Near infrared and chemometrics applied to non-invasive in vivo blood analysis: Overview of last twenty years of development.

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Abstract **- A blood test is critical to assess overall health and identify possible disorders: anemia, infections, leukemia, diabetes, etc. However, currently available techniques involve invasive blood collection, which is very uncomfortable for patients. Near infrared (NIR) spectroscopy is a highly flexible form of analysis that can be applied to a wide range of analytical applications. Long a basic technology in remote sensing, NIR spectroscopy has become popular as an economical tool for chemical analysis. NIR spectroscopy can be used to analyze multiple constituents in a single scan and to identify a non-destructive or non-invasive analysis method. Chemometrics is an area that refers to the application of statistical and mathematical methods, as well as those based on mathematical logic, to more complex data treatments in order to relate the obtained signals (for example, intensities) to the desired results (concentrations). Thus, the association between NIR and chemometrics has led to the development of an unprecedented technology in blood analysis, precisely because it allows a fast, inexpensive, and non-invasive method. In this review, we have covered the major advances in this area over the last twenty years and, as you will see, technology for bloodless blood analysis is not a dream but a reality.**

keywords **- NIR; chemometrics; blood; non-invasive analysis.**

I. INTRODUCTION

It´s very known that blood is composed of plasma and blood cells. The blood cells - erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets) -are suspended in the plasma with other particulate matter. Plasma is a clear straw - colored fluid that makes up more than half the volume of blood. It is distinguished from serum, which remains liquid after blood clotting. Nowadays, blood analysis is usually performed on a blood sample taken from the arm or finger vein. Hundreds of tests and procedures have been developed, and many can be carried out simultaneously on a blood sample. However, the invasive blood collection is very uncomfortable for patients and the analytical methods present relatively long time to get the results. Some papers describe non – invasive methods for analyzing blood using various techniques [1-4]. Nevertheless, the use of near infrared (NIR) spectroscopy associated with chemometrics deserves special mention for use as a non-invasive analytical method for glucose in humans.

NIR is a type of vibrational spectroscopy that corresponds to the wavelength range of 750 to 2,500 nm (wavenumbers: 13,300 to 4,000 cm^{-1}). The analytical methods resulting from the use of the NIR spectroscopic region reflect its most significant characteristics, such as: fast (one minute or less per sample), non-destructive, non-invasive, with high penetration of the probing radiation beam, suitable for in-line use, nearly universal application (any molecule containing C-H, NH, S-H or O-H bonds), with minimum sample preparation demands. The principal advance in the technological applications of this technique was possible by computation development and the new discipline of Chemometrics [5,6]. Chemometrics involves the application of statistical and mathematical methods, as well as those based on mathematical logic, to chemical analysis, providing the tools for gathering information and its wise use [7,8].

The purpose of this review is to cover the major advances in the use of NIR and chemometrics for blood analysis over the last twenty years and opens up opportunities for further technological and innovation development. For clarity in our explanation, we have divided the review into two parts: scientific articles and patents, as follows.

Scientific Articles

Zhang et al. [9] presented the investigation of the feasibility of non-invasive in vivo measurement of blood hematocrit and factor affecting the accuracy for using cardiopulmonary bypass patients as subjects (twenty in all) by using NIR spectroscopy and partial last-squares (PLS) calibration model development. Despite observed various limitations (for example: variability in probe placement and location and poor control over the range of hematocrit values in the patients studied), multi-subject models were developed for prediction of independent subjects. The authors argue that if sources of the limitation could be eliminated, the procedure used is promising for measuring hematocrit with an accuracy of 1 ± 2 % that is an acceptable accuracy for application in the operating room, emergency room, ambulance or clinic.

When it comes using NIR to obtain quantitative data in non-invasive methods, it is important to note the ability of light in the NIR region of the spectrum to penetrate tissues. Arimoto et al. [10] investigated the magnitude of spectral change in blood glucose measurements with diffuse reflectance spectroscopy. Spectral change was estimated by simulation of light propagation in

skin tissue and measurements of absorbance spectra of an aqueous glucose solution. It verified that required sensitivity of spectrophotometers for monitoring change in the blood glucose concentration as small as 10 mg/dL it´s of order 1 x 10-4 nm.

