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The Uses and Limitations of Absorption Spectroscopy in the Development of Non Invasive Blood Glucose Monitoring Systems

Nanoscience, Physics and Chemistry of Advanced Materials

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Type I and II diabetes rates and their associated mortality rates are increasing day by day. Careful, constant glucose monitoring is paramount in treating the disease and the development of an accurate, easily implementable and non-invasive technique is currently in the research spotlight. Absorptive spectroscopic techniques are at the forefront of research into viable solutions to this problem. For diabetes sufferers' reliability, simplicity and ease of use are of critical importance. NIR spectroscopy is currently seen as the most promising technique however its limitations include extreme sensitivity to outside and physical factors and lack of a suitably accurate data calibration method. MIR spectroscopy has often been discarded due to its low penetration power and subsequent inability to obtain measurements through the skin, however, with new advances in attenuated total reflection (ATR) technology this method could definitely be reconsidered as a viable future method of detection. MIR spectroscopy shows both less sensitivity to outside factors and less need for calibration than NIR methods. There are advances to be made before absorptive spectroscopic techniques can be implemented on an industrial scale as feasible and accurate alternatives to the fingerpick method. This paper

presents a review of the principles of these and their limitations, focusing on current and future research directions in order to combat these limitations and create a viable, non-invasive glucose monitoring technique which would be viable for future use.

Introduction

Diabetes mellitus is a metabolic disorder and one of the most prevalent diseases in the world today. About 4-5% of the world's Caucasian population suffer from it and it is estimated that about 40% of all blood tests are related to it (Steiner *et al.* 2011). In Type 1 or 'early onset' diabetes the pancreas does not produce any insulin. In Type 2 diabetes either it under-produces insulin or the cells in the body do not react to insulin. In both cases the sufferer develops abnormally high blood glucose levels (hyperglycemia) which can result in many devastating complications such as cardiovascular disease (Morrish *et al.*. 2001), neuropathy, blindness (WHO Geneva 2012), kidney failure or amputations (Roglic *et al.* 2005). Frequent and accurate blood glucose monitoring is paramount in the treatment of diabetes in order to delay and sometimes even prevent these complications.

Currently, the most popular and effective blood glucose monitoring technique is an invasive 'fingerprick' technique which is an electrochemical enzyme based method of detection. Devices usually consist of two carbon-based electrodes, a thin dry reagent layer and enzymes such as glucose oxidase or glucose dehydrogenase. The blood is placed in a capillary volume strip and mixed with the dry reagent in an enzymatic reaction to form a chemical product which is proportional to the blood glucose level. This capillary strip is inserted into the meter and the working electrode is polarised which generates an oxidation process that is converted to an electric signal by an electrochemical transducer to be read and outputted by the meter. This method is effective and accurate however the pain and risk of infection caused by frequent self-testing, along with possible nerve damage, discomfort and callousing from long term monitoring (Pickup *et al.* 2005) often deters patients from monitoring

glucose levels as often as recommended and also causes problems monitoring very young patients, elderly or less dexterous patients (Turner *et al.* 2005).

With 347 million people worldwide suffering from diabetes (Danaei *et al.* 2013) and glucose biosensors comprising over 85% of the estimated $5 billion market for biosensors worldwide (Newman *et al.* 2004) it is therefore not surprising that many resources are being put into the development non-invasive blood glucose detection methods to improve the lives of people suffering with the disease by providing an easy, painless and non-invasive method of glucose monitoring.

