Smart tattoos: an innovation in continuous glucose monitoring

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Acknowledgments

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Introduction

Diabetes is a disease that affects 25.8 million Americans every day. The United States has 18.8 million diagnosed cases of diabetes, 7 million undiagnosed cases of diabetes and 79 million prediabetic cases. One million nine hundred thousand new cases of diabetes have been diagnosed in people greater than or equal to 20 years old in 2010 (Jin et al., 2011). Some people have type 1 diabetes which is a catabolic disorder in which circulating insulin is virtually absent due to lack of production, plasma glucagon is elevated, and the pancreatic beta cells fail to respond to all known insulinogenic stimuli. Other people have type 2 diabetes which is a heterogeneous disorder leading to reduced insulin sensitivity and/or relative insulin deficiency. This is sometimes attributed to a mismatch between insulin production and insulin requirements which can range from those with severe insulin resistance and minimal insulin secretory defects to those with a primary defect in insulin secretion. The diagnosis of diabetes is done through blood testing. Fasting blood glucose of 70-110 mg/dL is considered normal, whereas, 111-125 mg/dL could indicate a possibility of prediabetes, and anything greater than 126 mg/dL may indicate a potential diabetic condition. The gold-standard diagnosis of diabetes is done through the measurement of glycated hemoglobin (HbA1c). This relates to an integrated average of blood glucose levels over a past history of 6-8 weeks; levels of HbA1c of 6.5% or greater indicates there is a high probability of diabetes.

Due to the complex nature of this disease there are various complications that can occur. Microvascular complications affect the small blood vessels by thickening the capillary basement membrane while macrovascular complications consist of
accelerated atherosclerosis (German, 2011). Both of these pathologies contribute to heart disease and stroke, high blood pressure, blindness and eye problems, kidney disease, neuropathy (impaired sensation, slow digestion, and erectile dysfunction), amputation, complications during pregnancy, decreased immune system, and depression. Complications can lead to a shortened life span if a person’s diabetes is not properly controlled by insulin, oral medications, diet changes, and exercise. In 2007, diabetes contributed to 231,404 deaths (Jin et al., 2011).

To avoid these potential complications with diabetes it is important to monitor blood glucose levels. The most common way to keep track of blood glucose levels is by doing a finger stick to test the glucose level in the blood. The traditional blood glucose meters have two parts, an enzymatic test strip and the digital detector. A person’s blood reacts with the test strip to cause the enzymatic reaction. The digital detector can then read the reaction to produce the level of glucose in the person’s blood. There are many different types of enzymatic reactions that can be used. One reaction that can be used is a reactive dye. A color change will happen depending on the concentration of glucose. Another reaction used includes a biosensor that creates an electron which can be detected by the meter (Tonyushkina & Nichols, 2009).

“Smart tattoo” sensors are a way to help diabetics keep track of their blood glucose without the hassle of pricking their finger every time they need to check their glucose. A “smart tattoo” sensor consists of fluorescent microspheres that can be implanted intradermally and examined noninvasively using light (Stein, Grant, Zhu, & McShane, 2007). This is achieved by indirectly monitoring glucose levels by measuring relative changes in phosphorescent dye emission (Stein et al., 2007). This form of
monitoring could help increase patient adherence to glucose monitoring, in turn making it easier to control blood glucose levels and decrease diabetes related complications. This paper will further explore the design of the “smart tattoo” and how it can be useful in diabetes monitoring and management.
Background

There are a variety of techniques used for continuous glucose monitoring. Continuous monitors can be broken down into different types. The first type is nonreactive, meaning that glucose is not reacted in the monitoring process. In the nonreactive measurements an intrinsic property of the glucose solution is measured (Heller, 1999). The second type is reversibly reactive where glucose is displaced and a third type is irreversibly reactive where glucose is consumed (Heller, 1999).

Another group of continuous glucose sensors are amperometric sensors. The sensors are based on using the glucose oxidase enzyme. Using this method, a sensor can utilize the glucose oxidase –catalyzed oxidation of glucose. The sensor is designed for subcutaneous implantation and replacement by the patient once or twice per week (Heller, 1999). Another amperometric sensor uses the microdialysis technique to be able to continuously monitor glucose levels.