NIR imaging was used to quantify typical values of hemoglobin concentration, oxygen saturation, water fraction, scattering power, and scattering amplitude within the breast tissue of volunteer subjects (premenopausal normal women 41 to 47 ages). The images of breast lesions indicated that total hemoglobin-based contrast can be up to 200% relative to the background in the same breast. It verified the background hemoglobin values varied considerably among breasts, then, the maximum hemoglobin concentrations observed in cancer tumors may vary considerably as well. Thus, the authors conclude that it may be important to use hemoglobin contrast values relative to the background for a given breast, rather than absolute hemoglobin contrast when trying to compare the features of breast lesions. However, if near-infrared imaging can be implemented in a low-cost manner, the NIR imaging potentially as a method to categorize the tissue composition and risk of developing disease [11].

Also concerned about the sensitivity of glucose measurements using NIR spectroscopy, Du et al. [12] proposed a novel chemometric method, region signal correction (ROSC), to removal of interference signals due to water from in vivo NIR spectra of blood glucose and conclude that the ROSC is a potential chemometric technique in the pretreatment of the spectra. In the same way and as pointed out by Liu et al. [13], for the quantification of blood glucose using NIR spectroscopy and non-invasive method, some difficulties need to be considered, for example: glucose specific information presented within the spectral region probed is very small; the noise from the instrumentation and from movement of blood cells within the human body is unavoidable and should be reduced as low as enough and the complication of the spectral makes it difficult to validate the calibration model. To overcome these obstacles, Liu et al. [13] presented a custom-built NIR spectrometer, developing a fiber optic accessory for the tissue sampling on the left palm. Despite technological advances, in vivo experiments showed both satisfactory and unsatisfactory results. Therefore, the authors conclude that more carefully designed protocols would need be adapted for measurement of glucose. Zeng and Gindy [14] presented other technological development. In the method proposed, laser beams at several particular wavelengths were collimated and illuminated a sample with low energy NIR by an optical fiber probe, and a detector collected diffuse reflectance of the sample. The experimental conditions in vivo were non-diabetic, female volunteers (38 – 48 years old) and the measurement was made at a wavelength of 1556.19 nm. The diffuse reflectance signal was obtained from the index fingertip of the volunteers. The initial results showed good correlation between diffuse reflectance and glucose content at that wavelength.

Another aspect of application of NIR spectroscopy is to monitor blood flux. Still in 2008, Kuebler [15], considering the work so far, points out that further technological advancements would be necessary to control for interindividual variability and these must be validated in experimental and clinical studies before single measurements of absolute blood flow values can be accepted as a relevant parameter in individual patient care.

As the application of NIR spectroscopy in non-invasive blood analysis requires technological advances, the mathematical treatment of the spectra is very important and thus results obtained in vitro analysis can be corroborated with those in vivo. The work of Serebrennikova and collaborators [16], presented, at that time, on a new algorithm for accurate quantitative description of the diffuse reflectance spectra from blood cultures in terms of the relevant parameters of the blood culture components. The proposed method revisited the rigorous solutions to photon diffusion approximation and Mie scattering theory. According the authors, the success of new interpretation model lies in the utilization of non-linear wavelength dependence of the basic optical properties, i.e., refractive indices, of the chromophoric components. The displayed solution to the diffuse reflectance problem was found to give appropriate estimates of the blood culture parameters. The features of this quantitative theoretical eliminated the need for external calibrations and therefore led to superior interpretation of the measured spectra. Already in the year 2011, Uwadaira et al. [17] presented a pioneering work in that, a non-invasive blood glucose sensor using short-wavelength NIR spectroscopy was developed and its application to glycemic index (GI) determination was examined. A non-invasive blood glucose sensor was developed based on an existing spectrophotometer with fiber optics in interactance mode. In order to avoid spectral variation, measuring area, contact pressure and sample temperature were kept constant. NIR spectra in the short-wavelength region from 700 nm to 1050 nm were measured on the palm of the hand during standard food tolerance tests as part of GI determination. Partial least squares regression was employed to derive an individual calibration model for determining blood glucose content. The standard error of cross-validation for the developed calibration model was 9.1 mg/dL. The GIs of three test foods, white rice, boiled fish paste and yogurt, calculated using the blood glucose values measured by the developed calibration model, were 70 (calculated using actual values 80), 57 (49), and 45 (38), respectively. The authors concluded that the non-invasive blood glucose sensor using short-wavelength NIR spectroscopy showed promise for its applicability to GI determination. (The work was highlighted in the periodical Spectroscopy Solutions for Materials Analysis in 2011, with the title: "NIR spectroscopy used in first non-invasive blood sugar tests").

