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PHARMACEUTICAL USES OF NEAR-INFRARED SPECTROSCOPY

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ABSTRACT

Near-infrared spectroscopy (NIRS) has been used extensively in the food and agricultural industries for the past twenty years. Recent technological advances have made NIRS an attractive analytical method for use in the pharmaceutical industry. NIRS has been shown to be useful as a qualitative and a quantitative method. A review of pharmaceutical applications of NIRS as well as quality control and regulatory issues is presented.

INTRODUCTION

In recent years, near-infrared spectroscopy (NIRS) has become an important analytical technique in industry. It has been used extensively in the food and agricultural industries for the determination of moisture, protein and starch content in grains[1]. The use of NIRS to solve pharmaceutical problems is increasing because of technological advances in NIR analytical instrumentation and computer software.

Though the spectroscopy itself is not new, its applications and its use of chemometrics are new and innovative.

It is now recognized that NIRS offers significant advantages for a broad range of quantitative applications. NIRS is a rapid analytical technique that uses the diffuse reflectance of a sample at several wavelengths to determine the sample's quantitative composition. Sophisticated software stores calibration equations which correspond to the spectral features of a sample. In the pharmaceutical industry, NIRS has been shown to be useful in determining the percentage of active ingredient as well as in identifying specific tablet formulations. NIRS has potential as both a qualitative and quantitative method in the pharmaceutical industry[2]. Other pharmaceutical uses include raw material identification[3] as well as monitoring content uniformity in powder mixing operations[4].

The NIR region of the infrared spectra was discovered by William Herschel in the early 1800's. It involves the absorption of electromagnetic radiation in the range of 800 to 2500 nm[5]. The segment from 1100 to 2500 nm is known as the Herschel region, and is the range most often used in the analysis of pharmaceutical products.

NIR is more often used as a secondary analytical technique than a primary technique. When used as a primary technique, standards are prepared from reference materials, just as they are for other primary analytical techniques. A library of known spectra is created, then the instrument response is plotted for each sample, yielding a calibration curve. Sophisticated mathematical techniques are applied to the data via computer software, and the results may be calculated within a few minutes.

Historical Background

Near Infrared Spectroscopy (NIRS) has been used in the food industry for over twenty years to determine the components of feeds and grains. A major stimulus to interest in analytical applications of NIRS has been the success achieved in the analysis of agricultural products.

Pioneering work by Karl Norris and coworkers at the United States Department of Agriculture (USDA) resulted in the development of methods for determination of components of forage crops. Norris is credited with being the first to use NIRS to analyze chemically complex solid samples. He was also the first to utilize multivariate methods of analysis for quantifying the complex NIR spectra[6]. NIR reflectance spectra are widely accepted in the food and grain industry for the determination of protein, fat, moisture, and other factors. It is also used for compositional analysis of dairy products and meats.

Before 1990, most publications on NIRS concerned applications in the agricultural and food industries. NIRS research is ongoing in nearly all analytical disciplines. Since 1990, more NIRS papers were published in the field of general chemistry than in the field of agriculture[7].

Many of the well known analytical meetings, such as PittCon, Federation of Analytical Chemistry and Spectroscopy Societies (FACSS), American Association of Pharmaceutical Sciences (AAPS) and Eastern Analytical Society (EAS) have recently included technical sessions and posters involving NIRS. In October, 1993, the Association of Analytical Chemists (AOAC) held a special symposium on Pharmaceutical Process Control and Quality Assessment by Non-Traditional Means. The conference, the first of its kind, consisted solely of topics relating to applications of NIRS in pharmaceutical manufacturing and the use of neural networks in drug fingerprinting.

It is anticipated that adoption of NIRS methods and related technologies will be explosive because they offer the potential for major improvements in quality control, record keeping, and control of product uniformity. However, the requirements for pharmaceutical quality control are more severe than in other fields. Analytical methods are required to be extremely accurate, specific and precise. In addition, since active components are often present in small quantities, the methods must be very sensitive. Absorption in the near infrared region is generally weak, which is an advantage for major components since no sample dilution is needed. However concentrations of minor components are often at or near the detection limit of the instrument[8].

FUNDAMENTALS AND INSTRUMENTATION

Theory

NIRS deals with the absorption of electromagnetic radiation in the range of 800 to 2500 nm[9]. It is a rapid analytical technique, using the diffuse reflectance of a sample at several wavelengths to determine the sample's composition.

