

## A Brief Review on NIR Spectroscopy and its Pharmaceutical Applications

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### Abstract

Near-infrared spectroscopy (NIRS) is fast, non-destructive analytical method hence NIRS is suitable for analysis of solid, liquid and pharmaceutical forms. NIRS can also be implemented during pharmaceutical development, for production by process monitoring or in QC laboratories. Based on the principle and range of electromagnetic radiation spectroscopy is classified into several types. In the following review various aspects of NIR its introduction, principle, instrumentation, and its application in pharmaceutical industry have been implemented.

**Keywords:** Near infrared spectroscopy, Regression methods.

Access this article online	
<b>Website:</b>	www.innovativepublication.com
<b>DOI:</b>	10.5958/2394-2797.2016.00018.6

### Introduction

Near-infrared (NIR) spectroscopy is more accurate, less expensive way to capture the imaginations of pharmaceutical analyst and also to perform good quality checks required by the cGMP. NIR has long wavelength which ranges from 700 to 2500 nm, hence it can be widely used to analyses excipients, drug substances and also finished products by the packaging materials. It is a non-destructive method. Which can be used for the examination of production line, which in turn minimizes the usage of destructive testing with great loss of salable product, this helps for the elimination of lag time associated with waiting lab results.<sup>(1)</sup>

Use of NIR can also help in eliminating the quarantine time. Increase of consistency, inventory

requirements and product quality can be reduced by NIR. NIR is sensitive to water as compared to mid infrared radiation. NIR has deeper penetration depth which can be used in probing bulk materials. Hence, can be used for process analysis. The measurement depth of NIR depends on the wavelength, sample presentation, instrument settings, and physical and chemical properties of the sample. The penetration depth is in the range between 0.5–2.4 mm in powders and tablets at wavelengths 1050–1620 nm.<sup>(2)</sup>

### Basic principle of NIR Spectroscopy

NIR identification principle is based on the reason that a material will absorb NIR energy and will transmits or reflects it in a unique pattern according to the physical and chemical characteristics. Hence we can use NIR for both qualitative and quantitative analysis. The in the electromagnetic spectrum NIR region is located at the wavelength range between 780 and 2565 nm and wave number range 12820-3959  $\text{cm}^{-1}$ , hence it covers the wavelength range adjacent to the mid infrared, which may extend to the visible region.<sup>(3)</sup>

$\lambda$	0.1	20	170	400	800	2500	$10^6$	nm
$\nu$	$10^8$	$5 \cdot 10^5$	60000	25000	12500	4000	10	$\text{cm}^{-1}$
	Cosmic and $\lambda$ -rays	X-rays	Vacuum Ultraviolet (UV)	Near Ultraviolet (UV)	Visible	Near Infrared (NIR)	Infrared (IR)	Microwave radio

**Fig. 1: Electromagnetic spectrum**

The sample is irradiated with NIR light source. This light is then absorbed by molecules only when there is change in dipole moment because of molecular vibrations. O-H, N-H, S-H and R-H groups have a high dipole moment hence they show strong NIR absorbance. On other case some diatomic molecules like  $\text{H}_2$ ,  $\text{O}_2$ ,  $\text{N}_2$  do not absorb NIR radiation as there is no change in dipole moment due to molecular vibrations.<sup>(3)</sup>

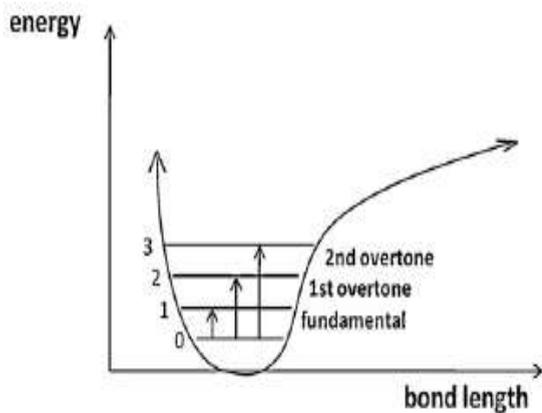


Fig. 2: Anharmonic vibration model

In NIR region overtones and combination bands of various fundamental vibrations due to  $-\text{CH}$ ,  $-\text{NH}$ ,  $-\text{OH}$  groups are seen as measure absorption band. The origin of overtone bands in NIR is due to multi-level energy

transitions. Polyatomic molecules show combination bands and usually it is a result of simultaneous energy changes of various other vibrational modes. Due to vibrational interactions combination bands will appear between 1900-2500 nm. Absorption in NIR region occurs in modes namely, stretching and bending. Stretching can be defined as a continuous change in the interatomic distance along axis between bonds of two atoms and no change in bond angle whereas bending is defined as change in the bond angle and no change in bond axis.<sup>(3)</sup>

### Instrumentation

Instrumentation used in NIR is based on need to have a faster and flexible analysis for different samples.