Microdialysis is one of the first techniques developed to continuously monitor glucose levels. The dialysis tube acts like a capillary blood vessel and allows diffusion of glucose across the semi-permeable membrane. A measurement of the glucose levels in the dialysate is taken which reflect the levels of glucose in the interstitial fluid (Bolinder, Ungerstedt, & Arner, 1992). In a study conducted by Bolinder, Ungerstedt, and Arner, microdialysis was found to be able to directly monitor glucose concentration in subcutaneous adipose tissue. This study has demonstrated using microdialysis to directly determine the absolute glucose concentration in subcutaneous adipose tissue. This technique may be used clinically for continuous glucose monitoring in diabetic patients (Bolinder et al., 1992). One of the major drawbacks with this method provides
incomplete recovery of glucose. This means that the actual glucose concentration is unknown making it unreliable to use as a basis of monitoring glucose concentrations, and basing treatment plans off of these values (Bolinder et al., 1992).

Taking this concept a step further, Bolinder and Ungerstedt conducted another study testing the microdialysis technique in ambulatory insulin-dependent diabetic patients (Bolinder, Ungerstedt, & Arner, 1993). In this experiment, a microdialysis probe was implanted and then plasma was flushed through by a pump. Glucose particles that made it through the microdialysis probe were collected every 1 or 2 hours for 75 hours. Insulin therapy of individual patients was adjusted according to the glucose readings and resulted in a decrease in Hemoglobin A1C that lasted for 9 months (Bolinder et al., 1993). This result demonstrates the usefulness of continuous monitoring as a reliable way to help manage diabetes.

There are patient-replaced microsensors which are commercially available. These monitors use a sensor probe inserted by the patient into the subcutaneous tissue. The sensor relays the glucose concentration to the transmitter which in turn sends the concentration level to the display unit. The display unit keeps track of glucose concentrations so the patient can trend his glucose levels. Sensors such as the Medtronic Paradigm® Real Time System and the Medtronic Guardian® RT can stay in the skin three days. Whereas sensors such as Abbott FreeStyle Navigator System and DexCom Seven Plus® can stay in the skin five to seven days ("What is continuous glucose monitoring?" 2009). It is most useful for trending glucose levels and a patient would still have to perform finger sticks for daily monitoring.
A major advantage that “smart tattoos” have over these systems is that there is no external device that must be hooked up for use. They are not connected to a display unit so the patient would not have to worry about a bulky display unit interfering with their everyday life.

Along with the microdialysis sensors and the microsensor described above, there is an innocuous microsensor which is replaced by the patient twice a week and a self-contained surgeon implanted transmitter containing package that operates for more than 100 days (Heller, 1999). Compare this with the patient replaced electrode lasts for three days. One advantage of these microsensors is it is small enough that the patient cannot feel them under the skin. Other advantages to the surgically implanted sensor are that it is wireless and it has a longer lifetime (Heller, 1999). The two-week lifespan is considerably longer than three days as other sensors use. The surgically implanted sensor seemed to be the most convenient because it allowed for continuous monitoring without the hassle of an external wire to collect the data like the sensors previously described.

A large problem that arose with these sensors was the body’s immune reaction to a foreign substance. The body formed an immune response causing cells around the capsule to use up glucose that they needed (Heller, 1999). An inaccurate reading by the sensor is more likely due to the oxygen consumption by the infiltrating cells. The sensor would need to be replaced after some time because a capsule would form around it as the immune reaction attempts to isolate the foreign sensor rendering it useless. This was studied with glucose sensors implanted into rats. It was found that the sensors in vivo were only 70% effective after three to four day partially due to the rat’s immune
system reaction (Bobbioni-Harsch, Rohner-Jeanrenaud, Koudelka, de Rooij, & Jeanrenaud, 1993).

Another problem that arose was the glucose transport limiting membrane. This is an essential component for an implanted glucose sensor. The need for a full range sensor was specified and these sensors were not at that level. Monitoring of the full range of glucose concentrations encountered in diabetes is difficult and creates strict demands on the flux-limiting membrane (Heller, 1999). Due to this concept most of these sensors could detect hypoglycemia only. A possible solution to the influx predicament is the development of an oxygen permeable membrane that could restrict the influx of glucose but not oxygen (Heller, 1999). A consideration that must be made with the glucose limiting membrane is the possibility that if one substance can move easily in and out of the membrane what is stopping another substance from doing the same thing? The toxicity of second and third generation mediator is limited (Gerritsen, Jansen, & Lutterman, 1999). Solutions to this issue would be making sure the mediator is tightly bonded to another substance within the sensor that would make it extremely difficult for that bond to be broken or to entrap the mediator inside the sensor (Gerritsen et al., 1999).