The absorption of infrared radiation is the result of transitions between molecular vibrational and rotational states (twisting, bending). Upon interaction with infrared radiation, portions of the incident radiation are absorbed at specific wavelengths. One of the features of an infrared spectrum is that absorption in a specific region can be correlated to functional groups in the molecule (e.g., fingerprint region 7690-15,380 nm). Multiple vibrations occur simultaneously and produce a complex absorption spectrum that is uniquely characteristic of the functional groups that make up the molecule and of the overall configuration of the molecule.

The NIR region of the spectrum contains overtones and combination bands which are mainly due to hydrogen vibrations (OH, CH, NH). These overtones and combination bands are much weaker than the fundamental vibrations, so the molar absorptivities are between 10 and 1000 times smaller than those of the corresponding infrared bands. Due to the smaller molar absorptivities, it is possible to use undiluted samples and obtain remarkable depth of penetration into solid samples. The NIR range is adequate for studying most organic compounds.

There are some important differences between the near infrared region and other infrared (IR) spectrophotometry. Conventional laboratory IR instruments can operate in either the near, mid, or far IR regions, depending on the energy source and the detectors used. The wavelength range used for NIR is just beyond the visible end of the electromagnetic spectrum, from about 700 nm to 2500 nm. Other regions of the IR spectrum are referred to in terms of wave numbers. Thus the

near infrared region is from 14,300 to 4000 cm^{-1}, the mid infrared range is 4000 to 200 cm^{-1}, and the far infrared range is from 200 to 10 cm^{-1}.

Instrumentation

NIR instrumentation comprises four categories: monochromator, filter, selective diode, and Fourier-transform near-infrared (FT-NIR). Most laboratory NIR instruments depend on the dispersion-type monochromator for generating the monochromatic beam. Holographic gratings, which are produced by a photoetching process, have replaced the old mechanically grooved and replicated gratings. The newer gratings are easier to manufacture and cost less than their predecessors.

The energy sources used in most NIR instruments are long-lasting, tungsten-halogen lamps with quartz envelopes. A lamp which is used for 40 hours per week may be expected to last approximately 100 weeks. Detectors may be silicon photo voltaic sensors (360 to 1000 nm range) or lead sulfide (900 to 2600 nm range). Both types integrate diffusely reflected light.

NIR radiation is readily scattered by particles, making reflectance analysis an ideal technique for the analysis of solids. When the light from a NIR source is directed on a sample, both specular and diffuse reflected light are generated by the sample. However, only the diffuse reflected light contains the desired chemical information. An integrating sphere is used to segregate the diffuse and specular reflectance and to focus the diffuse reflected radiation onto the detector. A scanning grating monochromator between the source and the sample is used to obtain the desired spectrum.

Instrumentation developed for NIRS can be implemented either *at-line*, where a technician routinely extracts a sample from the process stream and transfers it to the instrument; *on-line,* where the sample is moved automatically to the instrument mechanical device; or *in-line*, where a fiber optic probe is place directly in the process stream.

Since ordinary glass is transparent in the NIR wavelength range, the optical components of NIR instrumentation don't have to be made of fragile materials. This lack of response by glass as well as quartz

enables these materials to be used as transparent containers and also permits the use of optical fibers to transmit the spectra.[10] Glass cannot be used in instruments designed for use in the mid and far IR regions.

MARKETED EQUIPMENT AND SUPPLIERS

Pharmaceutical Applications

NIRSystems of Silver Spring, Maryland (formerly Pacific-Scientific) supplies most of NIR laboratory instrumentation used by the pharmaceutical industry. These instruments are scanning monochromators with interchangeable ("modular") sampling systems that include transmission, reflectance, and fiber optic models. NIRSystems manufactures a Rapid Content Analyzer, which can be fitted with specially designed sample holders to analyze the contents of transdermal patches, tablets, capsules, and various pharmaceutical packaging. The company, a division of the Swedish company Perstorp Analytical, specializes in process and laboratory instrumentation primarily for food and agricultural, pharmaceutical, chemical, and polymer applications.

