A Review On Near Infrared Spectroscopy And Its Application In Tablet Evaluation

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Abstract- *Near infrared is attracting growing interest in pharmaceutical analysis by virtue its ability to provide a wealth of information from a single sample. 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 basics, advantages, limitation and pharmaceutical application of near infrared spectroscopy. Its also involve example of measuring modules for different sampling systems. A nondestructive evaluation of tablets is possible with the application of near-infrared spectroscopy and appropriate statistical techniques. Tablet hardness, content uniformity, dissolution, etc. are possible with the help of near-infrared spectroscopy. The established methods using this technique are rapid and simple. The technique also has found its place in quality assurance and quality control of tablets.*

Keywords- Near Infrared Spectroscopy, Pharmaceutical, Tablet evaluation, Spectroscopy.

I. BASICS OF NEAR INFRARED SPECTROSCOPY[1]

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.

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.

II. PRINCIPLE OF NEAR INFRARED SPECTROSCOPY[2,3]

The record of NIR region of the electromagnetic spectrum involves the response of the molecular bonds O=H, C=H, C=O, N=H. These are subjected to vibrational energy changes when irradiated by NIR frequencies, and two vibration patterns exist in these bonds including stretch vibration and bent vibration. The energy absorption of organic molecules in NIR region occurs when molecules vibrate or is translated into an absorption spectrum within the NIR spectrometer. These special bonds also play an important part in the field of chemical food chemical analysis, and could extract information to analyze the chemical structures.

The NIR region mainly contains overtones and combination bands that are due to hydrogen (CH, OH, NH) vibrations. These overtones and combination bands are called secondary vibrations and are weaker than the fundamental vibrations. Therefore, the molar absorptivity 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 absorptivity 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. Thus, interpretation of NIR spectra is usually combined with mathematical and statistical methods such as chemometrics methods in order to extract the necessary information.

III. INSTRUMENTATION OF NEAR INFRARED SPECTROSCOPY[1,4]

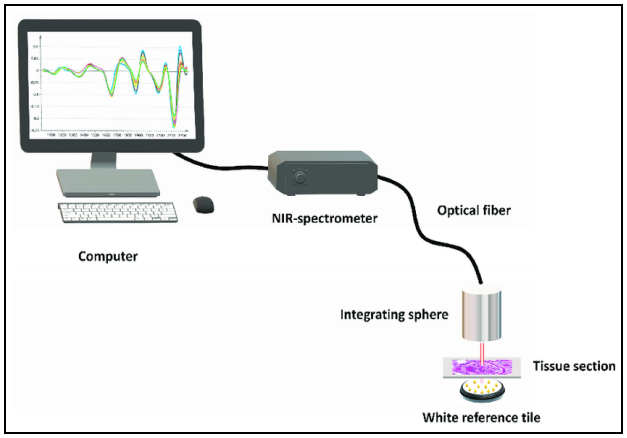

Figure 1: Instrumentation of Near Infrared Spectroscopy

A NIR spectrophotometer can be assembled with optical components employed for UV-Visible instruments. This fact imparts a lower cost to the NIR instrument, when compared with the mid-infrared (MIR) spectrophotometer. When necessary, as when a long optical guide needs to be employed to probe a distant sample, low OH containing materials should be employed. Furthermore, the instrument is, overall, more robust because its optical parts are not harmed by environmental humidity. MIR instruments, at present, have similar characteristics but they are far more expensive.

The most frequently employed detectors for the NIR spectral region are based on silicon, PbS and InGaAs photoconductive materials. In particular, the latter possess a very high detectivity (D*) and a very high response speed. Together with high powered radiation sources (a tungsten coil or a halogen lamp is employed by the majority of manufacturers) these detectors can impart a very high signal-to-noise ratio for NIR measurements. This fact partially compensates for the lower intensities of NIR absorption bands.

Table 1: NIR Instrument Classification Based on Wavelength Selection Technology

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I. Filter Instruments
Fabri-Perrot (interference)
Acousto-Optic Tunable Filter (AOTF)
II. LED source self band selection instruments
III. Dispersive
Grating - Plane or Concave
Single Beam
Dual Beam
Multichannel (detector array)
Multiplexed (Hadamard)
IV. Interferometric (Fourier Transform)

IV. BENEFITS OF NEAR INFRARED SPECTROSCOPY[5]

1. Save analysis time, faster time to market

   - Results in seconds
   - No sample preparation – analyze samples as-is
   - Multiparameters measured simultaneously

