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Performance characterization of an abiotic and fluorescent-based continuous glucose monitoring system in patients with type 1 diabetes

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ABSTRACT

A continuous glucose monitoring (CGM) system consisting of a wireless, subcutaneously implantable glucose sensor and a body-worn transmitter is described and clinical performance over a 28 day implant period in 12 type 1 diabetic patients is reported. The implantable sensor is constructed of a fluorescent, boronic-acid based glucose indicating polymer coated onto a miniaturized, polymer-encased optical detection system. The external transmitter wirelessly communicates with and powers the sensor and contains Bluetooth capability for interfacing with a Smartphone application. The accuracy of 19 implanted sensors were evaluated over 28 days during 6 in-clinic sessions by comparing the CGM glucose values to venous blood glucose measurements taken every 15 min. Mean absolute relative difference (MARD) for all sensors was 11.6 ± 0.7%, and Clarke error grid analysis showed that 99% of paired data points were in the combined A and B zones.

1. Introduction

The prevalence of diabetes mellitus continues to increase in industrialized countries, and projections suggest that this figure will rise to 4.4% of the global population (366 million individuals) by the year 2030 (Wild et al., 2004). Glycemic control is a key determinant of long-term outcomes in patients with diabetes, and poor glycemic control is associated with retinopathy, nephropathy and an increased risk of myocardial infarction, cerebrovascular accident, and peripheral vascular disease requiring limb amputation (Group, 1998). Despite the development of new insulins and other classes of antidiabetic therapy, roughly half of all patients with diabetes do not achieve recommended target hemoglobin A1c (HbA1c) levels < 7.0% (Resnick, 2006).

Frequent self-monitoring of blood glucose is necessary to achieve tight glycemic control in patients with diabetes mellitus, particularly for those requiring insulin therapy (Farmer et al., 2007; Klonoff, 2007). Continuous glucose monitors (CGMs) enable frequent glucose measurements as well as detection and alerting of impending hyper- and hypoglycemic events (Clarke and Kovatchev, 2007). The use of CGMs by type 1 diabetics has been demonstrated to significantly reduce their time spent in hypoglycemia (Battelino et al., 2011). Moreover, integration of CGMs with automated insulin pumps allows for establishment of a closed-loop "artificial pancreas" system to more closely approximate physiologic insulin delivery and to improve adherence (Clarke and Kovatchev, 2007). However, currently available transcutaneous CGM systems have short durations of use and require replacement every 5–7 days (Calhoun et al., 2013; Christiansen et al., 2013; McGarraugh et al., 2011). Sensor in vivo lifetime may be limited by stability of the enzymes used for glucose recognition, by bio-fouling at the surface of the sensor electrodes, by ongoing inflammatory responses surrounding the sensors as a consequence of the partial implantation (i.e., sensor protrudes through the skin), or by a combination of these effects. To overcome these limitations, a fully subcutaneously implantable sensor has been developed that uses a fluorescent, non-enzymatic (bis-boronic acid based) glucose indicating hydrogel and a miniaturized optical detection system.

The present report describes the technology of the continuous glucose monitoring system and presents accuracy and performance data of sensors implanted for 28 continuous days in patients with type 1 diabetes.

2. Materials and methods

2.1. Continuous glucose monitoring system

The components of the novel CGM system are shown in Fig. 1. A small, fully subcutaneously insertable sensor measures glucose concentrations in interstitial fluid. An externally worn transmitter

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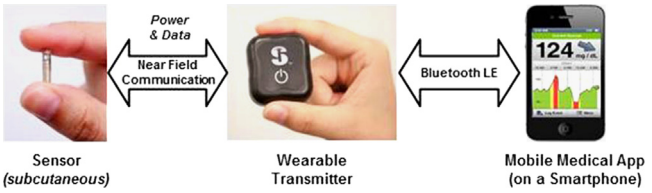

Fig. 1. Continuous glucose monitoring system components.

remotely powers and communicates with the inserted sensor to initiate and receive the measurements. This information is communicated wirelessly via Bluetooth™ to a Handheld Application running on a secondary display and can be downloaded and configured through a Universal Serial Bus (USB) port. A web interface has also been developed for plotting and sharing of uploaded data.

2.1.1. Subcutaneously insertable fluorescent sensor

The sensor (Fig. 2A) is a micro-fluorometer that is encased in a rigid, translucent and biocompatible polymer capsule 3.3 mm [0.13″] in diameter and 15 mm [0.62″] in length (Colvin and Jiang, 2013). Glucose concentration is measured by means of fluorescence from the glucose-indicating hydrogel, which is polymerized onto the capsule surface over the optical cavity. The optical system contained within the capsule is comprised of a light-emitting diode (LED), which serves as the excitation source for the fluorescent hydrogel; two spectrally filtered photodiodes, which measure the glucose-dependent fluorescence intensity; an integrated circuit with onboard temperature sensor; and an antenna, which receives power from and communicates with the transmitter.