The use of one-dimensional NIR spectroscopy is the principal method to bloodless blood analysis. However, Zhang et al. [18] investigated two-dimensional correlation spectroscopy (2DCOS) on chance of correlations in the spectral data, generated from the correlations between glucose concentration and some undesirable experimental factors, such as instrument, sample temperature variations and interferent compositions in the sample matrix. Through a systematic investigation of the spectral data by using 2DCOS analysis, the impact of the overlapped peaks, which cannot be detected by the traditional one-dimensional spectral analysis, can be excluded with the two-dimensional correlation analysis. The results obtained encourage the widespread use of the proposed analysis in the biomedical optics field. Though the results were promising, in order to assess the validity of the spectral data comprehensively, future work should include experiments involving the spectral variances induced by other resources. Despite research with two-dimensional NIR spectroscopy, in the same year, was described a non-invasive device with NIR light for the analysis of tissue components, particularly the blood oxygen saturation and hemoglobin concentration, by using the photon diffusion equation and Monte Carlo simulation to analyze how photons transmit in tissue at different depth levels [19]. The device was equipped with a multispectral (seven wavelengths) LED and multiple sensors set at different spatial distances to the LED source. An optimal fitting of the measurement data obtained from these sensors was employed to achieve a more accurate

estimation of the concentrations of tissue components, such as hemoglobin, water, and lipids in tissue samples, which are often of interest in clinical diagnosis. According to the simulation results, the proposed method introduced a method for tumor detection by reducing the effect of shallow layer and by increasing detection accuracy for deep layer tumors. The device was also evaluated by phantoms and clinical data acquired from the patients with neck tumors. Results indicated that the device is not only sensitive to the presence of neck tumors but also could be applied to study other clinical diseases. Yadav et al. [20] also used near-infrared LED-based measurements, however, applied to non-invasive blood glucose sensor and encountered promising results for potential use of NIR for glucose measurement.

Nevertheless, and probably, blood glucose content is the researcher's biggest concern when applying NIR spectroscopy for in vivo blood analysis. This is because diabetes, a disorder in the control of blood-glucose levels, is a disease that is associated with other metabolic diseases and affects a large number of people around the world. Goodarzi et al. [21] presented in 2015 a critical review of multivariate calibration of NIR spectroscopic sensors for continuous glucose monitoring. The authors conclude that pre-processing and multivariate-calibration techniques, which allow exploiting expert knowledge on the potential interferences, are important to possible solutions. The combination and first overtone bands in the ranges 2050 – 2300 nm and 1500 – 1800 nm, respectively, are the most informative regions. However, Goodarzi et al. [21] recommended selecting the most informative variables and exploiting the available expert knowledge on known interferences in pre-processing or multivariate calibration to develop an NIR-based glucose sensor for in-vivo use. A year later, Uwadaira et al. [22] continuing with their research, presented a work in which investigated the correlations between "glucose-linked wavelengths" in the short-wavelength NIR region with the light intensity reflected from the palm of the hand and found good results. In this study, a total of 34 healthy Japanese females (age: 20.7 ± 0.5; body mass index: 20.3 ± 1.8 kg/m$_2$) participated. For a carbohydrate tolerance test (CTT) the acquisition of the NIR spectra (700 – 1050 nm, 1-nm intervals) of the right-hand palm of each participant was performed almost simultaneously with the standard methods for self-monitoring of blood glucose (SMBG) that require a finger-stick blood sample. The absorbance spectrum was obtained in 15 s as the average of 50 scans with an exposure time of 300 ms each. This study provided the first verification of the correlation between the blood glucose value and the light intensity at a single wavelength in the short-wavelength NIR region as measured in a CTT using a large data set. The work established the existence of glucose-linked wavelengths that correspond to the absorption peaks observed in the spectra of the hands (836, 846, 1013, 1030, and 1040 nm) at which the light intensity is strongly correlated to the blood glucose value; however, these wavelengths fluctuate daily even for the same person. This fluctuation complicates the development of a universal prediction model for an individual. Nonetheless, the fluctuation was sufficiently small to allow the construction of a model that is applicable for a 2-h period.