Process and Laboratory Applications

NIR instruments are manufactured for use in process, at-line, on-line and laboratory applications. Bran & Luebbe Analyzing Technologies, of Buffalo Grove, IL is a German-based company that supplies NIR instruments for use in raw materials release and identification. Buehler also supplies instruments for raw materials release and identification. Other manufacturers of NIR instrumentation include the following:

ABB Process Analytics, Lewisburg, WV
Axiom Analytical, Irvine, CA
Dickey-John, Auburn, IL
Guided Wave, Inc., El Dorado Hills, CA
Infrared Engineering, Inc., Waltham, MA

Katrina, Inc., Hagerstown, MD
LT Industries, Inc., Rockville, MD
Ocean Optics, Dunedin, FL
Perkin-Elmer, Pomona, CA
Trebor Industries, Inc., Gaithersburg, MD

CALIBRATION

NIR instruments collect full spectra of a sample and use the statistical technique of chemometrics to infer physical and chemical parameters from a spectral scan. Chemometrics is a technique which links analytical information to properties other than concentration of chemical species. Chemometric methods are applied to the design and implementation of analyses so that the most efficient and informative experiments are carried out. They are also applied to the experimental results to enhance accuracy in interpretation. Calibration techniques, such as multiple linear regression (MLR), principal components regression (PCR) and partial least squares (PLS) may be utilized via the instrument software, and are linear functions of the reflectance of absorbance.

A calibrated mathematical model is created to calculate the desired parameters. Calibration involves taking spectra from a great many samples varying over the measurement range and also measuring the desired parameters. A rugged chemometric model for a complex sample may require thousands of samples taken from all possible situations, in and out of specification, that it may encounter. Samples selected for calibration must contain all the variables affecting the chemical and physical properties of the samples to be analyzed. In order to characterize each source of variation, it is recommended that 15 to 20 samples be run.

Because NIR bands are mixtures of overtones and combinations, the intensity of the absorbance at any particular wavelength does not necessarily respond linearly to a change in concentration. In the case of

a mixture, band mixing may further disrupt any linear relationship between the intensity and the concentration. For these reasons, the simple application of Beer's Law (A = ebc, where A = absorbance, e = absorptivity, b = path length, and c = concentration) to NIR bands may not generate equations suitable for quantitation.

To avoid this problem, calibration equations are generated using multiple regression techniques. A series of samples representing the concentration range of interest are selected and their spectra obtained. This group of spectra is divided into two groups: a calibration, or training, set and a test, or prediction, set. The spectra of the calibration set are used to correlate the constituents of known concentration with those of the prediction set.

The quality of the calibration equation is determined by a number of factors, including the multiple correlation coefficient (MCC), the F-value, and the standard error of estimation (SEE). These parameters are measures of the fit between the actual training set concentrations and the values predicted by the calibration equation. Ideally, it desirable to obtain a MCC value as close to 1.0 as possible, indicating 100 % correlation. The value of the SEE should be as minimal as possible, since it indicates the standard deviation of the differences between the actual and predicted values for the calibration set.

One of the major drawbacks of NIRS is the degree of difficulty in calibration of the instruments. A calibration is required for each constituent in the sample. The mathematical models used can depend critically on the character of the sample, its preparation, and operator technique. Laboratories that analyze many samples will be the most satisfied users of this technique; labs that analyze only a few samples a week may have trouble justifying the setup time.

Another issue is that of "transferability" of the calibration model, including transferable correlation coefficients, that would be usable on all instruments. A model built on extensive samples and spectra is much more readily transferable that one developed with only a few samples. Although some progress has been made in making calibration transfers

between instruments, the situation is far from ideal, and careful monitoring is needed to obtain satisfactory results.

QC AND REGULATORY

The pharmaceutical industry's interest in NIR technology is in the production of better products at a lower cost, while the regulatory interest is in product control and uniformity and the detection of deviations from the approved formulations.

Validation of a NIRS method is necessary for acceptance by regulatory bodies. The error of the primary method must be well known. Accuracy, linearity, reproducibility, specificity, sensitivity, and robustness of the method must be demonstrated. The accuracy of the NIR results is obtained by comparison with the reference analytical method. Specificity of the method can be determined through the use of instrument software which qualify the sample. Since sample placement is an important source of error, the same sample should be measured, removed and remeasured several times to determine reproducibility. Robustness of the assay may be tested by varying the operating conditions.

