Engineering, **2013, 5, 42-46**
doi:10.4236/eng.2013.55B009 Published Online May 2013 (http://www.scirp.org/journal/eng)

Scientific Research

Development of Wearable Semi-invasive Blood Sampling Devices for Continuous Glucose Monitoring: A Survey

Gang Wang*, Martin P. Mintchev
Centre for Bioengineering, University of Calgary, Calgary, Canada
Email: *gawang@ucalgary.ca

Received 2013

ABSTRACT

Semi-invasive blood sampling devices mimic the way female mosquitoes extract blood from a host. They generally consist of a microneedle, a microactuator for needle insertion, a blood extraction mechanism and a blood glucose sensor. These devices have great potential to overcome the major disadvantages of several current blood glucose monitoring methods. Over last two decades, extensive research has been made in all of these related fields. More recently, several wearable devices for semi-invasive blood sampling have been developed. This review aims at summarizing the current state-of-the-art development and utilization of such wearable devices for continuous monitoring of blood glucose levels, with a special attention on design considerations, fabrication technologies and testing methods.

Keywords: Continuous Blood Glucose Monitoring; Semi-invasive Blood Sampling; Mosquito; Bio-mimetics; BioMEMS; Wearable Devices

1. Introduction

1.1. Impact of Diabetes Mellitus

Diabetes Mellitus is a systemic disorder that results in elevated blood glucose levels due to insulin deficiency in the body and subsequently leads to many secondary complications [1]. More than 180 million people suffer from diabetes worldwide. This figure is expected to almost double by the year 2030 [1]. Both type 1 and type 2 diabetes mellitus (T1DM andT2DM, respectively) require long-term treatment, the goal of which is to achieve optimal glucose monitoring and control with the long-term aim of decreasing the risk of vascular complications while minimizing daily glycemic variations [2].

1.2. Evolution of Glucose Monitoring Devices

Glucose monitoring devices can be classified according to the level of invasiveness, the type of target biofluid, *i.e.* blood or interstitial fluid (ISF) and the sensing technique [3].

Standard diabetic monitoring relies on finger-prick testing by a miniature device [4]. Though highly accurate in detecting blood glucose levels, finger-prick testing is painful and inconvenient. Therefore, patients, especially those in their youth and at active maturity, are often unable to adhere to the test schedule. As a result, irregular measurements limit the applicability of the finger-prick test and disturbes the management of diabetes [4].

Continuous glucose monitoring (CGM), introduced in 1960s, is a concept which measures glucose levels in the interstitial fluid (ISF). CGM is less invasive than the finger-prick test. However, its accuracy is dependent on the equilibrium of glucose levels between ISF and blood. The balance between the two glucose levels further accounts for a time delay in the measurement [4] and requires frequent recalibration using finger-pricking test [5].

Retrospective continuous glucose monitoring (retrospective CGM) device can be subcutaneously inserted and record ISF glucose level but only for 3 - 7 days [4]. Clinicians rely on retrospective CGM to understand the glucose level trend within this short period and guide the diabetes management [3].

Wearable devices featuring real-time continuous glucose monitoring (rt-CGM) emerge on the market [5]. These devices apply low electric current to extract glucose from ISF through the skin and therefore minimize the pain and invasiveness, which make them popular among diabetes patients. However, the techniqueisbeset by old problems inherited from the indirect ISF glucose monitoring. In other word, the term “real-time” is somewhat of a misnomer. Also, rt-CGM does not fully replace conventional blood sampling as it also requires calibration by using a finger-prick test per use. The price of achieving lower invasiveness is the decrease in measurement accuracy: especially the false positive rate in-

*Corresponding author.

creases significantly due tosweat, to temperature changes, to electrostatic noise sources, etc. [5].

There is an obvious need for wearable semi-invasive blood sampling devices which would be able to automatically obtain and analyze a series of static blood samples over an extended period of time with minimal pain and limited user intervention. This can be achieved by inserting a hypodermic needle to a level where capillaries are abundant but nerve endings are rare [6]. In this survey, the contemporary technologies of semi-invasive blood sampling devices will be reviewed, with a focus on the types of needle used, actuation mechanisms and glucose sensing methods.