Of course, careful animal testing is usually conducted before a procedure or technique is studied in humans. Jintao et al. [23] investigated the NIR spectroscopy and calibration models in rats with diabetes and normal rats. Two calibration models were generated by different multivariate strategies: PLS, a linear regression method, and artificial neural networks (ANN), a non-linear regression method. The PLS model was optimized individually by considering spectral range, spectral pretreatment methods and number of model factors, while the ANN model was studied individually by selecting spectral pretreatment methods, parameters of network topology, number of hidden neurons, and times of epoch. The results of the validation showed the two models were robust, accurate and repeatable. Compared to the ANN model, the performance of the PLS model was much better, with lower root mean square error of validation (RMSEP) of 0.419 and higher correlation coefficients (R) of 96.22%. Their conclusion was that NIR spectroscopy and PLS model shows good performance and extensive potential for non-invasive measurement of blood glucose, and it could be carried out for human subjects. Despite the use of animals and glucose like principal analyte in humans, another important aspect of blood is its viscosity (because it may be related to cardio-cerebrovascular diseases), rapid and non-invasive analyses of blood viscosity are also the focus of some researchers. To this end, Chen et al. [24] proposed a rapid analytical method of human whole blood viscosity with low, medium, and high shear rates using visible and near-infrared (Vis-NIR) spectroscopy combined with a moving-window partial least squares (MW-PLS) method. Two groups of peripheral blood samples (circulating blood of the body) were collected for modeling and validation. Separate analytical models were established for male and female groups to avoid interference in different gender groups and to improve the homogeneity and prediction accuracy. Modeling was performed for multiple divisions of calibration and prediction sets to avoid over-fitting and achieve parameter stability. The joint analysis models for three indicators were selected through comprehensive evaluation of MW-PLS. The selected joint analysis models were 812 – 1278 nm for males and 670 – 1146 nm for females. Results indicated high prediction accuracy, with prediction values similar to the clinically measured values. Overall, the findings confirmed the feasibility of whole blood viscosity quantification based on Vis-NIR spectroscopy with MW-PLS modeling. The researchers mentioned that the proposed technique is a promising tool for surveillance, control, and treatment of cardio-cerebrovascular diseases in large populations.

How previously mentioned the results obtained in vitro analysis can be corroborated with those in vivo. Miskal et al. [25] proposed a new preprocessing technique, which combines Chebyshev filtering with baseline correction technique Asymmetric Least Squares (AsLs) and Savitzky-Golay transformation to improve the prediction of Glucose from NIR spectra through linear regression as performed by PLS and Principal Component Regression (PCR). To investigate the performance of the proposed technique, a calibration model was first developed and then validated through prediction of glucose from NIR spectra measured on a mixture of glucose, urea, and triacetin in a phosphate buffer solution, where the component concentrations were within their physiological ranges found in blood. Results indicated that the proposed technique improves the performance of both PLS and PCR and achieves a standard error of prediction (SEP) as low as 12.76 mg/dL, which is at a clinically acceptable level. Also in 2018, Beganovic et al. [26] published a work in which they investigated the applicability of two elimination techniques for interferences occurring in measurements with cells of short pathlength using Fourier transform near-infrared (FT-NIR) spectroscopy. Aqueous solutions of d-(+)-glucose were prepared and split into a calibration set and an independent validation set. All samples were measured with two FT NIR spectrometers at various spectral resolutions. Moving average smoothing (MAS) and fast Fourier transform filter (FFT filter) were applied to the interference-affected FT-NIR spectra in order to eliminate the interference pattern. After data pre-treatment, partial least squares regression (PLSR) models using different NIR regions were