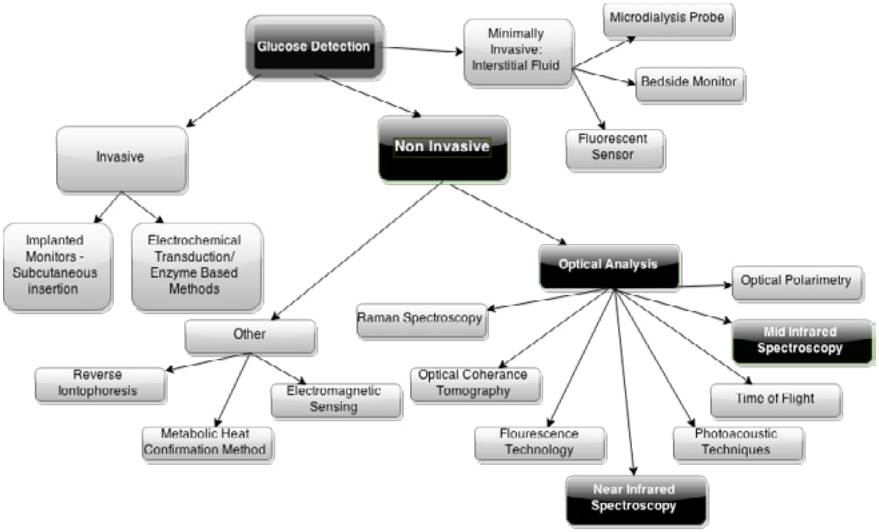

FigURE 1: An overview of the available glucose monitoring techniques, from invasive, to minimally invasive (interstitial fluid) to non invasive techniques. *(Adapted from diagrams and information included from So et al. (2012), Poddar et al. (2006) and Amaral & Wolf (2008).) The shaded subsections are the spectroscopic methods detailed in this review.*

This review will focus specifically on absorptive spectroscopic techniques as an alternative to invasive techniques in measuring *in vivo* glucose levels and will provide a chemical background to these techniques and a complete critical analysis of their limitations. Optical analysis is currently the most promising and researched technique of non-invasive *in vivo* glucose analysis, with over 100 small companies and universities working on monitoring devices

using these methods (Coté, 2001). Within the range of optical analysis techniques, near infrared (NIR) spectroscopy has been the primary area of interest and focus (McNichols & Coté, 1998, Gabriely *et al.* 1999), with mid infrared (MIR) spectroscopy being researched in particular cases (Heise *et al.* 1989, Yu *et al.* 2014) as a very promising glucose monitoring technique.

Spectroscopic Techniques

Near Infrared Spectroscopy

Principle

NIR involves the focusing of a beam of light onto the sample which penetrates to a depth of 1 - 100 mm (Vashist, 2012). Light of wavelengths of 1050 - 2450 nm are used for most studies (Malin *et al.* 1999) although NIR wavelengths are defined as the set of wavelengths between 800 -2500 nm (Sileoni *et al.* 2013). NIR measures the absorption of light caused by the rotation or vibration (Teixeira *et al.* 2009) of excited aliphatic, aromatic or alkene carbon-hydrogen bonds, amine nitrogen-hydrogen bonds, and oxygen-hydrogen bonds(Reich, 2005). Glucose ($C_6H_{12}O_6$) scatters and absorbs the incident light resulting in characteristic interactions and absorption spectrums determined by the transmitted light (Stuart 2004, Poddar *et al.* 2006)NIR uses the overtones and vibrational modes of a compound to obtain physical and chemical information of the sample and shows the characteristic peak of glucose.

Most apparatus consists of a deuterium-halogen light source (Fernández-Novales *et al.* 2008), NIR spectrometer and bundles of fiber optic cables which are arranged systematically around the site to be tested (Amaral & Wolf, 2007). The equation used to determine the attenuation of light is $I = I_o e^{-u^*d}$, in accordance with the light transport theory where I_o represents the incident light intensity, I the reflected light intensity, d the path length of the beam in the tissue and u* representing the effective extinction coefficient which can be calculated as a function of both the absorption and scattering coefficients (Tura *et al.* 2006)

Although the overtones and vibrational mode spectra often overlap, making it harder to distinguish glucose peaks, the NIR range is still extremely suitable for the evaluation of compounds in human tissues due to the high concentration of water molecules. At these shorter infrared wavelengths water absorption is weak (Amaral & Wolf, 2007) allowing the spectrum of glucose to be distinguished. If longer wavelengths are chosen, the absorption of water would be the most prevalent signal and the spectral bands of glucose would overlap and be hidden by the high water absorption band. Conversely, if the wavelengths were shorter, the spectrum would transverse into the visible spectrum in which visible light would be absorbed by the pigments in skin. (Tura *et al.* 2006)