### Components

Basic components include a light source, wavelength selection system, sample holder, sample presentation interface and a detector.<sup>(4)</sup>

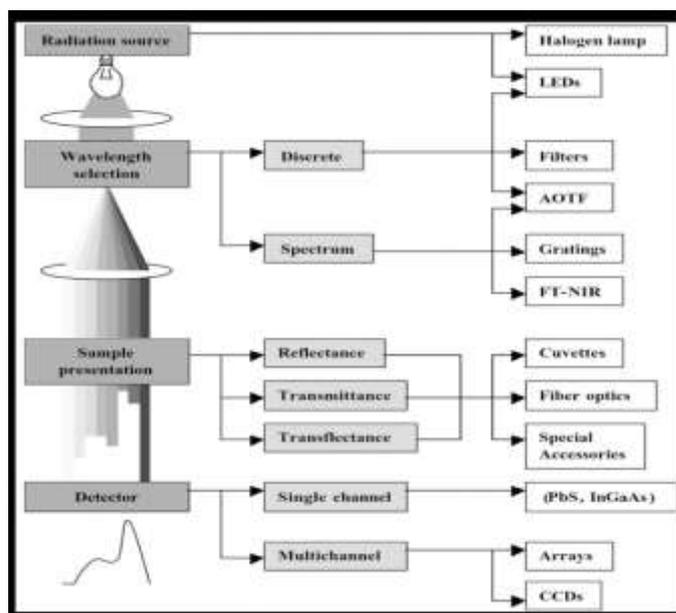


Fig. 3: Instrumentation of NIR

### Light source

The light source will generate a beam that irradiates the samples to be analyzed. Commonly used light source is halogen light with tungsten filament and quartz window which is capable of emitting continuous spectrum in the ranges of 320 nm to 2500nm. Which can be used are LEDs (Light Emitting Diodes), which is able to emit up to 1600 nm depending on their composition. The halogen lamps will require a wavelength selection system, while LEDs do not.<sup>(4)</sup>

### Types of NIR spectrophotometers

NIR spectrophotometers can be classified in two types based on the wavelength selection system as dispersive and non-dispersive instruments.

- Dispersive instruments which are the most commonly used wavelength selection systems are the monochromators.
- Non-dispersive instruments, here the variety of selection systems is broad. Different selection devices such as conventional filters, Fourier transform (FT)-NIR type and AOTFS (Acousto-Optic Tunable Filters) are used. The chosen wavelengths will use radio-frequency signals will alter the refractive index of a crystal usually  $\text{TeO}_2$  and hence it transmits light of any given wavelength or performs a wavelength scan much more rapidly.<sup>(5)</sup>

## Detection

NIR spectroscopy uses devices comprising semiconductors such as PbS or InGaAs, like single channel detectors, multi-channel detectors, several detection devices are arranged in rows or planes charged coupled devices (CCD) in order to record different wavelengths at once, to increase the speed at which spectral information can be acquired regarding the sample, usually 3 modes are available to take a NIR spectrum reflectance, transmittance and transfectance, these will completely in the nature of the sample.<sup>(6)</sup>

**Table 1: Detectors used in NIR spectroscopy**

Detector	Wavelength range (nm)	Region	*Responsivity/* detectivity	Remark
PbS	1100-2500 400-2600 1100-4500	NIR UV-NIR NIR-MIR	Intermediate/ Intermediate	PbS 'sandwiched' with silicon photodiodes, often used for VIS- NIR
PbSe	1100-5000	NIR-NIR	Fast /high	The detector will be cooled with liquid nitrogen
InGaAs	700-1700	NIR NIR Raman	Fast/ very high	Linear arrays High sensitivity, dynamic range , signal-to-noise performance and stability FT- NIR Diode arrays spectrometer
InSb / InAs	1000-5500	NIR MIR IR	Fast/ very high	High quality detector Photodiodes Detector
CCD	800-2200	NIR	Fast /high	High performance detector Applied in camera Diode arrays spectroscopy.