constructed using untreated (interference affected) spectra and spectra treated with MAS and FFT filter. The prediction of the independent validation set revealed information about the performance of the interference elimination techniques, as well as the different NIR regions. The results showed that the combination band of water at ~ 5200 cm^{-1} is of great importance since its performance was superior to the one of the so called first overtone of water at ~ 6800 cm^{-1}. Furthermore, this work demonstrated that MAS and FFT filter are fast and easy-to-use techniques for the elimination of interference fringes in FT-NIR transmittance spectroscopy. Yang et al. [27] reported the determination of NIR informative wavebands for transmission non-invasive blood glucose measurement using a Fourier transform spectrometer, and compared the results found in vitro with those found in vivo. Two sets of experiments were designed for the investigation. The first set focused on glucose absorption in aqueous solution in the shortwave band and the first overtone band (shortwave band (~900 – 1450 nm) and the first overtone band (~1450 – 1500 nm)) at temperatures of 37 oC. Then, the oral glucose tolerance tests (OGTT) was performed with seven healthy male volunteers (ages 23 to 27 years). Each of them drank 100 ml of water containing 75 g glucose in the morning after fasting for 8 hours overnight. NIR transmission spectra were collected from the middle fingertip in the shortwave band and the first overtone band (the temperature of each volunteer was measured to be 36.7 ± 0.2 oC). In the experiment, the reference blood glucose had a mean concentration of 124.54 mg/dL (range: 75.6≈178.2 mg/dL), which increased gradually to a peak value and then decreased. Absorption by the glucose solution was observed in the shortwave band at ~930 – 970 nm, ~1040 – 1100 nm, ~1280 – 1300 nm, and in the first overtone band at ~1600 –1650 nm. However, the characteristic peaks of the fingertip spectra were only observed in the shortwave band. These data suggested that the first overtone band is not suited to use with a transmission method for non-invasive glucose measurement. Furthermore, high correlation coefficients between the light intensity and the reference blood glucose concentration were obtained in several wavebands, such as 950 nm and 1280 nm in the shortwave band. The study identified an effective blood glucose linked wavelength to provide a reference for wavelength selection, but more advanced detectors and filters are necessary. For detectors, Sultan et al. [28] used the free-space broadband frequency modulated NIR photon transmission and backscattering mode technique as an optical biosensor method to measure, identify and extract the optical properties of different blood types. The method depends on the measurements of broadband frequencies ranging from 30 up to 1,000 MHz to predict two important parameters related to the incident-modulated signal. Blind samples collected from 30 patients were examined using the optical NIR transmission mode system, and an additional 40 blood samples from random patients were examined using the optical NIR reflection mode system. The study was divided into two stages: the first stage was dedicated to measuring the insertion loss and insertion phase over 30 – 1,000 MHz in a transmission mode to characterize the behavior of modulated photons as they interact with the blood samples. The second stage was dedicated to performing non-invasive backscattering measurements using the optical band developed to match the first stage results. The results allowed the authors to conclude that the novel approach shows a highly accurate method in identifying different blood types instantaneously using optical sensing for both in vitro and in vivo procedures, thereby saving time and effort.