The major pharmacopoeias allow manufacturers to use alternative analytical methods for compliance testing. However, these alternatives must be validated in order to demonstrate that they arrive at the same conclusions as the conventional methods. Official approval of a NIR method requires acceptable performance using different instruments with the same samples. This may be difficult because there is no agreed upon model for instrument calibration; each company uses its own model and each type of sample requires a different model. It is usually necessary to customize a model to a particular sample and instrument. It may be possible to satisfy in-house quality control specifications for product consistency within one facility. However, these results must be reproducible at other manufacturing sites.

The United States Food and Drug Administration (U.S.F.D.A.) recently approved (May 1992) the use of a NIRS method in place of

compendial methods for moisture content, identification and assay for ampicillin trihydrate[11]. This was the first time the U.S.F.D.A. approved the use of a NIRS method for release testing of a bulk pharmaceutical product for human consumption. The method was developed at Gist-brocades bv, a Netherlands-based pharmaceutical company. Validation studies using the NIR method showed that it offered faster and more accurate results, eliminated the use of solvents, and produced no waste products. This approval is likely to be followed by other computer-based technologies which will rapidly come into use in the pharmaceutical industry. It is anticipated that "adoption of these technologies will be explosive because they offer the potential for major improvements in the control of product uniformity and quality and better record-keeping..." at a significantly lower cost[12].

Canada's pharmaceutical regulatory agency, the Health Protection Branch (HPB), recently (December, 1993) approved the use of a NIR method for identification of raw materials and packaging components developed at Merck Frosst Canada, Inc. to replace compendial methods of identification[13]. The method submitted utilized a data base of reference spectra of 185 different raw materials and packaging components. It contained examples of successful identification and differentiation between HDPE (high-density polyethylene) and LDPE (low-density polyethylene) using NIRS.

PHARMACEUTICAL APPLICATIONS

Moisture Determination

The classical methods for water determination are based on weight loss by drying or on Karl-Fischer Titration. The presence of water is indicated by a NIR absorption band in the 1900 to 2000 nm region due to the combination of fundamental bending and stretching vibrations of the OH bond. Moisture levels in grains[14] have been measured using the OH absorption at 1950 nm. The absorption maximum and peak shape

depends on the degree of hydrogen bonding occurring within the environment where the water is located. The stronger the hydrogen bond, the longer the wavelength of the NIR absorption maximum.

The physical and chemical properties of water and their functions of temperature were determined by NIRS by Lin and Brown[15]. Properties determined included density, refractive index, dielectric constant, surface tension, ionization constant, as well as various thermal and thermodynamic properties. It was concluded that NIRS, when used with multivariate regressions, can be used as a simple, fast and universal approach for the simultaneous determination of the physical and chemical properties of water.

NIR methods for the determination of water in freeze-dried products were developed by Jones, et al[16]. The authors were able to analyze 40 samples per hour using this method, and found good agreement (correlation coefficients up to 0.95) between NIR predicted values and the Karl Fischer reference values. It was concluded that the NIR method provided more accurate and precise data than Karl Fischer titration since it avoided the need to open the vials and risk contamination from atmospheric moisture.

Kamat, et al[17] reported a method of determining residual moisture in lyophilized sucrose through the intact glass vials. The peaks attributable to water appeared at 1450 and 1940 nm. Results indicated a water concentration in the range of 0.72 to 4.74 % with an RSD of 6.7 %. A prediction error of 0.27% was reported with a single scan.

Sinsheimer and Poswalk[18] measured the 1900 nm moisture band in solids, solvent systems, and a micellar system of dioctyl sodium sulfosuccinate (DSS). For solvent systems, they concluded that the range of conformity to Beer's Law is limited in weakly basic solvents to the lower concentrations.

Boehm and Liekmeier[19] studied the moisture content of solid dyes and organic solvents. They identified three working ranges for quantitative water determination (Table 1). Nonpolar, organic solvents,

Table 1.
Working ranges for quantitative water determination with NIRS [19]

Absorption bands (nm)	Working range for quantitative analysis
1400	0.1 to 5 %
1900	0.02 to 0.5 %
2700	10 to 200 ppm

such as carbon tetrachloride, were analyzed at 2400 nm, the most sensitive band. An indigo dye was analyzed at the 1900 nm wavelength.