2. Components of Semi-invasive BloodSampling Devices

2.1. Anatomy of Human Skin

On average the skin of an adult has a thickness of roughly 2 mm [7]. The outermost layer of the skin is the stratum corneum which is a thin but very dense and resistive compound of dead cells. The thickness of stratum corneum varies among different skin sites, ranging from 23.6 ± 4.33 μm for the forearm and 173.0 ± 36.96 μm for the palm [8]. Situated below is the epidermis which protects against the rays of the sun and has a thickness of 30 to 130 μm. The dermis, which is located under the epidermis and ranges 800 - 1500 μm in thickness, holds abundant blood vessels, hair follicles, sweat glands and few nerve endings [2]. Lastly, the subcutaneous tissue is a fatty layer located below the dermis and connects to internal organs. It is usually about 1.2 mm deep [2].

In order to successfully acquire blood sample, a needle has to penetrate the resistive stratum corneum and reach the dermis layer which contains capillaries. An analogy of this process in nature is blood extraction by female mosquito's proboscis.

2.2. Blood Extraction Mechanism of a Mosquito

The micro-scaled structure of the proboscis has been previously described by several biologists using an electron microscope [9,10]. It mainly consists of a large lip called the labium, which serves as the floor of all other components of the proboscis. At the tip of the labium, itends in two pieces of lobes called the labella. The labium forms a deep housing for a stylet-shaped labrum. The labrum is a hollow tube through which the blood is drawn.At the side of the labrum are two larger needle-like maxillae with fine saw-toothed tips. Their oscillation can facilitate the penetration of the labrum.

A recent study by Ramasubramanian *et al*. [11] uses high-speed video imaging to observe the skin penetration process. Axial pushing and retraction of labium at a frequency of about 15 Hz was observed during the early penetration stage. They compared their experiment with another electrical impedance measurement of mosquito biting [12] and confirmed that such vibration facilitates the penetration. Another group [13] further studied the movement of mosquito proboscis in transparent thin skins of laboratory rats and found out that the labium and two maxillas advanced into the skin alternatively at the same frequency. After the penetration process, a mosquito relies on not only the passive capillary pressure but also on a two-pump system in its head to suck a large portion of blood, the weight of which can reach nearly 3 times of its own weight within one minute [12,14].

These findings clearly indicate that the mosquito proboscis is a piece of sophisticated biological actuation mechanism made of components with highly specialized functions, rather than just a hypodermic needle as previously described. The anatomy of a mosquito's proboscis and the various functions of its components have, in different aspects, inspired the development of semi-invasive blood sampling devices, which generally consist of hypodermic needles, needle insertion actuators, blood sampling mechanisms and electrochemical glucose sensing methods.

2.3. Needle Design

Hypodermic needlesand microneedles are both widely used in the development of semi-invasive blood sampling devices. Hypodermic needles generally refer to those stainless-steel made needles that are conventionally used with syringes to inject drugs into a body or extract fluid from it. The outer diameter of hypodermic needles is indicated by needle gauge (G), which is usually ranged from 7G (4.572 mm) to 33G (0.2096 mm) [15]. Microneedles, which were first introduced in 1970s [16], refer to those smaller needles, the diameter and length of which are in micrometers. Microneedles can be made of different materials, including silicon, polymer, metals and glass, etc. In terms of mass production, silicon microneedles can be classified based on how they are manufactured. The "in-plane" needles are createdparallel to the substrate surface. "out-of-plane" needles are fabricated vertical to the substrate surface [8,17]. In-plane needles can be made relatively long and penetrate deeper below skin. Therefore, they are suitable for applications such as blood extraction [13]. The length of "out-of-plane" needles is limited during production process. Therefore, extensive research has been made on their applications in ISF extraction and therapeutic drug delivery in dermis layer. For metallic microneedles, special fabrication techniques are employed. For example, the RF magnetron sputtering, a method that had been used for rapid deposition of thin films, was appliedto coat titanium par-

ticles on a rotating copper wire. Finally, the core copper wire can be removed by an etching process so that the hollow cavity is formed in the needle [18].

Before starting any device development, the choice of an appropriate needle has to be made after comparing a number of mechanical properties of the needles, such as the Young's modulus, hardness, skin insertion force, fracture force, etc., to minimize insertion effort and maximize the safety margin [8].

2.4. Microactuator for Needle Insertion

The actuation mechanism for the needle insertion is important in the design of any blood sampling device. There are several actuation mechanisms that are relevant to the development of microactuators: piezoelectric, electrostatic, thermal and shape memory effect [19].