Mathematical models continued to receive attention of researchers. Suryakala and Prince [29] presented a comparative study to analyze the performance of the two regression models: partial least squares regression (PLSR) and principal component regression (PCR) models to arrive at the best regression model for the prediction of blood glucose measured non-invasively with NIR diffuse reflectance spectroscopy. The NIR spectrum of human skin tissue was acquired using diffuse reflectance spectrometer in the wavelength range of 750 – 1040 nm, illuminated using a tungsten halogen white light source optimized for the VIS–NIR (360 – 2500 nm). The study investigated 32 subjects both male and female of age 30 – 70 years. Multivariate analysis using PLSR was found to be a better regression model in terms of the fitted response and estimated mean square prediction error. It was observed that the mean square error value is 0.04 mg/dl for the tenth component in the PLSR model. The regression model using PLSR out- performed the PCR model and was claimed to be a useful tool in identifying the informative wavelength bands for blood glucose measurement. Another regression model, Huber's regression model, and an efficient NIR based optical detection system for non-invasive blood glucose analysis was proposed by Jain et al. [30]. After real-time data analysis, it was found that the coefficient of determination (R2) is improved with the value of 0.9084 using their proposed regression model. Mean absolute derivative was also increased with 3.87 mg/dL corresponding to predicted blood glucose concentration. Mean absolute relative difference had exceeded 3.25%, and average error was improved to 3.77% using their proposed regression model. Average accuracy had been analyzed 94 – 95% for predicted blood glucose concentration. In addition to mathematical aspect, researchers are looking for better devices for measurements. Jayarathan et al. [31] proposed a design, a cost effective and noninvasive glucose-monitoring device using NIR techniques. These authors employed a GSM module (a chip or circuit used to establish communication between mobile devices). The results obtained with measurements can be transmitted easily for examination, stored for future records, to analyze variations in blood glucose level, and adjustment of dosage of medicine.

The scientific articles presented here show that non-invasive blood analysis in vivo using NIR spectroscopy and chemometrics has received attention and the use of NIR spectroscopy in conjunction with PLS points the way for technological innovations in this area. Despite the difficulties, various patents have been acquired in the last twenty years. An overview of state of the art of innovations is shown below.

Patents

Ciurczak et al. [32] reported the invention of a near infrared blood glucose monitoring system. An individualized modeling equation for predicting a patient's blood glucose values is generated as a function of non-invasive spectral scans of a body part and an analysis of blood samples from the patient, and is stored on a central computer. The computer regenerates the individualized modeling equation as a function of the set of spectral scans and corresponding blood glucose values. In the same year, Scecina et al. [33] patented a method for monitoring the concentration level of a particular constituent or, alternatively, of measuring the concentration level of several different constituents in a non-invasive device using a NIR region between 500 to 1700 nm. A few months later, an apparatus and method for non-invasive determination of concentration of alcohol in human tissue using NIR spectroscopy were patented. The system includes subsystems optimized to contend with the complexities of the

tissue spectrum, high signal-to-noise ratio and photometric accuracy requirements, tissue sampling errors, calibration maintenance problems, and calibration transfer problems [34]. For analyte determination (preferably glucose) a compact analyzer was patented [35]. The apparatus is a spectrometer-based system that is attached continuously or semi-continuously to a human subject and collects spectral measurements (in the NIR region) that are used to determine a biological parameter in the sampled tissue. Some of the authors of the previous patent concerned with mitigating related technology problems and improving non-invasive analyte measurements, such as a non-invasive near infrared spectroscopy diffuse reflectance-based glucose concentration analyzer, have disclosed a device. The device is a hydration buffer that includes a fluoropolymer coupled to the analyzer [36]. Another method and apparatus for measuring blood glucose concentration a has been patented by Rosenthal [37]. The method uses two light sources: one introduces NIR energy into the blood present in an individual´s body part, and a second introduces red light energy. An LED detector was employed. The estimated blood glucose content was calculated using regression. Walker et al. [38] have patented a sensor for non-invasive glucose measurements one year later. Continuing glucose monitoring, Werner et al. [39] patented a portable, patient-operable analytical device for analysis of blood glucose. After the measurements are performed, the data are transmitted to a computer for processing. Moreover, in the same year, also using NIR spectroscopy for measurement, Chung et al. [40] patented a method for predicting the blood glucose level of a person, and Monfre et al. [41] patented a method of multi-tier classification and calibration in noninvasive blood analyte prediction that minimizes prediction error by limiting co-varying spectral interferents. Grata and Pitsakis [42] disclosed an apparatus for a non-invasive sensing of biological analytes in a sample. The instrument includes an optics system, a control/processing system, a user interface/peripheral system and a power supply system operatively coupled to the measurement system, the control/processing system and the user interface system for providing power to each of the systems. The biological analyte may be glucose, lipids, or alcohol. An emission spectrum of the radiation source may cover a range of about 1,200 nm to about 1,900 nm and a responsivity of the radiation detector may cover a range of about 1,200 nm to about 1,900 nm, if the biological analyte is glucose or lipids. The emission spectrum of the radiation source may cover a range of about 800 nm to about 1,300 nm and a responsivity of the radiation detector may cover a range of about 800 nm to about 1,300 nm, if the biological analyte is alcohol. The embedded software system processes signals obtained from the measurement system to determine a concentration of the biological analytes in the sample.

