch et al. NIR reflectance spectroscopy was used to evaluate the effect of coating composition. Tablets with ethylcellulose- or hydroxypropylmethylcellulose-based coating were evaluated at regular intervals during each coating run by NIR reflectance spectra. Multiplicative scatter correction or second-derivative calculations, and calibrations developed using either principal components or multiple spectral wavelengths were employed for the preprocessing of the spectra. The study results revealed that the film coating process can be successfully monitored using NIR reflectance spectroscopy.\textsuperscript{[101]}

Real time measurements made using a diffuse reflectance NIR probe was evaluated for the in-line analysis of the film coating thickness on tablets during a pan coating operation by Perez-Ramos et al. They carried out their study in sulfanilamide tablets which contained microcrystalline cellulose and anhydrous lactose as diluents and magnesium stearate as lubricant. The aqueous coating solution was prepared out of hydroxypropyl methylcellulose (10% w/w) and polyethylene glycol (1% w/w). Accela-Cota pan coater (24-in. diameter) was used for the film coating experiments. By checking the increase in the characteristic bands of a coating component and decrease in the characteristic bands of a tablet core component, they determined the film coat thickness. A good correlation was obtained between the estimated values and those obtained by using a digital micrometer. The method was explained to be very useful in that the coating process can be stopped whenever desired thickness is achieved.\textsuperscript{[102]}

**Process analytical technology and tablet evaluation by NIR**

The NIR spectroscopic method can be used as a routine technique for the monitoring of a manufacturing process and as a real time release testing. This technique is very useful in establishing a
valid process analytical technology.[32] The technique is a valid PAT tool for the rapid characterization of pharmaceutical tablet quality.[33] ICH Q8 (R1) guidelines have mentioned the possible use of NIR spectroscopy for real time release testing of tablets such as weight variation.[34] The guideline described the method to be superior to compendia end-product testing. Moes et al. developed NIR spectroscopic method as a process analytical technique to monitor the blend homogeneity, content uniformity of tablets, and tablet coating thickness. The developed method was able to accurately determine the drug concentration changes during blending. Blend homogeneity was found to be reached within 2 min of the blending step. They observed that the model based on reflectance spectra was more accurate in predicting coating thickness than that on transmission spectra.[33]

Conclusion

The nondestructive evaluation of tablets using the NIR technique has been studied in detail as an alternative for the current methods of evaluation. The increased hardness of tablets was found to cause increased absorbance of NIR radiation. Dissolution and disintegration time were also found to be quantitatively related to the absorbance of NIR radiation as these parameters are caused by a direct effect of tablet hardness. The identification and quantification of drugs and excipients were also found to be possible from the previously reported research works. Tablet coating processes were also found to be easily monitored with this technique. Various statistical techniques and software are reported to be useful for carrying out this technique. NIR spectroscopy is considered to be of high importance in terms of process analytical technology and is gaining wide acceptance as a rapid and simple real time in-process testing. The suitability of this technique even after packaging renders it highest suitability for pharmaceutical evaluation. It is also suitable for routine quality control of tablets.

Acknowledgements

Mr. Pramod K (Ph.D. Scholar) would like to thank National Medical Library, New Delhi, India, for providing library facility.

References


Source of Support: Nil, Conflict of Interest: None declared.