Maximum stroke and the insertion force are the two primary design factors. In order to successfully acquire blood, the actuator must be capable to move the needle to a depth about 150 ~ 1000 μm below the skin, where capillary vessels are abundant. To test the maximum stroke of an actuator at in-vitro experiment stage, one-dimensional or two-dimensional laser displacement sensor is usually used [20]. To observe the penetration characteristics beneath the skin during in vivo or human model test, various real-time monitoring methods have been employed, including optical coherence tomography, infrared spectroscopy and electrical impedance spectroscopy, etc. [21]. Among them, optical coherence tomography (OCT) is the most often used technique. OCT is a non-invasive imaging method which is capable of achieving an imaging depth of 2 mm below the skin. Its concept is similar to ultrasonic imaging: mapping is obtained by reprocessing the dynamic change of reflected light rays rather than ultrasound waves [22]. Due to the difference in geometry, materials and sharpness of the needle tip, the required force for skin penetration by different types of needles vary in a wide range. The actuation force can be tested by load cells, the force applied on which can be linearly converted to an output voltage by piezoresistive effect [20,23].Synchronization of the force and stroke monitoring can provide useful information such as the skin penetration force and event time.

The "electronic Mosquito" skin-patch blood sampling system was introduced in 2005 [6]. In its macro-size prototype, it utilizes a pair of piezoelectric actuators which can exerta force of nearly 100 gf and a maximum stroke of 1.25 mm [24]. An upgraded version of this system further incorporates an impedance sensor for the presence of a blood sample to form a closed-loop control of the actuator. It successfully extracted a blood sample of 10 μL in a chicken model test [25]. However, the force and stroke dropped proportionally to the scale of miniaturization and the development of this system is still during midway to a practically applicable level. Another group from Japan reported a blood extraction system which utilized an SMA actuator to insert a titanium-made microneedle [26]. Having a high power/size ratio, this SMA actuator is able to reach a maximum output force of 80gf and stroke of 3mm on a skin simulation model [18]. However, no report of in-vivo testing has been available so far.

Challenges to the microactuator design include the output force, the stroke as well as the price, the scalability and the input power consumption rate. Other not less important considerations in the device design include biocompatibility and temperature dependence. The selection of actuation mechanism for wearable blood sampling effect is further restricted by limited power supply and space.

2.5. Blood Extraction Mechanism

Two types of passive blood extraction mechanisms by a female mosquito were observed: pool feeding, where the mosquito creates a hemorrhage and feeds slowly via capillary action, and capillary feeding, wherein the mosquito taps into a capillary vessel and the feeding process is much faster, as the blood is driven under capillary blood pressure [14]. As described before [6], the "electronic Mosquito" system relies on these natural pressure gradients to extract blood. Several other groups tried to mimic the active pumping system in the mosquito's head to accelerate the extraction process. In [18], the authors introduced a pumping unit next to the proximal end of the microneedle using a bimorph PZT piezoelectric actuator. Powered by AC voltage @ 25 kHz, the piezoelectric actuator deflects and creates a pressure drop in the needle cavity, sucking blood at a rate of 2 μl/min. In [26], an electrolyte-controlled blood extraction mechanism was reported. It has beenclaimed its extraction speed reaches 5μl/s. However, the paper lacks details of its experimental setup and protocol. In [27], a vacuum-driven blood extraction system was implemented for an automated finger-prick test. It succeeded in extracting 12.7 μl of human blood within 2 seconds. However it is questionable that whether this mechanism can be transferred to a wearable device due to its bulky size.

2.6. Glucose Sensor

Compared to the other design aspects of wearable semi-invasive blood sampling devices discussed above, glucose sensing technology is a field that has been the most intensively studied for several decades [3,28-30].

Electrochemical glucose sensing methods from whole blood remain the most reliable approach for accurate glucose level testing [28]. The measurements by the

same electrochemical sensors from ISF may have discrepancies due to the dynamic imbalance of glucose level. Non-invasive approaches, which mainly rely on optical detection and analysis, have not presented any reliable results for continuous glucose monitoring, in spite of the extensive efforts that have been made [28].

The glucose sensing mechanism of a control meter for home testing of blood glucose can be directly connected to a wearable semi-invasive blood sampling device. The concept of this type of sensors relies on a chrono-amperometric operation in connection with an incubation step [3]. The challenge left for its application in wearable devices is the device miniaturization.

The advance of microfabrication techniques now allows the development of needle-shape glucose sensors. The underlying concept is a combination of microdialysis and enzymatic amperometric glucose measurement. The needle is made hollow and filled with isotonic fluids. Once being inserted into body, blood glucose molecules can diffuse into the needle and be transferred to the electrode in the needle [30]. Glucose measurement can be made on-site and in-situ rather than on the blood sample transferred from the patient's body to the device.