## Uses

NIR spectroscopy is used in the pharmaceutical industry before the PAT initiative was introduced in the early 2000s, but its use was limited to a few identification and the quantitative analyses of raw materials. NIR instruments were being adopted by larger multinational companies in the late 1990s for raw-material identification in order to reduce the cost of laboratory testing and also provide assurance that all materials delivered are correctly labeled. NIR technology also offers the means for 100% inspection.<sup>(7)</sup>

## Advantages

- NIR Spectroscopy is a flexible and versatile technique compared to other methods. Depending on characteristics of samples and analytical conditions broad variety of devices can be incorporated.
- Due to the advent of bright light sources, fiber optics and sensitive detectors, NIR optical paths for liquid samples is in mm or even cm rather than microns hence difficult sampling techniques of IR is solved by NIR.
- As NIR radiation has much greater penetration depth into the sample hence there is no need of sample dilution.
- Because of that it minimizes sample preparation errors and sample destruction.<sup>(8)</sup>

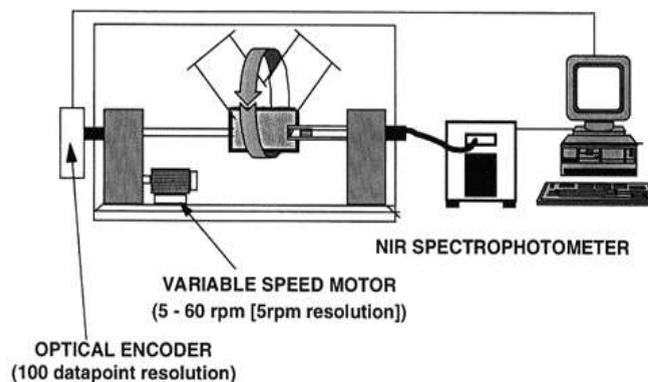
## Disadvantages

- NIR spectra is broad, has overlapping peaks as compared to IR spectra.
- Structural elucidation of wetted samples is not possible as water bands are too strong.<sup>(8)</sup>

## Pharmaceutical applications of NIR

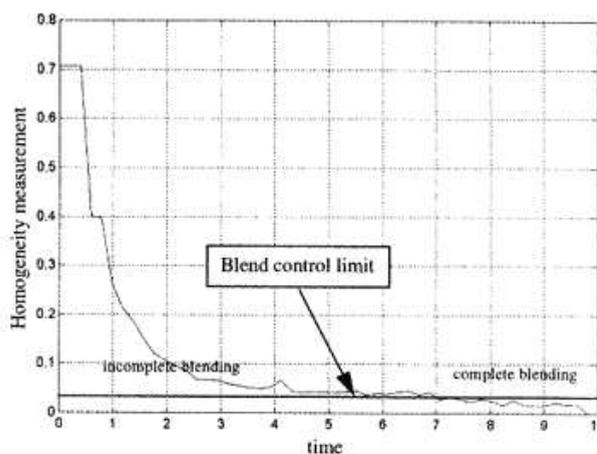
**At-Line Testing of Excipients:** When a drug product is manufactured, the first priority is to identify correct API, correct material and also correct grade of pharmaceutical excipients. NIR is sensitive to physical as well as chemical parameter; hence it can be employed as an excellent technique for such identification.<sup>(9)</sup>

**Blending Operations:** Next stage in manufacture of dosage form blending of API with excipients in order to a homogeneous blend. Here there is blending of non-cohesive powders will be considered. Usually a vessel is charged with the components of formulation and is mixed for a given period time. At end the vessel is sampled for analysis by HPLC in order to homogeneity and potency of API within a formulation. This approach does not take into account any quality measurements, by using any on-line approach to measurement by NIR hence greater understanding of the blending process is achieved.



**Fig. 4: Blending operation**

The NIR spectrophotometer configured with a fiber-optic probe interfaced blending vessel at the point of rotation. NIR Spectra are obtained in real-time and by using appropriate data pre-processing and chemometric analysis and blend 'homogeneity' plots are derived.



**Fig. 5: Blending Homogeneity Plot**

The approaches to developing control limits are many varied and can be used to develop 'Smart' manufacturing blenders.<sup>(9)</sup>

**Reaction monitoring:** Is one of the one applications of NIR following the progress of a chemical reaction as the reaction proceeds. It gives information on the formation of by-products, Concentration of reactants, and the end-point of a reaction. Simultaneously Multiple measurements made within a reaction from each spectrum which can record. Safety hazards which arise from need of sample to reactor can be reduced by directly interfacing the analyzer to the reactor. NIR can be used for process analysis of to monitor fermentation reactions, fluidized bed granulation and determine the end-point of a hydrogenation reaction.<sup>(10)</sup>