The apparatus must then be calibrated using results from both diabetic and healthy patients with varying BG levels. There is no general consensus for a universal calibration method, which is a drawback to the NIR technique. Multivariate data analysis techniques such as principal component analysis (PCA) and partial least squares fit (PLS) are used to mathematically separate the desired spectra from the matrix (Oliviera & Neves *et al.* 2012). This is a huge advantage of NIR treatment over UV or visible light spectroscopy which mostly require a manual separation of the sample from the matrix, mainly in the form of dissolution (Cozzolino *et al.* 2006). PCA eliminates variables by analysing the data in terms of its most prominent components instead of the normal x-y axis, whereas PLS eliminates variations by transforming the data into a linear model based on only a small number of orthogonal variables. These techniques begin to break down when there are a large number of variables present in the sample as it can no longer be considered a linear model.

Limitations and Adaptations

Possibly the most challenging aspect of the development of NIR spectroscopy is determining the site at which to measure glucose levels. Due to the fact that NIR measures the vibrational modes and overtones of compounds instead of the fundamental absorption spectra found in MIRS it is very susceptible to changes in skin

structural properties, for example: dryness, depth, fat content and environmental factors.

It was shown by Sibbald et al (1996) and Monnier et al (1999) that diabetic patients can develop a characteristic 'thick skin'. The incongruity between the structural properties of skin in diabetics and healthy patients could in turn lead to incorrect calibration, difficulty in analysis due to thickening of skin and a long term instability of the monitoring process. Hyperglycemia also affects the thermal properties of skin (Yeh *et al.* 2003) which greatly distorts the spectral measurements. A breakthrough occurred with the work of Burmeister and Arnold (1999) who conducted a study of six measurement sites: cheek, lower lip, upper lip, nasal septum, tongue and finger webbing. This study found that the tongue was the most feasible site for NIR measurements, demonstrating the highest signal to noise ratio. This is due to the fact that the tongue is a purely muscular structure, eliminating deviations due to the thermal and structural properties of skin (Burmeister & Arnold 1999). The tongue also exhibits low levels of fatty tissue and a very high blood supply which allows accurate glucose analysis without the need for deeply penetrating wavelengths. Their work, however, did not address the dependence on environmental factors.

Many environmental and physical factors can affect the results of calibrated NIR spectroscopic data, including background conditions - temperature, humidity, atmospheric pressure - and interference variables - varying CO_2 concentration, fats, proteins and hemoglobin levels present in human tissue. (Zhang *et al.* 2013). Multivariate calibration and data analysis is therefore necessary to avoid unreliable data sets when using the apparatus in a variety of conditions that do not correspond to those of original calibration. Methods have been examined to correct background variation: multiplicative scatter correction (MSC), polynomial fitting (Komsta 2011) and weighted least squares fit (Zhang 2009). In addition, alternative methods such as uninformative variable elimination (UVE) (Cai 2008) and randomisation tests (Xu 2009) have been developed to deal with the effect of interference variables. There are, however, no methods which successfully accomplish both of these tasks simultaneously. Researchers Li *et al.* (2014) succeeded in

devising a hybrid algorithm (a combination of UVE and least squares fit approaches) for multivariate calibration that could combine these two factors. They applied it successfully in a glucose level analysis on 35 diabetic and 11 healthy subjects. The human tongue was used as a sample test site and it was found that the correlation coefficient of prediction increased 31.21 % and root mean square error of prediction decreased 34.56 % from the originally calibrated methods (Li *et al.* 2014). This illustrates the possibility of hybrid analysis techniques to create feasible NIR spectroscopic devices which overcome variations in background conditions and are able to precisely determine glucose levels without being influenced by other compounds present in the tissue. Unfortunately the major assumption of these algorithms is that the data can be fitted to some sort of linear model, which proves inaccurate and untrue in most cases (Li *et al.* 2014).