NIRS was applied by Corti, et al[20] to the analytical control of the active ingredient and water content of tablets of ranitidine chlorhydrate. The maximum acceptable water content for ranitidine tablets was 2 %. The reference value using the Karl Fischer (reference) method was 1 %. Comparison of NIRS values to Karl Fischer values indicated higher errors occurring with samples having a water content of less than 1 % (by reference method). None of the NIRS values exceeded 2 %.

Solid dosage forms

Current methods of tablet analysis are destructive in nature, and do not allow for 100% quality control testing. NIRS is a non-invasive and non-destructive method which, in theory, would allow 100% inspection of every tablet. It is theoretically possible to determine the amount of drug in every tablet in every batch, and check to ensure that a tablet is placed in its correct container. In this respect, NIRS is attractive from both a quality control and a regulatory perspective. In addition to being a non-destructive method, other advantages of NIRS over other quantitative methods include relative ease of sample preparation and fast analysis.

Several authors have reported methods for the identification of active components in tablet[21, 22] and liquid[23] dosage forms, as well as for raw material identification[24].

A general method for the rapid verification of identity and content of solid dosage forms was devised by Ryan, et al[25]. The authors evaluated the use of mid (MIRS) and near infrared spectrometers to analyze tablet and capsule dosage forms containing either lovastatin, simvastatin, enalapril, finastride, or placebo in the range of 0.2 to 40 mg of drug. The minimum amount of active drug (in the presence of excipients) detected by both methods was 1% (w/w). It was reported that NIRS could not allow for differentiation between an a-hydrogen atom on the lovastatin ester group and an additional a-methyl group in simvastatin. However, the MIRS method was able to distinguish between the two structures, since it is well suited for structural elucidation and identification of compounds.

Lodder and Hieftje[26] described a NIRS method of analysis of intact aspirin tablets. The method involved the use of a double-reflecting aluminum sample holder which preserved the integrity of the tablet during the analysis.

Lodder, et al[27] reported a NIRS method for the detection of adulterated nonprescription drugs. This work was triggered by the 1982 incidents[28]. of potassium cyanide-laced Extra Strength Tylenol® capsules in the Chicago area that resulted in seven deaths The adulterants tested included potassium cyanide, sodium cyanide, ferric oxide, aluminum metal shavings, arsenic trioxide, and sodium fluoride . The detection limit for potassium cyanide was 2.6 mg, or two orders of magnitude less than the lowest reported lethal dose in humans (2.941 mg/kg, or 306 mg for a 70 kg person). One shortcoming of a NIRS method in this situation is that it is not possible to predict what contaminant might be placed in a particular product. The authors' results indicated that a variety of contaminants could be detected in intact capsules by using four wavelengths.

Drennan and Lodder[29] developed a non-destructive NIRS assay for determination of the degradation products for intact aspirin tablets. The authors concluded that the salicylic acid formed by hydrolysis of aspirin significantly changed the spectrum of aspirin tablets after exposure to moisture and that this correlation to salicylic acid resulted from salicylic acid formation rather than a correlated process. The mass of salicylic acid formed by hydrolysis in intact aspirin tablets was measured by NIRS with a reported error of 0.04% of the total tablet mass (400 ppm).

Ciurczak[30] reported a powder mixing study which utilized NIRS to check for homogeneity. For this study, aspirin and vitamin B12 were the active ingredients. Aliquots were taken at various times and analyzed via NIRS. A comparison was made between visual matching, spectral matching and principal component analysis. Visual matching provided an approximation, while spectral matching (using computer software) gave somewhat better results. Principal component analysis was the more rigorous method, in that it was able to distinguish between the penultimate and the true final mix. The author suggested that the use of NIRS could save many hours of analysis time in a routine mixing study.

Ciurzcak, et al[31] described a method of determination of the mean particle size of pure, granular substances. The method is based on the theories of reflected light, namely the Kubelka-Munk equation,

$$(1 - R)^2 / 2R = K / S$$

where K is the absorption coefficient and S is the scattering coefficient. Reflectance, R, increases as the mean particle size decreases, while R decreases as the absorptivity increases. Graphs were constructed from log 1/R values and used to assess the particle size of pure samples of ascorbic acid, aspirin, and aluminum oxide. The absorbance values for each spectrum at 1658 nm (the major peak) were plotted against the absorbance values at 1784 nm (the baseline), resulting in a linear plot with a correlation coefficient of 0.99999. The authors concluded that this method could be used as a quality control tool when new materials are received.