2. Improved product quality and manufacturing efficiency

   - Quality of product can be controlled during all steps of manufacturing
   - Fast analysis, real-time monitoring increases productivity and efficiency

3. Greater and faster return on investment

   - No reagents, no waste – reduced analysis cost and no waste disposal
   - Versatile analyzer –many possible applications

V. LIMITATION OF NEAR INFRARED SPECTROSCOPY[5]

- Secondary method (requires calibration against reference method)
- Dependence on a large reference set
- Influence of sample morphology
- Slow and costly method development
- Need for quantitative calibration model
- Troublesome calibration transfer
- Strict sample temperature control required
- Spectroscopic complexity (lack of specificity; no characteristic absorption bands)
- Lack in structural interpretative value (difficult to identify unknowns)
- Lack of reference data
- Need for sophisticated data evaluation algorithms (heavy computation load)
- Weak sensitivity to minor components: minimum concentration &get; 0.1% (no trace analysis)

VI. APPLICTION OF NEAR INFRARED SPECTROSCOPY IN PHARMACEUTICAL[6,7]

NIR spectroscopy has been utilized in the pharmaceutical industry for many years and is recognized by international pharmacopeias like the United State Pharmacopeia (USP), European Pharmacopoeia and Japanese Pharmacopoeia (JP). NIR applications can be implemented into several Pharmaceutical processes, from raw materials, to in-process monitoring and control to final product release.

1. Raw materials inspection

   - Compliant to GMP regulations, 100% testing of all incoming raw material containers
   - Identification of incoming raw materials
   - Specification control of raw material quality

2. Quality control of intermediate products

- Less out-of-spec products manufactured, less re-work time
- Determination of blend homogeneity
- Detect the effects of granulation time
- Real-time monitoring of drying process

3. Quality assurance of finished products

- Faster result without sample preparation and reduced workload of reference methods
- Determination of content uniformity
- Moisture determination in lyophilized products without destroying the sample vial
- Determination of active ingredients
- Counterfeit drugs detection

VII. DIFFERENT NIR MEASUREMENT METHOD FOR DIFFERENT TYPES OF SAMPLE[8]

NIR spectroscopy can be used to analyse different types of samples. Choosing the right measurement method, sampling module, and accessories is the most important step to developing robust NIR methods.

1. Diffuse reflection

- NIR light penetrates into the sample and interacts with the sample.
- The NIR energy that is not absorbed is reflected back to the detector.
- Suitable to measure solid samples without sample preparation
- Also suitable for Cream, paste, granulates, coarse, fine powders.

2. Diffuse transmission

- NIR light penetrates into the sample and interacts with the sample.
- Due to the particles, the light is scattered throughout the sample.
- The non-absorbed NIR light is transmitted through the sample reaching the detector.
- Suitable to measure solid dosage forms without sample preparation
- Suitable to measure tablets and capsule

3. Transflection

- This measurement method is a combination between transmission and reflection.
- A reflector is placed behind the sample, used to reflect the non-absorbed NIR light back to the detector.
- Suitable for liquid and gel samples

4. Transmission

- The sample is placed between the NIR light source and detector.
- NIR light is transmitted through the sample.
- The non-absorbed NIR energy continues to the detector.
- Suitable for clear liquids, suspensions, and solutions

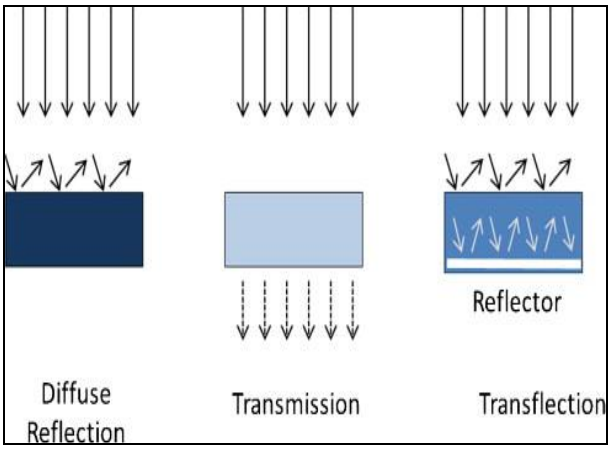

Figure 2: Different NIR Measurement Method for Different Types of Sample

VIII. SAMPLE ARRANGEMENT AND GETTING NIR SPECTRA USING NIRS[4]

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 stores in the data files. Various mathematical and statistical treatments may be applied to extract the information required.