Calibrating the sensor after implantation poses another drawback to the early technology. There are two types of calibration, one point calibration and two point calibration. Two-point calibration is considered the most reliable, but to put that into actual practice with the implanted glucose sensor does not seem reasonable (Gerritsen et al., 1999). If the sensor signal and the concentration can change predictably after implantation then recalibration is not required (Heller, 1999). There are background
currents that can interfere with the signal and produce an incorrect reading. This background current prevents one point in vivo calibration so the patient cannot confirm that the sensor operates properly (Heller, 1999).

“Smart tattoos” are a way of being able to continuously monitor glucose as well as allow for a spot reading to be done. Continuous glucose monitoring is used to trend glucose levels over a period of time. It is able to do this by checking the level of glucose in the interstitial fluid, in contrast to blood measurements as used in finger stick tests and blood draws. Interstitial fluid in adipose tissue was found to have glucose concentrations almost identical to venous blood, making it a reliable way to monitor glucose levels. It is this principle that current continuous glucose monitors and “smart tattoos” use. The drawback to using interstitial fluid is there is a slight time delay in glucose levels, meaning that it takes a little longer for the interstitial fluid to achieve the same glucose concentration as the blood. It has been found that changes in the circulating glucose concentration are usually detected in the adipose tissue within less than 5 minutes compared to blood glucose concentrations (Bolinder et al., 1993). In a study done by Heller, it was found that the capillary blood and subcutaneous glucose levels were statistically identical when there was a slow rate (less than 1.8 mg/dL min) of change (Heller, 1999).

While that type of system works, there is still a gap in monitoring glucose levels that “smart tattoos” will be able to fill. For this technology to be practical there is a general consensus as to what characteristics are needed to create a viable glucose biosensor. These characteristics include a wide range, reproducible and reversible signal, the technology should be easily made, and the biosensor should have an
extended lifetime. They are the same basic characteristics that are employed by the previously discussed glucose monitoring options. Different reactions have been studied to determine which reaction would be able to be employed in a glucose biosensor. (Moschou, Sharma, Deo, & Daunert, 2004).

The system most commonly used in the “smart tattoo” is the lectin-based fluorescence glucose sensing system (Russell, Pishko, Gefrides, McShane, & Cote, 1999). Fluorescence resonance energy transfer (FRET) and fluorescein isothiocyanate (FITC) dextran measurements utilize the plant sugar binding protein concanavalin A (Con A) which is specific to glucose to measure the glucose level in the subcutaneous tissue. This works by the FITC-dextran interacting with the Con A in the absence of glucose. Once glucose is in the system the FITC increases because the Con A will bind to the glucose instead of the FITC-dextran (Russell et al., 1999).

Another common system that is a possibility is the glucose oxidase and fluorescein-5(6)-carboxamido-caproic acid (Pickup, Hussain, Evans, Rolinski, & Birch, 2005). In this system there is a fluorescence change after glucose is added but the change is not proportional to the glucose that is added. Instead it is proportional to the time between the addition of the glucose and the change in fluorescence (Pickup et al., 2005). These are the pathways that are currently being pursued to create a viable “smart tattoo”.
Literature Review

To be able to use the reaction above, it is important to understand how the reaction works and how it can be effective in the design of the “smart tattoo”. The diffusion of glucose and oxygen across the membrane is a key in the microsensors design. Once diffused into the sensor, oxygen levels are proportionally reduced through glucose oxidase catalysis. Glucose oxidase is needed to be encapsulated in the microsphere to allow this reaction to take place. There have been various techniques used to encapsulate glucose oxidase such as physical entrapment (emulsion), chemical conjugation, and a combination of physical and chemical (emulsion-conjugation) (Zhu, Srivastava, Brown, & McShane, 2005). It was found that the emulsion-conjugation technique worked the best in the sense that it improved stability of glucose oxidase by reducing the leaching out of the microsphere; the glucose oxidase concentration was highest when using the emulsion-conjugation technique after one week when encapsulated in the poly-allyamine hydrochloride/sodium poly styrene sulfonate (PAH/PSS) coating. It allowed the glucose oxidase to have more activity in the microsphere compared to the other methods and this activity was consistent throughout the four week trial (Zhu et al., 2005).