**Polymorph determination:** NIR may be used in identification of the polymorphic form of a pharmaceutical compound for both laboratory and process settings. As there is NIR spectrum arising from changes in polymorphs. NIR is sensitive and rapid method for quantifying polymorphs. Hence

measurements can be made more rapidly than the crystallographic measurements by x-ray. NIR can be used to monitor the interconversion of crystalline products in a batch reaction process.<sup>(11)</sup>

**Testing of solid dosage forms:** Testing of tablets for content uniformity and active concentration can be performed using NIR in either reflection or transmission mode. At-line measurements are run in tablet manufacturing area by eliminating the need to take samples to a remote laboratory, and hence allowing for immediate product release.<sup>(12)</sup>

**Particle-size measurement during processing:** Particle-size measurements can be made by NIR they performed during granulation and blending processes. NIR can be used to measure the nanoparticles sized in high-solids dispersion. It can be used to control the end-point of the particle production, with accuracy of 2.4 nm.

The spectrum of the dispersion will change with second derivative spectrum and particle size in the significant signal changes related to change in effective path length of the NIR light.<sup>(13)</sup>

**Physical parameters:** NIR spectra contain information like chemistry and also physical properties of samples. Various pharmaceutical parameters can be analyzed quantitatively by NIRS such as particle size, hardness, compaction force, and dissolution rate. NIRS can be used in a pharmaceutical environment to determine a large variety of physical parameters on powders and tablets. Hardness of tablets can be determined in different studies by NIR with the help by well-established regression methods like (PLS, MLR).<sup>(14)</sup>

**Moisture determination:** An initial application of NIRS in pharmaceutical field was moisture determination. Water is a critical parameter in order to ensure the stability of any product. The H<sub>2</sub>O can be easily study studied in any compound such as it gives strong water signal in NIR spectrum region mainly two different bands. This can be seen at 1450 nm and 1940 nm. Hence NIR can be used for the determination of water in powders or granules tablets, capsule, Lyophilized vials and also be solutions. Moisture determination can be done on-line.<sup>(15)</sup>

**Content determination:** Determination of chemical compound content like API, excipients or moisture in various pharmaceutical products by various methods.

NIR spectroscopy can be used in combination life FT-NIR, FTIRPAS (Fourier Transform Infrared- Photo Acoustic Spectroscopy), FTIR-ATR (Fourier Transform Infrared Attenuated Total Reflectance), Influx reflectance Infrared Fourier Transform for determination of compound present in various formulations, like powders, films. NIR can also be employed for determination of ethanol, water and propylene glycol directly through amber plastic bottles. FT-Raman applied for the determination of vitamin C in powders and solutions.<sup>(16)</sup>

**Lyophilisation:** Lyophilisation is technique used for formulating substances which undergo degradation in aqueous solutions. The aim of will produce substance with increased shelf life and product can be used after reconstitution with water. NIRS can be used for residual moisture determination in inaction glass vials and it had many advantage over conventional methods like Karl Fischer titration (KF), Thermogravimetry (TG) or Gas chromatography (GC)

- 1) Non - destructive and Non- invasive
- 2) Opening of vials is avoided
- 3) Contamination of vial from outside moisture is prevented

NIRS can be used for determining protein structure and no structure change of protein occur due to the KBr pellet preparation. Risk of contamination of atmospheric moisture by avoiding the opening the vials. This can be result in error in the determination of residual water content.<sup>(17)</sup>

**Table 2: Quantitative Determination of NIRS**

Sr. No	Analyte	Regression Method	Reference
1	Paracetamol	PLS	18
2	Indapamide Powder	PLS	19
3	Alcohol	PLS	20
4	Glibenclamide	SIMCA, PLS	21
5	Avalide	PLS, PCA	22
6	Chlorpheniramine Maleate	PLS	23
7	Ibuprofen	PLS	24
8	Sodium Aescinate Y	PLS, PLSR	25
9	Vitamin E	MPLS	26
10	Jujube Fruit	PLS, PCA	27
11	Metformin hydrochloride	PLS	28
12	Sulfamethazine	PLS, MLR	29
13	Clonazepam	PLS	30
14	Theophylline	PLS	31
15	Diltiazem HCL	PLS	32

## Conclusion

Various drawbacks of other spectroscopy which had some limitations in the various pharmaceutical analysis and also some advancements which are used for the online monitoring of various process can be achieved with the use of NIR spectroscopy. NIR is wonderful diagnostic in trouble - shooting and can provide a fingerprinting for different pharmaceutical products. This spectroscopy requires no or reduced sample preparation and is non-destructive. The measurement is fast performed in less than a second for online applications.

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