3. Discussion and Conclusions

The use of wearable semi-invasive blood sampling devices shows great potential, overcoming the discontinuance of finger-prick test and the inaccuracy of optical and ISF tests. It aims at reducing pain and inconvenience experienced by diabetes patients and increasing the number of blood glucose tests per day thus at improving the health of diabetic patients. It further opens the possibility to connect with a wearable insulin pump device in order to form a closed-loop blood glucose control, or an external electronically-controlled artificial pancreas.

As discussed above, several attempts were already made by different groups to develop a practical product. However, to this day, no commercialized products have entered the market. The main challenges are (a) the device miniaturization and (b) integration. Safety issues like bleeding, infection and skin recovery may also hamper the implementability and marketability, the approval process from regulatory agencies and final commercialization. Despite the recent great efforts to solve the existing problems, research on novel materials and microfabrication technologies is also needed.

4. Acknowledgements

This study was sponsored in part by the National Sciences and Engineering Research Council of Canada.

REFERENCES

[1] American Diabetes Association, "Standards of Medical Care in Diabetes – 2012," *Diabetes Cares,* Vol. 35, No. 2, 2012, pp. S11-63.

[2] F. M. Hendriks, D. Brokken, C. W. J. Oomens, F. P. T. Baaijens and J. B. A. Horsten, "Mechanical Properties of Different Layers of Human Skin," Philips Research Laboratories, Eindhoven, 2000.

[3] N. Oliver, C. Toumazou, A. Cass and D. G. Johnston, "Glucose Sensors: A Review of Current and Emerging Technology," *Diabetic Medicine*, Vol. 26, No. 3, 2009, pp. 197-210. doi:10.1111/j.1464-5491.2008.02642.x

[4] A. Penfornis, E. Personeni and S. Borot, "Evolution of Devices in Diabetes Management," *Diabetes Technology and Therapeutics,* Vol. 13, No. 4, 2011, pp. S93-101.

[5] L. Hoeks, W. Greven and H. d. Valk, "Real-Time Continuous Glucose Monitoring System for Treatment of Diabetes: A Systematic Review," *Diabetic Medicine*, Vol. 28, No. 2, 2001, pp. 386-94. doi:10.1111/j.1464-5491.2010.03177.x

[6] G. Gattiker, K. Kaler and M. Mintchev, "Electronic Mosquito: Designing a Semi-Invasive Microsystem for Blood Sampling, Analysis and Drug Delivery Applications," *Microsysemt Technologies,* Vol. 12, No. 1, pp. 44-51, 2005. doi:10.1007/s00542-005-0015-9

[7] F. Martini, "Fundamentals of Anatomy & Physiology,"Upper Saddle River, N. J.: Prentice Hall, 2001.

[8] A. El-Laboudi, N. S. Oliver, A. Cass and D. Johnston, "Use of Microneedle Array Devices for Continuous Glucose Monitoring: A Review," *Diabetes Technology & Therapeutic,* Vol. 15, No. 1, 2013, pp. 101-115. doi:10.1089/dia.2012.0188

[9] A. Hudson, "Notes on Piercing Mouthparts of Three Species of Mosquitoes Viewed with the Scanning Electron Microscope," *The Canadian Entomologist,* Vol. 102, No. 4, 1970, pp. 501-509. doi:10.4039/Ent102501-4

[10] J. C. Jones and D. R. Pilitt, "Blood-feeding Behavior of Adult Aedes Aegypti Mosquitoes," *Biology Bulletin,* Vol. 145, No. 1, 1973, pp. 127-139. doi:10.2307/1540353

[11] M. K. Ramasubramanian, O. M. Barham and V. Swaminathan, "Mechanics of a Mosquito Bite with Applications to Microneedle Design," *Bioinspiration & Biomimetics,* Vol. 3, No. 4, 2008, pp. 1-10. doi:10.1088/1748-3182/3/4/046001

[12] P. Kashin, "Electronic Recording of the Mosquito Bite," *J. Insect Physiol,* Vol. 12, No. 3, 1966, pp. 281-286. doi:10.1016/0022-1910(66)90143-0

[13] H. Izumi, M. Suzuki, S. Aoyagi and T. Kanzaki, "Realistic Imitation of Mosquito's Proboscis: Electrochemically etched Sharp and Jagged Needles and Their Cooperative Inserting Motion," *Sensors and Actuators A,* Vol. 165, No. 1, 2011, pp. 115-123. doi:10.1016/j.sna.2010.02.010

[14] B. H. Kim, H. K. Kim and S. J. Lee, "Experimental Analysis of the Blood-sucking Mechanism of Female Mosquitoes," *The Journal of Experimental Biology,* Vol. 214, No. 7, 2011, pp. 1163-1169.doi:10.1242/jeb.048793

[15] "Hypodermic Needle Gauge Chart," TED PELLA, Inc, [Online]. Available: http://www.tedpella.com/company_html/needlegauge.htm. [Accessed 12 March 2013].