The other reaction that is utilized in fluorescence based glucose sensors is the use of the plant lectin concanavalin A (Con A). This molecule has competitive binding sites for glucose or dextran (Pickup, et al., 2005). Utilization of this molecule is through the using dextran as well as the binding of glucose to obtain a measurement. Fluorescein isothiocyanate (FITC) combined with dextran will readily bind to the Con A in the sensor. Glucose has a higher affinity for Con A than the FITC-dextran which
causes the FITC-dextran to be displaced from the Con A. When the FITC-dextran is displaced there is an increase in concentration of FITC-dextran which increases the signal in the lumen (Pickup et al., 2005). A major problem with this reaction is that over time the sensor signal tends to drop due to Con A leaking out of the membrane, which causes a problem not only with sensor function but the effects of Con A into the human system (Pickup et al., 2005).

The developers need to be able to test the sensor in a larger model before being able to scale it to a micro-sized model that would be able to be implanted into someone. There needs to be a ratio between glucose and oxygen diffusion and reaction in the larger scale whose sensitivity and specificity can accurately be correlated to the smaller scale. It has been found in multiple studies that glucose and oxygen reach a steady state in the interstitial fluid within 3 seconds after the initial change in glucose concentration. The model in the glucose sensor calculates the average oxygen concentration to calculate the glucose concentration allowing the sensor to predict step changes in glucose (Brown & McShane, 2006). The diffusion of oxygen is different than that of glucose into the sensors. Oxygen tends to diffuse smoothly into the sphere while glucose tends to sharply diffuse into the sphere. This is due to the fact that oxygen diffuses faster than glucose. Because of this fact it is imperative that the sensor be able to control the rate of glucose diffusion comparative to oxygen. This principle must be taken into account when trying to maintain this ratio into a microsphere. It is a natural concept that substrates will diffuse into different size containers differently depending on the equilibrium.
This brings around the question of “how small is too small?” At what point would the size of the sensor loose the capacity to accurately and effectively monitor the glucose/oxygen concentration. Brown and McShane studied the size of the sphere in relationship to the sensitivity of monitor glucose concentration over different ranges. They found that spheres with a radius of at least 20 micrometers will cover the range of 0-12 millimeters. Also they found the range could be increased with a larger sphere but as expected the larger sphere increases response time most likely due to increased time needed to reach equilibrium (Brown & McShane, 2006).

This concept was combined with a phosphorescent dye to be able to read the sensor noninvasively. The dye becomes coated in oxygen allowing the glucose oxidase reaction previously discussed above to be utilized to interpret glucose concentration. In this reaction there is a uniformed distribution throughout the sensor allowing for a more accurate reading. To be able to determine the accuracy of the reading three key properties were identified. One was step changes in glucose concentration. The next property identified was a buffer solution which is needed to help return the phosphorescent dye back to baseline reading. The third was making sure the emission remained independent of modulations in glucose concentration (Stein et al., 2007).

Knowing this is the goal for the readings of the sensor, it is difficult to accomplish this over the full range needed to monitor glucose concentrations specifically for hypoglycemia.

Previous problems with utilizing this reaction were containing the substances inside the sphere and the reversibility of the dextran displacement within a reasonable amount of time (Russell et al., 1999). An aqueous based sphere was used but these
problems were not resolved which led to the development of using photopolymerized poly ethylene glycol (PEG) hydrogel coating instead of the alginate-poly (L-lysine) spheres. The PEG hydrogel allows greater specificity when compared with other approaches. With the new capsule in place this technology is potentially agreeable to place into the subcutaneous tissue similar to a tattoo.