Dempster, et al [32]developed noninvasive tests to confirm the identity of blister packed tablets to be used in clinical trials. The authors investigated the use of three different sample presentation methods to a NIR instrument: the unpackaged, single tablets were exposed directly to the NIR window; the unopened blister packaged tablets were placed on the NIR window; and, a fiber optic probe was used to examine the tablets through the blister packaging. Four potencies of an experimental drug were compared with a placebo and a comparator's product. When the single tablets were analyzed directly, the spectra of the tablets containing 5, 10 and 20 % w/w of the experimental drug, placebo tablets and comparator product were identified correctly when compared to wet chemical methods. The lower potency of 2 % was not distinguishable from the placebo, and was not further measured. Likewise, when analyzed through blister packaging directly on the NIR window and using the fiber optic probe, the 5% potency was not distinguishable from the placebo. The authors concluded that although the "naked tablet window" method could identify a wider range of tablet potencies, this was not a practical or convenient method for use in clinical trials. The fiber optic probe method was more convenient but was not as sensitive.

The suitability of NIRS as an alternative to several compendial methods has been demonstrated by Plugge and Van Der Vlies [33, 34] with ampicillin trihydrate. Their work led to the U.S.F.D.A.'s acceptance of NIRS as an official method of testing for the identification, water content and assay of ampicillin trihydrate. The NIR method was compared to a hydroxylamine colorimetric method as described in the Code of Federal Regulations (CFR). Other workers[35, 36] have reported the development of NIR methods for quality control in pharmaceutical analysis, but this was the first time that a regulatory agency approved the use of a NIR method for release testing of a bulk pharmaceutical product for human consumption. The U.S.F.D.A. has accepted NIRS as the official method for determination of the lincomycin content in an agricultural mixture containing soybean meal [37], but until 1992 there had not been any approved pharmaceutical uses.

Liquid Dosage Forms

Dubois, et al[38] reported a method of determination of five components in a liquid formulation of otic drops. The product contained two active components (phenazone and lidocaine), two solvents (ethanol and glycerol) and one antioxidant (sodium thiosulfate). Results indicated that the NIRS method was well suited to the quantitation of both of the solvents and one of the active compounds (phenazone). The concentration of lidocaine in the formulation (1 %) was at the detection limit of the instrument, thus the accuracy of the method was insufficient.

Kumar and Raghunathan[39] used NIRS to examine the nature of the water pool formed in the reverse micellar system, lecithin/nonpolar solvent/water. The three nonpolar solvents used in the study were benzene, carbon tetrachloride and cyclohexane. The NIR spectra indicated the presence of two types of water in the lecithin reverse micellar solutions. One was water-dispersed in the organic phase and the other was water-solubilized in the reverse micellar interior. Results revealed that the amount of water present in the organic phase was negligible at all water concentrations in all three solvents.

Grant, et al [40] investigated the quantitative analysis of solutions containing various concentrations of sodium hydroxide, sodium chloride and sodium carbonate using NIRS. It was observed that the addition of these salts caused changes in the absorption spectrum of water, even though sodium carbonate and sodium chloride do not themselves absorb in the NIR region.

Other Possible Uses

The hydroxyl value is an indicator for the stages of an esterification reaction. Hansen reported a NIRS method by which the shifting of the hydroxyl value of a reaction could be monitored [41]. This work suggests that it may be possible to monitor the degradation of a reaction, and possibly be useful in stability testing of raw materials.

Tudor, et al [42] investigated the use of near-infrared Fourier-transform (FT) Raman spectroscopy in the molecular structural analysis

of drugs and biomedical polymers. The authors developed a technique by which the concentration of a drug within a polymer vehicle could be determined over a wide drug concentration range. The FT-Raman spectrum of diclofenac dispersed in a sodium alginate matrix was monitored, as well as the spectrum of the alginate alone. It was concluded that this method illustrated the potential for quantification of degradation kinetics in certain polymers using FT Raman infrared spectroscopy.

CONCLUSION

Recently, there has been a large increase in the amount of research in the near infrared region. NIRS has been shown to be a valuable tool for a number of important applications. It has gained official acceptance in the food and agricultural industries, and is now becoming more recognized in the pharmaceutical industry. Specially designed instrumentation for use in the pharmaceutical industry has become more widely available, and is made more powerful by software improvements.

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