[16] M. Gestel and V. Place, "Drug Delivery Device," United States of America Patent 3,964,482, 1976.

[17] H. J. G. E. Gardeniers, R. Luttge, E. J. W. Berenschot, M. J. d. Boer, S. Y. Yeshurun, M. Hefetz, R. V. Oever and A. V. D. Berg, "Silicon Micromachined Hollow Microneedles for Transdermal Liquid Transport," *Journal of Microelectromechanical Systems,* Vol. 12, No. 1,2003, pp. 855-862. doi:10.1109/JMEMS.2003.820293

[18] K. Tsuchiya, N. Nakanishi, Y. Uetsuji and E. Nakamachi, "Development of Blood Extraction System for Health Monitoring System," *Biomedical Microdevices*, Vol. 7, No. 4, 2005, pp. 347-353. doi:10.1007/s10544-005-6077-8

[19] M. Kohl, "Shape Memory Microactuators," Microtechnology and MEMS, 2004. doi:10.1007/978-3-662-09875-2

[20] P. Senthilkumar, G. Dayananda, M. Umapathy and V. Shankar, "Experimental Evaluation of a Shape Memory Alloy Wire Actuator with a Modulated Adaptive Controller for Position Control," *Smart Materials and Structures,* Vol. 21, No. 1, 2011, pp. 1-11.

[21] J. Gupta, H. Gill, S. Andrews and M. Prausnitz, "Kinetic of Skin Resealing After Insertion of Microneedles in Human Subjects," *Journal of Control Release*, Vol. 154, No. 1, 2011, pp. 148-155. doi:10.1016/j.jconrel.2011.05.021

[22] S. Coulman, J. Birchall, A. Alex, M. Pearton, B. Hofer, C. O'Mahony, W. Drexler and B. Povazay, "Invivo, insitu imaging of microneedle insertion into the skin of human volunteer using optical coherence tomography," *Pharmaceutical Research,* Vol. 28, No. 1, 2011, pp. 357-361. doi:10.1007/s11095-010-0167-x

[23] H. Lee and J. Lee, "Evaluation of the Characteristics of a Shape Memory Alloy Spring Actuator," *Smart Materials and Structures,* Vol. 9, No. 6, 2000, pp. 817-823. doi:10.1088/0964-1726/9/6/311

[24] G. Gattiker, PhD Thesis: Designing a BioMEMS-based Blood Sampler, Calgary: University of Calgary, 2006.

[25] G. Thomas, MSc Thesis: Electronic Mosquito: A Feedback-Controlled Semi-Invasive Microsystem for Glucose Monitoring, Calgary: University of Calgary, 2009.

[26] S. Chakraborty and K. Tsuchiya, "Development and Fluidic Simulation of Microneedles," *Journal of Applied Physics,* Vol. 103, No. 1, 2008, pp. 1-9.

[27] Y. Matsuura, T. Uenoya, K. Tsuchiya, Y. Uetsuji and E. Nakamachi, "Development of a Blood Extraction Device for a Miniature SMBG System," in *Proc. SPIE 6799, Bio MEMS and Nanotechnology III*, Canberra, 2007.

[28] J. Wang, "Electrochemical Glucose Biosensors," *Chemical Reviews*, Vol. 108, No. 1, 2008, pp. 814-825. doi:10.1021/cr068123a

[29] S. Vashist, Zheng, Al-Rubeaan and F. J. H. Luong, "Technology Behind Commercial Devices for Blood Glucose Monitoring in Diabetes Management: A Review," *Analytical Chimica Acta*, Vol. 703, No. 2, 2011, pp. 124-136. doi:10.1016/j.aca.2011.07.024.

[30] J. Pickup, F. Hussain, N. Evans and N. Sachedina, "In Vivo Glucose Monitoring: The Clinical Reality and the Promise," *Biosensors and Bioelectronics,* Vol. 20, No. 10, 2005, pp. 1897-1902. doi:10.1016/j.bios.2004.08.016