Another feature that the microsphere must have is the ability to allow leaching of molecules while still encapsulating the original macromolecules. The main objectives of the coating is to provide a diffusion barrier to inhibit leaching of material out of the capsule, provide a transport barrier to slow diffusion of molecules into the capsule, and to create internal intensity reference to allow for ratiometric measurements (Brown, Srivastava, & McShane, 2005). This was assessed in a study done by Srivastava and McShane (Brown et al., 2005). In the study, the alginate sphere was made and a special technique was used to coat the outer layer of the sphere. The technique was a layer-by-layer self-assembly technique. This means that polyelectrolytes of opposite charge were stacked onto templates creating stable multi-layers. These layers were tested to see if there were any macromolecules that leached out into the surrounding area. The conclusion of this study was that the multi-layer coating around the capsule was effective in helping to decrease leaching of macromolecules into the surrounding area. (Brown et al., 2005). This has helped to allow for further investigation into the effectiveness of the nanofilm coating. The coating was tested to see if the sensitivity would still be as high as it was before the extra layers were added. The sensors were tested to see if they were able to measure glucose concentrations over significant range with greater sensitivity than the measured response. Brown and associates found that
the sensors were limited to less sensitive measures over the significant range due to the combination of enzyme concentration and oxygen transport (Brown et al., 2005). By discovering this, it allowed the creators to pinpoint what needs further improvement on the sensor design like sphere size, enzyme concentration, permeability, and film thickness.

The layer-by-layer technique is effective in allowing control in the thickness of the film making it reproducible on a nanoscale. It is important to control film thickness because thickness can affect the diffusion rate and sensitivity of a sensor. Conversely a nanofilm is needed to help control the diffusion of glucose and oxygen across the sensor to permit an accurate reading. When testing various thicknesses compared to no coating, it was found that a thickness of 12 nanometers PAH/PSS resulted in a range of 0-12 millimeters whereas a thickness of 32-36 nanometers PAH/PSS resulted in a range of 0-30 nanometers. It was found that anywhere above or below these thicknesses were not as reliable, making this a target range for microsensor development (Brown & McShane, 2006).

This concept was again demonstrated by Stein, Singh, and McShane. They tested not only the coating thickness but also what would work best for the range in glucose monitoring specifically hypoglycemia and hyperglycemia. The hypothesis was that by increasing the thickness that would slow glucose diffusion into the sensor and increase local oxygen levels and subsequently increasing the range of the sensor. The authors found that by adjusting the nanofilm thickness and assembly it was possible to create sensors that are sensitive to hypo, normo, and hyperglycemia (Stein, Singh, & McShane, 2008).
Another factor to consider when discussing thickness of the nanofilm is porosity. Porosity can be utilized to help increase the range of monitoring once the desired thickness is set. As proven in previous studies the thickness can only be manipulated to a point. Once that point is reached it is then the fine tuning of the coating’s porosity that might be able to help increase the range of the sensor to allow in vivo testing. Highly porous microspheres made from silica were tested. This material was found to have a linear correlation with glucose meaning that as the glucose concentration increased the response of the sensor increased up until 600mg/dL. This warranted the prediction that PAH/PSS layer-by-layer coatings that are about 65nm thick would be able to respond over the physiological range of glucose (Singh & McShane, 2011).

With having the basic design set, “smart tattoo” research has been able to advance by focusing on the problems that have surfaced. Such problems include maintaining sensitivity and specificity, fighting against the body’s inflammatory process, and prolonging the implantation time. These problems have plagued designers because without these problems being solved the “smart tattoo” will not be able to be viable.

Sensitivity and specificity have been previously discussed. These factors can be correlated to the size and thickness of the sphere. Taking into account both of these factors is necessary to create a sensor that is small enough to be implanted into someone, but large enough to hold the reaction needed to take place to produce an accurate reading. The larger sensor size would allow for a broader range of glucose readings, in lieu of that if the porosity of the coating is increased then the range can be increased without increasing the overall size. This would permit the original concept of the “smart tattoo” to be upheld.
A large problem with any implanted device is the body’s inflammation process against a foreign object. The body will have two reactions to the implantation of the glucose sensor. The first is the initial reaction of cutting the skin and tissue to insert the sensor. The second is the body’s ongoing reaction to fight a foreign object that is within the body. Both of these reactions must be taken into account due to the fact that all cells use glucose and oxygen, potentially skewing the results from the implanted sensor. With the long term reaction to the sensor, the body will build up a barrier around it rendering it unable to function as a glucose sensor.