Although several patents have been filed relating to the monitoring of blood analytes, another patent of interest directly related to the scope of this review was filed only four years later by Yodfat and Kaidar [43]. Their patent reports a skin adherable device for delivering therapeutic fluid into a body of a patient. The device includes monitoring apparatus and dispensing apparatus, and a tip for delivering the therapeutic fluid into the body of the patient and for monitoring analytes in the body of the patient. If the analyte is glucose, spectra in the NIR, mid infrared or visible light range can be used (altogether or separately) in the monitoring apparatus. The following year, Poeze et al. [44] patented methods, devices, and systems for measuring various blood constituents or analytes, such as glucose. In an embodiment they reported, the light source was comprised of LEDs and super-luminescent LEDs. The light source emits light at least wavelengths of about 1610 nm, about 1640 nm, and about 1665 nm (NIR region). The detector is comprised of photodetectors arranged in a special geometry, either a linear, equal spaced geometry, a linear, non-equally spaced geometry, or a grid geometry. Concerning LED sources, Bruinsma et al. [45] patented an emitter driver configured to be capable of addressing substantially 2N nodes with N cable conductors configured to carry activation instructions from a processor. An address controller is used to output an activation instruction to a latch decoder configured to supply switch controls to activate particular LEDs of a light source that can be adapted to NIR. Also in 2009, Peatfield and Gravesen [46] patented several methods and systems of imaging using optical interferometry in the NIR region. In 2014, Gulati et al. [47] patented another noninvasive system for detection/measurement of glucose and other analytes in a medium such as tissue. According to these authors, when near-infrared light is applied to tissue, the light is both scattered by cells and structures under the skin and is absorbed by substances in the tissue, including glucose. The amount of absorbance due to glucose in this wavelength region, however, is extremely small. To solve the problem, their model is based on conditioned spectral features which contain frequency components specific to glucose or the other analytes. The method permits estimate of the concentration of glucose or other analytes without requiring personalized calibration. Antony [48] patented a device for measuring glycated hemoglobin (Hbalc) and blood glucose in diabetic patients without the need for of real blood sample using a sensor based on a NIR emitter at 980 nm and a photodiode detector at 1100 nm. Finally, Martins et al. [49] disclosed a method that applies a digital filter to a set of luminous signature spectra provided by a spectrophotometer. The digital filter breaks down the spectrum into sub-spectra which show the digital signatures of relevant markers and, through a digital decoder, the concentration of a set of several biomarkers is obtained simultaneously and in real time. Multivariate calibration and using a portable spectrophotometer in the spectral interval between 400 to 2500 nm with a fixed optical design produced results for the amount of the marker compound in real time. For this reason, the equipment can universalize the clinical analysis.

Conclusion

In this brief review of the last twenty years of the application of NIR spectroscopy and chemometric for non-invasive in vivo blood analysis, it is apparent that a good part of the scientific articles is dedicated to improving chemometric methods. PLS regression has been used with success in the quantitative interpretation of NIR spectra of non-invasive in vivo blood analysis. The focus of patents is on device enhancement and on technological innovation, principally in methods and systems. Despite the difficulties in finding suitable detectors for the measurement of analytes by non-invasive NIR methods, LED sensors are being used with good results. Like this, it is clear that with existing technology it is already possible to analyze blood chemistry without the need to draw blood samples, especially when glucose is the analyte and, therefore the dream of a reliable non-invasive analysis for glucose is beginning to come true. The question is why this technology is not yet available to the general public? Nevertheless, as mentioned in this paper, it´s in progress in this company (and we believe that also in other institutions) the improving measuring instruments with the goal of having available, finally, to the population, a painless, fast, efficient, and accurate method for analyzing blood without blood.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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