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Percutaneous fiber-optic sensor for chronic glucose monitoring *in vivo*

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Abstract

We are developing a family of fiber-optic sensors called Sencils™ (*sen*sory *cil*ia), which are disposable, minimally invasive, and can provide *in vivo* monitoring of various analytes for several weeks. The key element is a percutaneous optical fiber that permits reliable spectroscopic measurement of chemical reactions in a nano-engineered polymeric matrix attached to the implanted end of the fiber. This paper describes its first application to measure interstitial glucose based on changes in fluorescence resonance energy transfer (FRET) between fluorophores bound to betacyclodextrin and Concanavalin A (Con A) in a polyethylene glycol (PEG) matrix. *In vitro* experiments demonstrate a rapid and precise relationship between the ratio of the two fluorescent emissions and concentration of glucose in saline for the physiological range of concentrations (0–500 mg/dl) over seven weeks. Chronic animal implantation studies have demonstrated good biocompatibility and durability for clinical applications.

Keywords: Optical fiber; Chemical sensor; Fluorescence resonance energy transfer; Affinity-binding assay; Glucose; Quantum dots

1. Introduction

Clinical studies have concluded that fine-tuning of insulin administration on the basis of frequent glucose measurements provides substantial advantages in the management of diabetes (Diabetes Control and Complication Trials Research Group, 1993; UK Prospective Diabetes Study Group, 1998). Such treatment can dramatically reduce mortality and complications from the chronic metabolic fluctuation in either hyperglycemia or hypoglycemia. Ideally, insulin could be administered by "artificial pancreas" consisting of a chronically implantable sensor, a pump and an algorithm to adjust dosage continuously.

Presently, insulin delivery technology (insulin formulation and pump designs) is well developed but glucose sensors remain problematic (Steil et al., 2004). A suitable sensor should have a low cost to operate, which is related to the cost of the sensor itself, the cost to install it and the frequency at which it must be changed. It should be ergonomically unobstructive and easy to use to facilitate frequent measurements. It must have sufficient accuracy (as defined clinically by error grid analysis; Clarke, 2005), ideally without requiring intrusive calibration.

In the current clinical environment, choices for glucose monitoring are limited. Intermittent self-monitoring of blood glucose (SMBG) is the clinical method of choice. Typically, glucose measurements are done by pricking a finger (or other more insensitive region such as upper arm) and extracting a drop of blood, which is then applied to a test strip composed of chemicals sensitive to the glucose in the blood sample. An optical meter is used to analyze the blood sample and gives a numerical glucose reading. Most conventional SMBG devices have 95–99% accuracy in Clarke error grid analysis (Clarke, 2005). Because of the associated pain and inconvenience, however, few patients take more than a couple of readings per day, and so are at risk from unexpected and undetected peaks and valleys of glucose

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concentrations. The FDA has conditionally approved 4 short-term (<72 h) continuous monitoring sensors. All measure interstitial fluid glucose concentrations using the long-established enzymatic method involving glucose oxidase. This assay method consumes glucose enzymatically, creating a concentration gradient that may become steeper as the sensor is walled-off by the foreign body reaction. The glucose oxidase deteriorates over time and is sensitive to pH and temperature (Usmani and Akmal, 1994; Tamada et al., 2002; Wentholt et al., 2006). Limited or uncertain stability and accuracy (<80% in Clarke error grid analysis) prevent them from being used exclusively, so patients must still calibrate and cross-check using SMBG methods. The percutaneous probes are inherently complex and expensive to manufacture and include a multipin electrical connector that must be fixed mechanically to the skin surface near the point of entry. This fixation interferes with physical activity and hygiene and itself limits the long-term use of such percutaneous sensors.

We are developing a family of disposable, minimally invasive, *in vivo* sensors that can measure various analytes in a patient over a period of several weeks. The key element is a chronically implanted optical fiber (Fig. 1) with size and flexibility similar to a human hair, which would enable it to be both mechanically stable and unobtrusive when implanted in any convenient patch of hairy skin. Optical fibers are thin, lightweight, chemically stable, and generally biocompatible, all desirable properties for medical devices. Fiber communication technology is well established and has the advantages of high capacity, low attenuation, immunity to electromagnetic interference, and inherent electrical isolation that are attractive for this application.