The glucose-indicating hydrogel (Fig. 2B) consists primarily of poly(2-hydroxyethyl methacrylate) (pHEMA) into which a fluorescent indicator (Fig. 2C) is copolymerized. In contrast to other CGMs, which utilize electrochemical enzyme-based glucose sensors, no chemical compounds are consumed (i.e., glucose, oxygen) or formed (i.e., hydrogen peroxide) during use, and the glucose-indicating hydrogel is not subject to the instability characteristics of enzymes. Instead, glucose reversibly binds to the indicator boronic acids groups (which act as glucose receptors) in an equilibrium binding reaction (James et al., 2006). Subsequent disruption of photoinduced electron transfer (PET) results in an increased fluorescence intensity upon glucose-binding. When glucose is not present, anthracene fluorescence is quenched by intermolecular electron transfer (indicated by the curved arrows in Fig. 2c) from the unpaired electrons on the indicator tertiary amines. When glucose is bound to the boronic acids, the Lewis acidity of boron is increased, and weak boron-nitrogen bonds are formed. This weak bonding prevents electron transfer from the amines and consequently prevents fluorescence quenching. Of note, the indicator is not chemically altered as a result of the PET quenching process. Fluorescence increases with increasing glucose concentrations until all indicator binding sites are filled at which point the signal reaches a plateau (James et al., 2006; Shibata et al., 2010). The measurement of a given glucose concentration can be modeled by the following equation:

$$Glucose = K_d \frac{F_{meas} - F_{min}}{F_{max} - F_{meas}}, \quad (1)$$

where F_{min} is the integrated fluorescence in the absence of glucose, F_{max} is the integrated fluorescence when all of the accessible indicator is bound to glucose, F_{meas} is the integrated fluorescence at a given concentration of glucose, and K_d is the dissociation constant for the indicator. Eq. (1) serves as the core of the CGM system glucose algorithm that also incorporates kinetic and

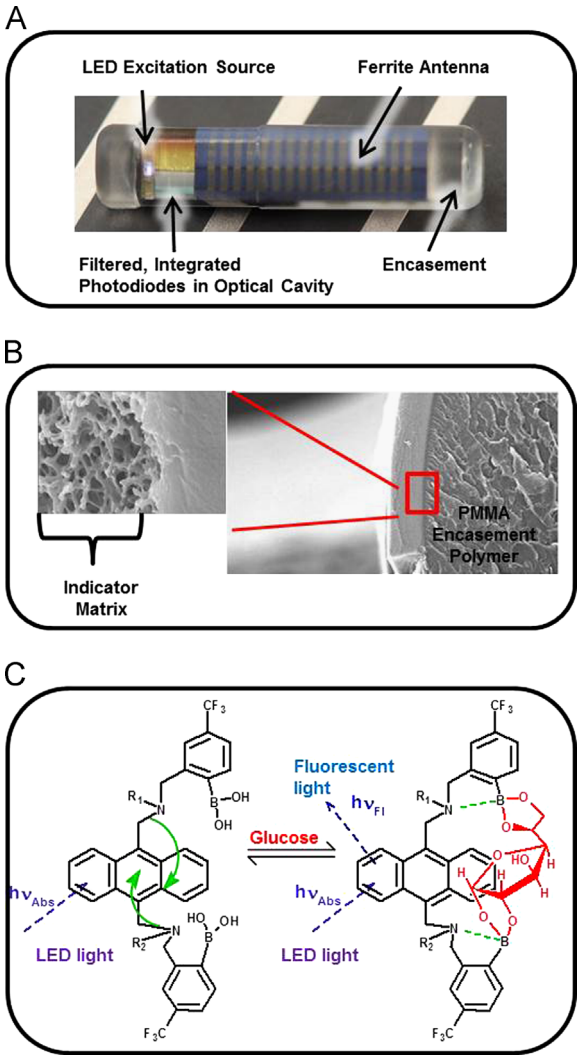

Fig. 2. Implantable optical-based glucose sensor. (A) Photograph of the implantable glucose sensor (shown without glucose-indicator hydrogel coating); (B) scanning electron microscope (SEM) images of the glucose indicator hydrogel grafted onto the outside of the PMMA sensor encasement; and (C) chemical structure and glucose binding mode of indicator moiety. R_2 shown in the figure denotes connectivity to the hydrogel backbone, while R_1 represents a propionic acid side chain.

temperature dependences, as previously described (Wang et al., 2012). Since self-monitored blood glucose (i.e., finger-stick) measurements are used to calibrate the CGM system, a time and glucose dependent lag time model is used in the algorithm to correct for differences between blood glucose and interstitial fluid (ISF) glucose concretions (Rebrin et al., 1999). A 10-nm layer of platinum, deposited onto the sensor by sputter coating, serves to prevent in vivo oxidation of the indicator phenylboronic acids groups. Platinum catalytically degrades the reactive oxygen species that are otherwise generated by the body's normal wound healing response to sensor insertion and by the body's response to a foreign body (Colvin and Jiang, 2013). A glucose-permeable membrane covers the hydrogel and provides a biocompatible interface.

The sensor contains a custom integrated circuit (Dehennis et al., 2013) that has been fabricated specifically for this application. Additionally, it includes on-board electrically erasable programmable memory (EEPROM) for local configuration storage and production traceability. Its ability to communicate is mediated by a near field communication interface to the external transmitter. The sensor consists of only six electrical parts encased within the