This has been a foreseeable problem since the original design of implantable glucose sensors because of other implantable devices, such as chemotherapy ports and time released hormone therapy. Hickey, Kreutzer, et al. used the same concept from these previous devices to see if there could be a way to keep the body immune suppressed to allow these devices to operate properly. The authors used a dexamethasone/poly(lactide-co-glycolide) (PLGA) microsphere system that would be capable of releasing an initial burst of anti-inflammatory reagent followed by a longer acting anti-inflammatory reagent released second. They implanted a sensor model (cotton thread) to test the ability of the microsphere to fight off the inflammatory process. They tested this system over one month. The results were promising in that it was found that the inflammatory response was increased at day one then decreased over the one month time period. This study showed that the dexamethasone/PLGA microsphere system suppressed the acute and chronic immune reaction for four weeks. (Hickey, Kreutzer, Burgess, & Moussy, 2002). This research led the way to allow further studies into this concept that could be focused towards the implantable glucose sensors.
In a more recent study this same concept was used with implanted glucose sensors. This study comprised of using a microsphere with dexamethasone and diclofenac sodium to help against the acute and chronic phases of inflammation. The goal of the study was to deliver 100% of the anti-inflammatory drug to suppress the immune system reaction caused by the “smart tattoo” for three to four weeks. The results showed that the technique in which the microspheres were built helped with the overall outcome. The layer-by-layer technique used to create the anti-inflammatory microsphere reduced the initial burst and prolonged the induction phase. These results also suggest that high drug loading is not required. The inflammatory response answered to an optimal amount of drug. The conclusion of the results showed that the microspheres not only helped fight the inflammatory response of the body but did help increase the life of the implanted glucose sensor (Jayant, McShane, & Srivastava, 2011). This technology helped to prevent a fibrous capsule from being formed which would allow the “smart tattoo” greater longevity.

Another study, done in 2011, concluded similar results further supporting the use of this technique to increase the biocompatibility of the implanted glucose sensor. The “smart tattoo” prototype was implanted into Sprague-Dawley rats along with an anti-inflammatory drug loaded microsphere. The anti-inflammatory drug was released over thirty days and it was released at zero-order release kinetics. This differs from the previous study by allowing a steady state of anti-inflammatory drug release to constantly fight against the immune reaction instead of the initial burst then a continuous release for a shorter time. The result was that the anti-inflammatory drugs did suppress the inflammatory response at the site of implantation. This allowed the sensor to function
properly over the thirty day period. Because of this study it shows promise in improved biocompatibility to allow an implanted “smart tattoo” to thrive in the body over an extended period of time. (Srivastava, Jayant, Chaudhary, & McShane, 2011). Using these findings, it would be reasonable to think that a layer could be incorporated into the “smart tattoo” that could break down in the body to continuously fight off the inflammatory response (Jayant et al., 2011). This concept would cut back on foreign objects in the body and allow for less invasive measures for the patient.

While the anti-inflammatory microspheres help to keep the area surrounding the sensor clear, the glucose sensor itself has a limited lifespan. The glucose sensor uses the phosphorescent dye reacting with oxygen to create the luminescent readout. The proteins used are sensitive and selective, have a tunable response range, and a quick response time (Singh & McShane, 2010). The proteins in this reaction are sensitive and thus creating the issue of longevity. It has been found in prior studies that the longevity can be improved by incorporating the enzyme catalase (CAT). A problem with the glucose oxidase reaction is the reaction that happens between hydrogen peroxide and glucose oxidase. This can be neutralized by CAT because hydrogen peroxide is a substrate of CAT thus causing the hydrogen peroxide to want to bond with CAT instead of the glucose oxidase (Baker & Gough, 1993). This was the basis for another study done in 2010 by Singh and McShane. The authors wanted to test the stability of the design of the glucose sensors with and without CAT. The results showed that the glucose sensors with glucose oxidase and CAT had a less than ten percent variation in response. This test was performed over a month. The stability in the glucose oxidase is attributed to the fact that the scheme is diffusion limited. In the glucose sensors without
CAT there was a forty percent loss of sensitivity after four days. Overall the glucose
sensors that incorporated CAT had five times the stability when compared to the
glucose sensors without CAT. The authors of this study were able to conclude that this
could be used to test the glucose sensor over three months and theoretically the
change in sensitivity would decrease ten percent. (Singh & McShane, 2010).
Conclusion

Diabetes is a growing problem in the United States population and complications of diabetes can be life threatening. Constant glucose monitoring is imperative to help control the course that diabetes can take. “Smart tattoos” are a compromise between doing constant finger sticks and having a continuous monitor that must be changed out every few days. They are able to sense the glucose levels at a snap-shot in time like the traditional finger stick method but use the technology like the continuous monitors to alleviate the hassle and pain of a finger stick. They are more convenient for the patient because the patient no longer has to be hooked up to an outside source for a reading.

