Optical Sensor for Single-port In-vivo Glucose Sensing with Simultaneous Insulin Infusion

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Introduction

Continuous glucose monitoring has proven to be beneficial for diabetes patients, especially for children with type 1 diabetes and for adult type 1 patients with nocturnal hypoglycemic events. Here, we present a new system that performs continuous glucose monitoring in subcutaneous tissue and insulin infusion simultaneously. The glucose sensor is applied onto a commercial insulin infusion set as a thin coating. It uses glucose oxidase as a glucose specific receptor which covers a luminescent dye with an absorption maximum at 617 nm and maximum emission at 768 nm. As radiation with wavelengths in the near infrared region can easily penetrate tissue, the sensor can be interrogated by an optical reader from outside the body.

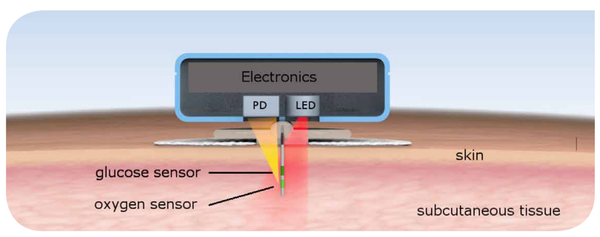

Fig. 1: *Scheme of transcutaneous sensor readout*

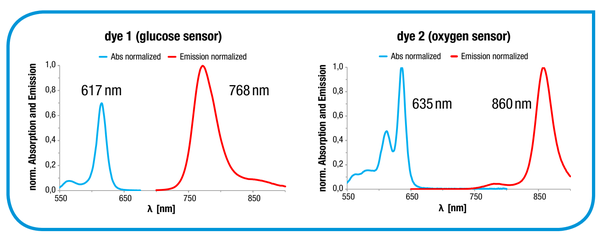

Fig. 2: *absorption – and emission spectra of the used luminescent dyes*

Due to possible variations of tissue oxygen levels over time, a second sensor is used as a reference oxygen sensor with an absorption maximum at 635 nm and maximum emission at 860 nm.

Methods and Results

Fig. 3: *left: SPIDIMAN glucose reader with 1 Euro coin for size comparison; right: Insulin infusion set with two sensors applied onto the needle*

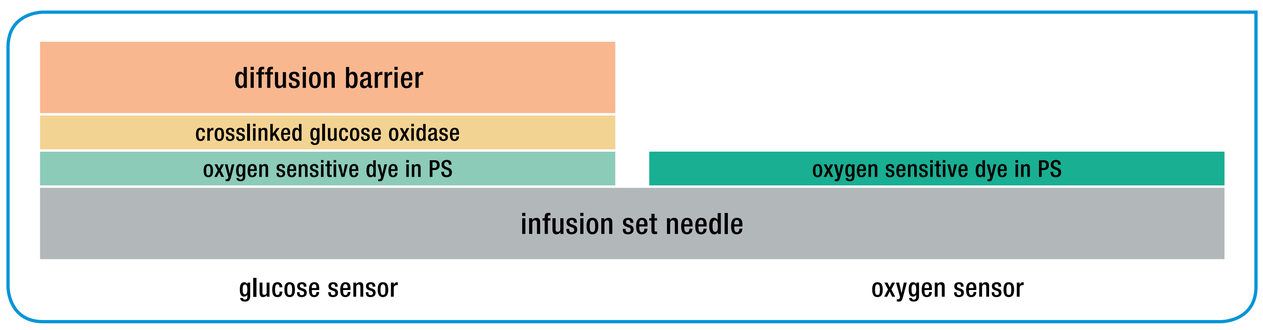

Fig. 4: *Layer structure for glucose and reference oxygen sensor*

In-vitro testing of the optical measurement system was carried out in a custom built flow-through cell. The dose-response relationship showed a linear correlation of luminescence phase-shift and glucose concentration in the measured range between 0 and 360 mg/dl glucose. The sensor drift that has been measured at two selected glucose concentrations was minimal over more than 50 hours.

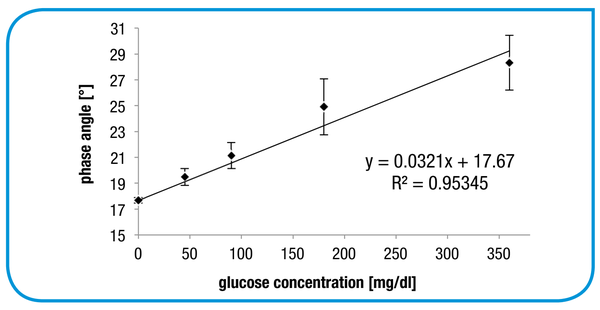

Fig. 5: *Sensor characteristics: change of phase angle dependent on glucose concentration*