The glucose sensor measures glucose concentration by the much-studied fluorescence resonance energy transfer (FRET) assay based on the selective binding of saccharides by the

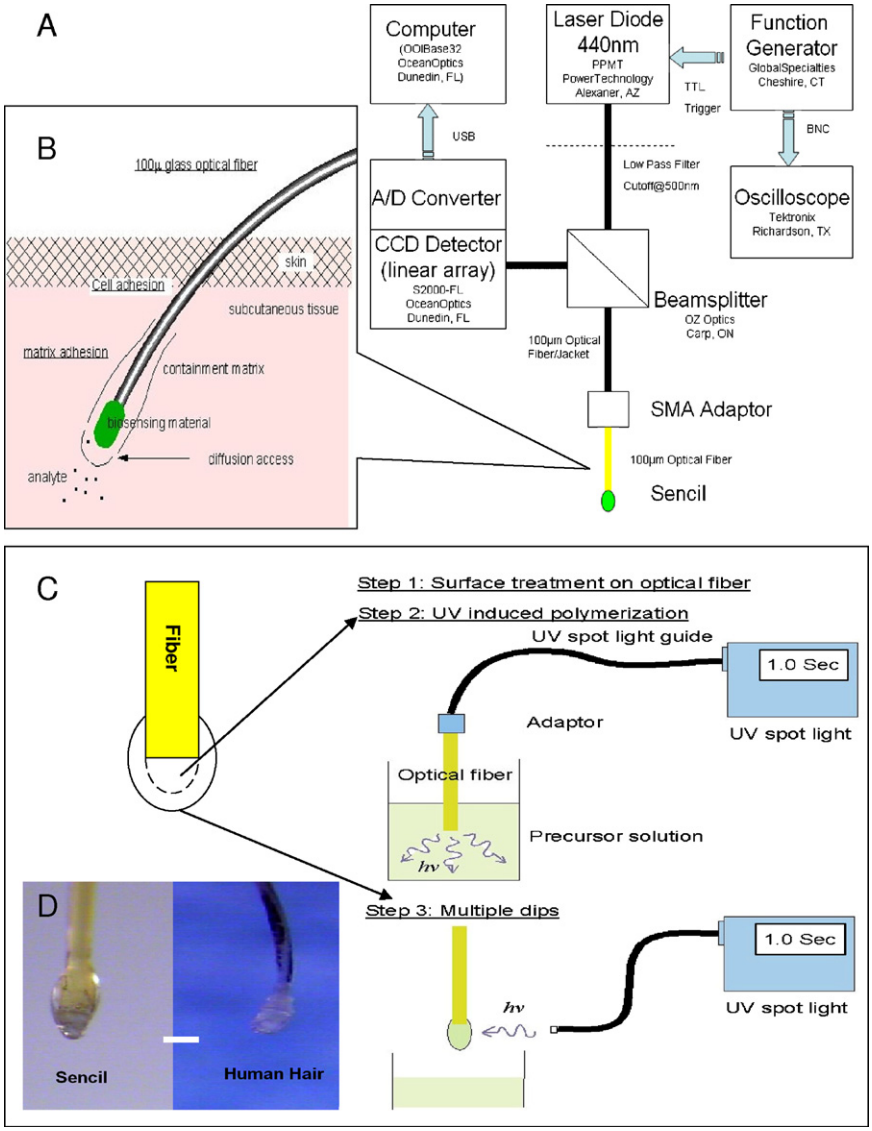

Fig. 1. Basic components and fabrication of Sencil prototype. (A) Laboratory spectroscopic instrumentation used to test prototypes; similar functionality must be miniaturized for portable clinical reader. (B) Sensor components and relationships to tissue *in vivo*. (C) Scheme of manufacture method with adhesion enhancement. (D) Similarity of shape and size between Sencil and human hair with attached follicle (white bar = 100 μm).