An Optical, Polymer-Based Sensor for Metabolic Profiles in the Intensive Care Setting

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Statement of Purpose: Frequent monitoring of metabolites is desirable in many biomedical settings, particularly of patients in the intensive care unit (ICU). Currently the majority of testing in the intensive care setting has an associated time lag due to analysis in a central laboratory and large sample sizes required. This work focuses on the development of a reusable sensor array system for *in vitro* point-of-care, to simultaneously test multiple analytes using a single drop of blood. The sensor uses an optical sensing scheme based on a multilayer polymer structure with optode membranes that change color in response to analytes' concentrations. We present sensor response in preliminary clinical trials as well as manufacturing protocols utilizing a piezoelectric based printing system for deposition of polymer films for sensor production. Multiple polymer layers deposited allow reusability of the sensors. The slide can be read by the naked eye or digitally and is a self-contained unit, thus it does not require any reagent or power supply, when read by the naked eye. Utilizing the reusable slide for multiple screenings for a patient at the bedside, makes the device cost-effective, improves turnaround time and compliance for disease management.

Methods: *Sensor Substrate:* 1mm diameter holes were etched in glass slides ~20µm deep to prepare 4 sensing wells. *pH sensors*:pH sensitive optode membranes were prepared by mixing PVC:DOS (mass ratio 1:2) and adding 25mmol chromoionophore (L), 100 mmol sodium ionophore (NaIV), and 27.5 mmol HFPB, and finally dissolving them in THF. 0.3µL of this solution was cast into designated sensing wells. *Glucose sensors:*0.3µL pH sensitive membranes were cast into designated sensing wells. To introduce glucose oxidase, GOX to the sensing layer, 0.5 µL of 7.5mg GOX dissolved in 200 µl was added to the sensing wells.*Reference spots*: Designated reference wells were filled with Teflon powder:PEG mixture to provide a uniform white color. *Protective membrane and sample holder:* HEMA membranes, 7 µm thick, were printed using a MicroFab 4 printer and polymerized using UV exposure and placed on the substrate, covering the sensing wells. Holes were drilled in PMMA slabs to overlap with the sensing wells and placed on top, attached to the substrate using silicone glue. *pH and glucose calibrations:* sensors were exposed to solutions of various pH and glucose concentration to determine the color response and response time of the slide. *Sodium interference studies*: pH sensitive optodes were tested to determine pH response with different sodium concentrations in PBS. *Image acquisition and analysis*: Images of the slide were acquired using a Nikon D5000 CCD camera. ImageJ software was used to measure RGB spectral components of the individual sensing and reference wells. Each sensing capsule was then normalized to the reference capsule, followed by Pythagorean normalization.

Results: Red and blue intensity color response of pH sensing wells in PBS, serum, and blood, with resolution of 0.08 pH units were achieved. Green intensity response was minimal, and was used as an additional internal reference in response to pH. Response times for pH changes ranged from 4 to 12 minutes, varying with the different pH change measured. Reversibility of sensors to pH changes showed minimal hysteresis. Glucose response in PBS and blood was shown to be linear between 0 – 200 mg/dl using two sensing wells with different chromoionophore:NaIV ratios of the pH sensitive optode layer. Examining ratios of Red/Blue intensities increased the dynamic range. Sodium interference studies showed that there is minimal sodium interference of pH sensitive optode in the pH range of 5.5-8.0.

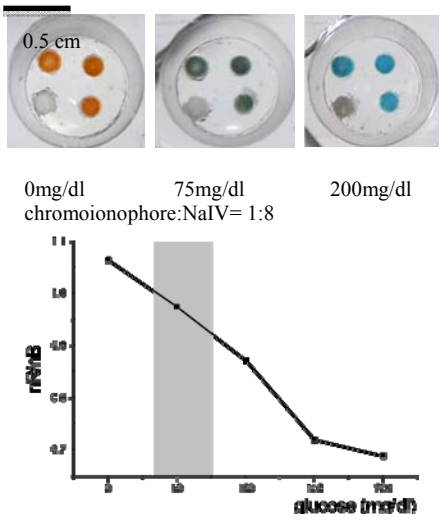

Figure 1. A) Color response of sensor to different glucose concentrations in PBS. B) Corresponding color response plot of red/blue color intensity ratio to glucose concentrations in PBS

Conclusions: We introduce a small, polymer-based reusable, optical, multi-parameter slide which can be used to measure concentrations of various analytes from a single drop of blood without the requirement of reagents or a power supply. The unique, multilayer system enhances reproducibility and allows reusability. We show high sensitivity and fast response to pH and glucose in PBS and blood. Additionally, protocols for polymer deposition of multiple layers are used to improve reproducibility and scale-up. Implementation of additional optode-specific wells for metabolic parameters (e.g. K^+, lactate), can provide a metabolic snapshot at from a single sensor at the bedside, improving turning time and patient compliance.

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