

Imperial College London

Minimally Invasive Sensors

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Wearable, Minimally Invasive Continuous Monitoring Devices

Daily Wear Devices Patient-Centric



Continuous Glucose Monitoring (CGM)

- Why?
 - Missed Excursions
 - Trending
 - Event prediction
 - Closed loop control



Despite these advantages only a few % of Type 1 Diabetics use CGM

Why?

Challenges in Continuous Glucose Monitoring

Implanted Sensors: Foreign body response Capsule formation Drift-Sensor and Environment Chemical Interferents



Non-Invasive Sensors Lack of specificity Complex instrumentation Sampling ('Inline') Sensors 'Local' concentrations Sampling rate Carry over

An Area of Great Academic & Commercial United State Activity Clark, Jr. [54] CUTANEOUS N BODY SUBSTA [75] Inventor: Lela



d States Patent [19]		[11]	Patent Number:	4,458,686
r		[45]	Date of Patent:	Jul. 10, 1984
TANEOUS METHODS OF MEASURING DY SUBSTANCES		4,269,516 5/1981 Lubbers et al		
itor:	Leland C. Clark, Jr., Cincinnati, Ohio	Primary Examiner-Benjamin R. Padgett		
nee:	Children's Hospital Medical Center, Cincinnati, Ohio	Assistant Examiner-T, J. Wallen Attorney, Agent, or Firm-Wood, Herron & Evans		
No	491.402	[57]	ABSTRACT	
5	May 4, 1983	Cutaneous methods for measurement of substrates in mammalian subjects are disclosed. A condition of the		
Related U.S. Application Data		skin is used to measure a number of important sub- stances which diffuse through the skin or are present		
sion of 1,122.	Ser. No. 63,159, Aug. 2, 1979, Pat. No.	the techr	th the skin in the blood or ique, an enzyme whose a	tissue. According to ctivity is specific for
ц.) сі		a particu under the then det	lar substance or substrate skin for reaction. The co ceted by suitable means	e is placed on, in or endition of the skin is as a measure of the
of Se 28/63	areh	amount of enzymati detected amount of	of the substrate in the boo c reaction or by-produc directly through the skin of substrate. Polarograph	by For instance, the t of the reaction is as a measure of the ic electrodes or en-
	References Cited	zyme ele	trodes are employed as si	kin-contact analyzers
U.S. 1	PATENT DOCUMENTS	in the tra	nscutaneous measurement	of oxygen or hydro-
39 3/ 50 5/ 53 6/ 07 1/ 56 7/ 40 8/	1974 Eberhard et al. 128/635 1976 March 128/633 1976 Larrabee 23/230 LC 1977 Luobers et al. 128/633 1977 Higgeshi et al. 128/633 1978 Larbers et al. 128/260 1980 Lubbers et al. 356/41	quantitat heated or laries wh detection	uch as glucose and alco ve technique, the skin otherwise treated to arte en the measurements are methods are also employ	is arterialized, i.e., rialize the skin capil- made. Colorimetric yed.
53 3/	1980 Updike et al		23 Claims, 3 Drawing	Figures
38 12/ 53 3/	1980 Updike et al		23 Clai	ms, 3 Drawing

ENZYMATIC TRANSCUTANEOUS GLUCOSE MEASUREMENT

[73] Assignce: Child

[62] Division of Ser. 1 4,401,122.

U.S. PAT 3,795,239 3/1974 3,958,560 5/1976 3,960,733 6/1976 4,003,707 1/1977 4,034,756 7/1977 4,215,940 8/1980 4,240,438 12/1980 4,255,053 3/1981

[51] Int, CL³ [52] U.S. Cl.

No.: 491. [21] Appl







Edited hy David D. Cunningham Julie A. Stenken

Measurement Compartments and Technologies

Principle	Modality	Compartment	Invasive
Kromoscopy	Optical	ISF	Non-invasive
Photoacoustic spectroscopy	Optical	ISF	Non-invasive
Optical coherence tomography	Optical	ISF	Non-invasive
Scattering/occlusion spectroscopy.	Optical	ISF	Non-invasive
Polarimetry	Optical	ISF/anterior chamber	Non-invasive
Thermal infrared	Optical	ISF	Non-invasive
Fluorescence	Optical	ISF	Non-invasive
Raman spectroscopy	Optical	ISF	Non-invasive
MIR spectroscopy	Optical	ISF	Non-invasive
NIR spectroscopy	Optical	ISF	Non-invasive
Impedance spectroscopy	Transdermal	Capillary blood	Non-invasive
Skin suction blister	Transdermal	ISF	Non-invasive
Sonophoresis	Transdermal	ISF	Non-invasive
Reverse iontophoresis	Transdermal	ISF	Non-invasive
Micropore/microneedle	Subcutaneous	Capillary blood/ISF	Minimally invasive
Intravenous implantable	Intravenous	Venous blood	Invasive
Microdialysis	Subcutaneous	ISF	Invasive
Subcutaneous sensor	Subcutaneous	ISF	Invasive

(Oliver et al. Diabetic Med 2009)

Conventional Implanted Needle Electrodes







Epoxy-polyurethane

HEMA Hydrogel

Probing Membrane Diffusivity with SECM



Membrane 1





SECM



The Epidermal Interstitial Compartment



No vasculature No nerve endings

Measurements in epidermal Interstitial Fluid (ISF) Metabolites, drugs, cytokines

Design Concept



Fabrication of in situ uspike Sensors



Master Machined by Electric Discharge Milling



Silicone Mould

SU8-100 Microspikes

Gold Coated µSpikes

Then functionalised

Minimally Invasive Glucose Sensors and Controlling Diffusion



Epoxy-polyurethane

Nafion

System is Membrane Transport Limited



Lactate Too



Mechanical characterisation

• Transverse Fracture tests:

- Method
- Result : (n=11)
 - Mean : 24 N (range 19-29N)
 = 3N/µSpike

High Safety Margin Axial Force/Insertion Force 100N/5N =20:1



Skin Penetration



50N





Mean % Height Reduction

Membrane Survives Skin Penetration & Removal

Comparison of CV before membrane, post membrane & post insertion at 10N for



Devices can be Sterilised by γ -Irradiation

Current [A] VS Time [s] Sample 7 - Pre-Sterilization Pre-Insertion 1.80E-07 1.60E-07 1.40E-07 1.20E-07 1.00E-07 8.00E-08 •I [A] 6.00E-08 4.00E-08 2.00E-08 0.00E+00 0 $\begin{array}{c} 124\\ 168\\ 2556\\ 2556\\ 3344\\ 3388\\ 3384\\ 3388\\ 3388\\ 3388\\ 3388\\ 3388\\ 3388\\ 556\\ 660\\ 660\\ 660\\ 660\\ 660\\ 8872\\ 778\\ 8872\\ 9960\\ 0048\\ 9960\\ 0048\\ 00$

Post-sterilizatio



Post insertion too looks good!

Titration Sample 7 - Overlay



Time (sec)

A Platform for Other Analytes Therapeutic Drug levels



Kiang et al. JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 101, NO. 12, DECEMBER 2012

Measuring Conformational Change on a Nanoparticle Surface





 K_D =200nM cf 300 nM in solution

Electrochemical Sensing: Exploiting Distance Dependence of Electron Transfer

 $k_{et} \propto e^{-\beta(d-d_0)]} e^{\frac{-(\Delta G^0 + \lambda)^4}{4RT\lambda}}$

Far=Low Current

Near= High Current

A DNA Aptamer Against Lysozyme







Aptamer Beacon Assembly





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