“Smart tattoos” use the reaction of FITC-dextran interacting with the Con A in the absence of glucose. Once glucose is in the system the FITC increases due to the Con A binding to the glucose instead of the FITC-dextran. This reaction allows the correlation of oxygen to glucose creating an indirect path to measure the glucose concentration in the interstitial tissue. The glucose concentration in the interstitial tissue while is not the same as the direct measure of blood glucose is proved to be a reliable monitor for diabetics.

While there are many components to the “smart tattoo” that are positive there are still a few drawbacks that must be considered before testing can progress. One such consideration is the sensitivity and specificity of the glucose sensor. The sensitivity and specificity must be maintained throughout the lifespan of the glucose sensor. Some solutions to this problem are the additive enzyme catalase. This enzyme can help block hydrogen peroxide from combining with glucose oxidase allowing the glucose sensor to retain its sensitivity and specificity.
Another issue that arose was the body’s natural reaction to a foreign object. By adding an anti-inflammatory component to the microsphere it is possible to fight off this reaction in the acute and chronic phase. The slowly dissolving microsphere that releases dexamethasone and diclofenac sodium is able to extend the lifespan of the glucose sensor up to one month.

The question with that becomes “how long can we stretch time between replacing the sensors?” This needs to take into account not just the body building up a capsule around the sensor but the sensitivity and specificity without the capacity to recalibrate the sensor. It has been shown that with the anti-inflammatory microsphere that it is possible to keep the sensitivity of the glucose sensors in vivo for one month. With adding the catalase enzyme further studies are need to see if the lifespan of the sensor can be prolonged up to three months. It seems to be reasonable that if this technology could last for three months then possibly it could be extended to six months. Telling a patient that he needs a new “smart tattoo” twice a year would increase compliance and use. The research has not been done in this capacity but it seems as though it is heading in this direction.

One last obstacle that must be overcome to truly see the capacity of the “smart tattoo” is United States Food and Drug Administration (FDA) premarket approval. There are four steps that must be accomplished on the application for approval. First the application will get reviewed to make sure it is filled out completely. Next the FDA must do an in-depth review. The third step is the panel review and lastly there will be deliberations over what has been found (Gutman et al., 2002). This means that the FDA premarket review of “smart tattoos” comprises of a comprehensive analytical, clinical,
and manufacturing assessment of devices (Gutman et al., 2002). The FDA will work
with manufacturers to develop clear labeling and appropriate educational programs to
ensure correct device use (Gutman et al., 2002).

An issue that seems to be hindering the process is that the technology is not yet
well understood. Noninvasive glucose monitoring is still a relatively new concept even
though there have been the recent advances as explained throughout this paper.
Another issue that is apparent is the information obtained by “smart tattoos” is different
from traditional glucose monitors. “Smart tattoos” use the readings from the interstitial
fluid instead of directly from the blood. While this has shown to be an adequate source
for glucose monitoring the FDA must still look further into this topic to allow approval
(Khalil, 2004). This falls under the increased need for analytical and clinical review.

Hopefully these issues can be worked out in a timely manner. “Smart tattoo”
technology shows a promising way to improve the lives of diabetics throughout the
United States. It will allow healthcare providers to better manage the diabetic patient
and all the complications that can occur through the disease process.
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Abstract

Uncontrolled diabetes is accompanied by multiple complications to multiple organ systems making it important to monitor blood glucose levels for glycemic control. Traditionally this is done by performing a finger stick. Objective: “Smart tattoo” sensors are fluorescent microspheres that can be implanted intradermally and interrogated noninvasively using light. This is achieved by indirectly monitoring glucose levels by measuring relative changes in phosphorescent dye emission, making monitoring easier for the patient. Method: A review was conducted of current literature through PubMed, CINAHL, EBESCO, and MEDLINE, on the technology that comprises “smart tattoos” and recent advances that have been made. Results: Advances occurred through increasing the sensitivity, specificity, range, and longevity. There are drawbacks that must be considered such as leaching, immune reaction to sensor, prolonging the implantation time, and FDA approval. Conclusion: Improvements have been made in “smart tattoos” but the drawbacks must be fixed before human testing can occur.