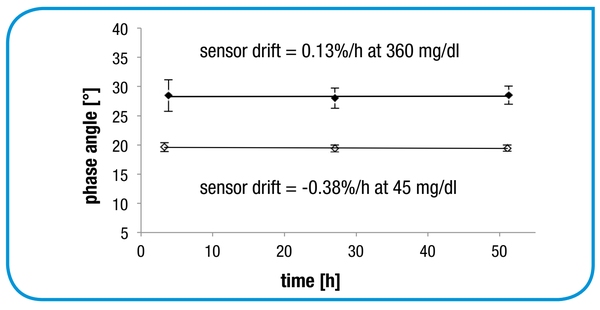

Fig. 6: *Sensor drift over time tested at two different glucose concentrations*

Preclinical in-vivo sensor performance was tested in three pigs. Each animal had inserted 6 glucose sensors in their abdominal subcutaneous adipose tissue: 2 for insulin infusion, 2 for physiological sodium chloride solution (0.9 %) and 2 with no infusion. Glucose concentration profiles are shown for one sensor from each infusion group. The profiles were calculated from a retrospective calibration using a linear regression of the measured phase shift and the reference blood-glucose values.

Sensor	Infusion	Mean ARE	Median ARE	PRESS
1	Insulin infusion 1.2 U/h	46.7 %	42.5 %	33.8 %
2		31.0 %	16.4 %	20.7 %
3		17.5 %	8.5 %	14.4 %
4		22.8 %	15.5 %	20.2 %
5		35.6 %	22.6 %	29.8 %
6		40.2 %	24.4 %	30.3 %
mean ± SD		32.3 % ± 8.3 %	21.6 % ± 5.7 %	24.9 % ± 6.3 %
1	0.9 % NaCl infusion 12 µl/h	27.3 %	18.5 %	19.7 %
2		41.5 %	20.4 %	25.4 %
3		27.7 %	17.1 %	25.4 %
4		13.8 %	8.1 %	15.8 %
5		51.5 %	24.5 %	36.3 %
6		40.1 %	20.3 %	25.8 %
mean ± SD		33.6 % ± 13.0 %	18.1 % ± 5.8 %	24.8 % ± 6.6 %
1	no infusion	33.2 %	22.7 %	23.2 %
2		63.2 %	29.8 %	34.1 %
3		16.7 %	9.8 %	15.1 %
4		19.3 %	12.8 %	16.9 %
5		33.1 %	18.0 %	26.7 %
6		41.3 %	22.3 %	28.8 %
mean ± SD		34.5 % ± 18.8 %	19.2 % ± 7.9 %	24.1 % ± 8.1 %

Table 1: *No significant difference of sensor performance dependent on kind of infusion*

Clinical in-vivo sensor performance was tested in 12 type 1 diabetic patients. Biocompatibility tests were passed prior to the clinical trial in humans. The 12h sensor tests started before breakfast and ended before dinner in the evening. Glucose dynamic was induced by high glycemic index breakfast and lunch followed by a late and overdosed insulin bolus. Preliminary results are shown as a glucose concentration profile. Statistical analysis will be available after completion of the trial.

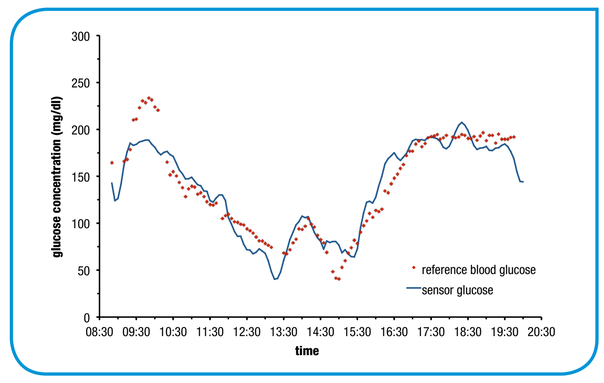

Fig. 7: *Glucose profile measured during clinical trial in type 1 diabetic patients*

Conclusion

- These results demonstrate a good proof-of-concept for our novel single-port system, which combines continuous glucose monitoring with insulin infusion within one device.
- The preclinical experiments showed that sensor-derived glucose profiles correlate well with the reference blood-glucose values, independent from the infusion type via the sensing catheter. There is no significant difference between the 3 infusion groups.
- Biocompatibility was proven for the system and preliminary clinical data demonstrated good sensor performance in humans.

Outlook

Based on the data collected during the clinical trial, optimized models for the calculation of the glucose concentration from the measured phase angle values will be developed. Furthermore, the data analysis from the tissue oxygen sensors will be used to improve the oxygen compensation model which should improve the accuracy of the glucose sensor readings.