Mid Infrared Spectroscopy

Principle

The principle and methodology of MIR spectroscopy is very similar in nature to that of NIRS, but the MIR spectrum is defined as wavelengths in the 2500 - 10,000 nm range (Khalil *et al.* 2004), although many studies are carried out in the 8382 - 9708 nm range (Martin *et al.* 2002, Malchoff *et al.* 2002). Much less research has been carried out on this method due to its limited light penetration capabilities of only a few micrometers (Brancaleon *et al.* 2001) which greatly hinders the ability to use transmitted light data. As a result, only scattered light can be considered. However MIRS results in more distinct glucose peaks than NIRS. This is due to the higher absorption coefficients (Landgrebe *et al.* 2010) and the fact that MIRS ranges are able to induce an excitation and fundamental vibration spectrum whereas NIRS spectra consist of the overtones of a fundamental vibration, resulting in more distinct, less overlapping spectra (William & Norris 1987, Rhiel *et al.* 2002). The diffusion of light in the MIR range is also much less than in the NIR range, which creates less noise in the signal, making MIR data much less skewed by factors which affect the diffusion of light, for example porosity or

hydration of the tissue (Bellon-Maurel & McBratney 2011). The need for developing accurate multivariate data analysis is therefore much less. Some treatment of the data is still required, however it does not constitute as much of a limitation as in the NIR range.

Limitations and Adaptations

Many researchers have dismissed MIRS as a viable spectroscopic technique for the measurement of blood glucose levels due to its poor penetration qualities (Tura *et al.* 2006) however Sandor et al (2013) in a comparative study of non-invasive monitoring using both NIRS and MIRS methods argues that MIRS is the most accurate technique in monitoring a single analyte as it had a root mean square error (RMSE) of 0.16 g/L where as NIRS had a RMSE of 0.36 g/L. However, during their experimentation the MIR probe had to be purged with nitrogen gas at 20 mL/min to prevent unwanted absorption bands of CO_2 and water vapour, which greatly limits the adaptability of this technique. (Sandor *et al.* 2013).

Harvey & McNeil (2006) found that the problem of limited penetration could be circumvented by the use of attenuated total reflection (ATR). This method uses total internal reflection of a light beam through a crystal which is placed on the skin. The reflected light creates an electromagnetic field which can then reach the dermis (location of most of the skin glucose) (Thennadil 2001). The beam absorption will change, depending on the levels of blood glucose. However this requires more expensive and fragile fibre optic MIR probes (Roychoudhury *et al.* 2006). Saiko *et al* (2014) successfully developed a MIR attenuated total reflection glucose monitoring system using a hollow optical fibre probe. Owing to the results of Burmeister and Arnold (1999) mentioned earlier the tests were carried out on oral mucosa where the capillaries are found very close to the surface, allowing for precise glucose measurement. Their results indicated that the accuracy and reproducibility of the results were high enough to deem this a viable blood glucose monitoring instrument (Saiko *et al.* 2014).

Conclusions

The principles, limitations and adaptations of absorptive spectroscopic techniques have been discussed in this review. It highlighted NIR as the most promising technique for feasible implementation in terms of efficiency and cost of the sensing probe. However a more complete and accurate method of data calibration and analysis is necessary before this method can be implemented. This limitation was partially solved by Li *et al.* (2014) in creating a hybrid data analysis model although an even more highly sophisticated technique is required if these devices are to be implemented as an accurate alternative to invasive methods. MIR has the advantage of having much more distinguishable peaks and therefore requires less final data calibration, however, the sensing techniques are not as advanced as it has been discarded as an area of research by many companies and research groups. This is mainly due to the poor penetration of the MIR spectrum. Recent ATR advances (Saiko *et al.* 2014) have greatly increased the penetration power and combining this with the work of Burmeister and Arnold (1999) for determining the most effective monitoring site, may generate a successful MIR glucose monitoring device, making MIR a candidate to be strongly reconsidered in the future to provide a more effective solution to NIR.

In the area of blood glucose detection, the reliability and accuracy of results are of paramount importance because inaccuracy or misdiagnosis of blood glucose levels can have extreme ramifications for patients. It is challenging to create a method which meets all bio-compatibility specifications while maintaining high stability, robustness and accuracy which is not influenced by outside factors. Absorptive spectroscopic techniques could become a viable future solution with a few advancements and adaptations. The race for the next generation of commercially available, user friendly and painless methods of glucose detection has begun. Absorptive spectroscopic techniques are not currently feasible for industrial implementation due to the limitations discussed here but are definitely forefront candidates for a possible solution in the not too distant future.

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