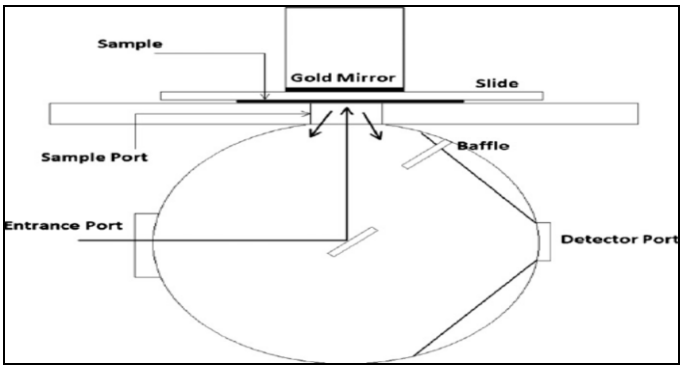

Figure 3: Sample Arrangement and Getting NIR Spectra Using NIRS

IX. QUANTITATIVE AND QUALITATIVE ANALYSIS OF NIR SPECTRAOF SAMPLE[9,10]

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 pharmaceuticals 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 wide 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.

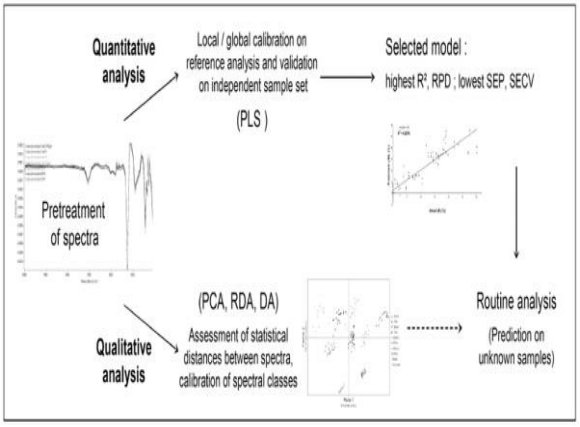

Figure 4: Quantitative and Qualitative Analysis of NIR Spectra of Sample

X. APPLICATION OF NIR SPECTROSCOPY IN EVALUATION OF TABLET PROPERTIES[11,12,13,14]

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.

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. 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 helpful in determining dissolution rate of the tablet with NIRS. Quantitative modelling 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.

A) 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.

B) 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 testes such as the Erweka tester, the Stong-Kobb tester and the Pfizer tester. 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 non-destructively via NIR method throughout the production run, avoiding destruction of tablets that had been ruined by the destructive test). 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.

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. 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 micro porous structure of the tablet due to compression pressure.

C) 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. 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. 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.

XI. EXAMPLES OF MEASURING MODULES FOR DIFFERENT SAMPLING SYSTEMS[15]

1. NIRS XDS Rapid Content, Multi Vial, and NIRS DS2500 Analyzer

   - Measured using diffuse reflectance mode
   - The NIRS XDS Rapid Content Analyzer and the Solids Module offer analysis of any solid form
   - The NIRS XDS Multi Vial Analyzer provides the analysis of a tray of solids in vials
   - The NIRS DS2500 can analyse materials in bags or sample cups, with a rotation feature for nonhomogeneous powder.

2. NIRS XDS Master Lab Analyzer

   - Measured using diffuse transmission
   - The NIRS XDS Master Lab Analyzers perform automated transmission and reflectance analysis of a tray of multiple tablets. Automated reflectance analysis of a tray of multiple vials is also possible
   - Integrated variable spot size for optimized sample illumination

3. NIRS XDS Smart Probe, OptiProbe, and Rapid Content Analyzer

   - Measured using transflection mode
   - The NIRS XDS Rapid Content Analyzer with the liquid sample kit offers liquid analysis using the gold diffuse reflectors
   - The NIRS XDS Interactance OptiProbe and the NIRS XDS Smart Probe offer the immersion probe with high energy mirror for liquid analysis

4. NIRS XDS Rapid Liquid and Transmission OptiProbe Analyzers

   - Measured using transmission mode
   - The NIRS XDS Rapid Liquid Analyzer performs temperature-controlled transmission analysis of liquids in cuvettes or vials up to 65 °C
   - The NIRS XDS Transmission OptiProbe Analyzer is designed for laboratory monitoring of liquids. The optional Vial Heater Module allows more difficult samples to be analyzed up to 200 °C.

XII. ADVANTAGES OF NIR SPECTROSCOPY OVER CONVENTIONAL METHODS USED FOR TABLET EVALUATION[11]

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 laboratory.

XIII. LIMITATION OF NIR SPECTROSCOPY USED FOR TABLET EVALUATION[16]

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 NIR 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, unscored 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

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