Biotechnology Advances 34 (2016) 331–341

Contents lists available at ScienceDirect

Biotechnology Advances

journal homepage: www.elsevier.com/locate/biotechadv

Research review paper

Transforming the blood glucose meter into a general healthcare meter for in vitro diagnostics in mobile health

Tian Lan [a], Jingjing Zhang [b], Yi Lu [b]

[a] GlucoSentient, Inc., 60 Hazelwood Drive, Champaign, IL 61820, USA
[b] Department of Chemistry, University of Illinois at Urbana–Champaign, 601 S. Mathews Ave., Urbana, IL 61801, USA

ARTICLE INFO

Article history:
Received 21 January 2016
Received in revised form 20 February 2016
Accepted 1 March 2016
Available online 3 March 2016

Keywords:
Blood Glucose Meter
In vitro diagnostics
Point of care
Immunoassay
Aptamer
DNAzyme
Molecular diagnostics
Enzymatic activity assay
Biosensors
Mobile health

ABSTRACT

Recent advances in mobile network and smartphones have provided an enormous opportunity for transforming in vitro diagnostics (IVD) from central labs to home or other points of care (POC). A major challenge to achieving the goal is a long time and high costs associated with developing POC IVD devices in mobile Health (mHealth). Instead of developing a new POC device for every new IVD target, we and others are taking advantage of decades of research, development, engineering and continuous improvement of the blood glucose meter (BGM), including those already integrated with smartphones, and transforming the BGM into a general healthcare meter for POC IVDs of a wide range of biomarkers, therapeutic drugs and other analytical targets. In this review, we summarize methods to transduce and amplify selective binding of targets by antibodies, DNA/RNA aptamers, DNAzyme/ribozymes and protein enzymes into signals such as glucose or NADH that can be measured by commercially available BGM, making it possible to adapt many clinical assays performed in central labs, such as immunoassays, aptamer/DNAzyme assays, molecular diagnostic assays, and enzymatic activity assays onto BGM platform for quantification of non-glucose targets for a wide variety of IVDs in mHealth.

Contents

1. Introduction . . . 332
2. The development of glucose meter . . . 332
3. Design of the BGM-based biosensors for IVDs of non-glucose targets . . . 333
   3.1. Components of the BGM-based IVDs for non-glucose targets . . . 333
   3.2. Signal transduction and amplification strategies for BGM-based IVDs for non-glucose targets . . . 333
      3.2.1. Glucose-generating enzymes . . . 334
      3.2.2. Encapsulated glucose . . . 334
      3.2.3. NADH-generating enzymes . . . 334
   3.3. Target recognition elements for BGM-based IVDs for non-glucose targets . . . 335
      3.3.1. Employing antibodies as target recognition elements in BGM-based IVDs . . . 335
      3.3.2. Employing aptamers and DNAzymes as target recognition elements in BGM-based IVDs . . . 336
      3.3.3. Employing nucleic acid hybridization as target recognition elements in BGM-based IVDs . . . 337
      3.3.4. Employing direct enzyme recognition in BGM-based IVDs . . . 338
      3.3.5. Other target recognition methods . . . 339
4. Conclusion and perspectives . . . 339
Acknowledgments . . . 339
References . . . 339

E-mail addresses: tianlan.1983@gmail.com (T. Lan), yi-lu@illinois.edu (Y. Lu).

http://dx.doi.org/10.1016/j.biotechadv.2016.03.002
0734-9750/

1. Introduction

Coinciding with the rise of the aging population, the prevalence of chronic diseases and the associated healthcare costs has skyrocketed, making it challenging to improve both the quality and the reach of healthcare to those in need. One promising solution is to shift healthcare from hospitals and centralized laboratories to small clinics in the communities and at home or the point of care (POC). To achieve the goals, enormous effort has been made in the past decade to develop technologies that allow rapid patient-provider communications and more convenient diagnostic tests to use by less trained staffs at a lower cost. These efforts have been empowered by today's computational power, fast and reliable networks, and rich software content, with particular impact on POC in vitro diagnostics and mobile health.

Recent advances in mobile technologies have led to significant advances in personal health monitoring and healthcare delivery. For example, many wearable devices, such as wristbands and smartwatch, have been commercialized to monitor an individual's vital signs, such as blood pressure, heart rate, and body temperature, and behavior like medication adherence and physical movement (mHealth, 2012). In addition, without needing to be physically at the clinic, communications and consultation with healthcare providers as well as health education can be delivered to anyone with a smartphone or tablet. All the information can be transmitted and stored in the cloud for patients and their caregivers to access and monitor their health status. However, these technologies are mostly limited to delivering information about fitness and healthy state of the users using physical parameters and they miss a critical component of performing diagnostic or screening tests, i.e., using biomarkers inside a human body, which are known to be much more informative and accurate. Furthermore, many therapeutic drugs are known to have narrow therapeutic windows and careful monitoring of the drug levels in the patients regularly at home or other places of POC is critical to successful therapy.

To develop mHealth meters to detect and quantify biomarkers and therapeutic drugs inside a human body, such as those in the blood, urine or saliva, it requires much more advanced technology and thus research and development efforts and funding. Currently, the blood glucose meter (BGM) is the only widely used in vitro diagnostic (IVD) device that has been integrated with mHealth application, either as an attachment to a smartphone (iBGSTAR, 2011) or directly integrating cellular capability (Telcare, 2013). With the growing prevalence of diabetes worldwide, it is not surprising that the BGM is at the forefront of IVDs adapting to the mHealth trend. Decades of research and development, engineering, and marketing efforts have made glucose sensing technology more affordable, accurate, portable, easy to use and low cost to manufacture. In addition, BGM technologies are continuously under development to address needs of the growing population of people with diabetes (Hones et al., 2008). Therefore, instead of developing a brand new platform for IVD tests with mobile devices, leveraging the existing BGM platform to quantify other clinical relevant biomarkers can mitigate risk and lower the costs. Guided by this strategy, we and others have recently transformed unmodified commercially available BGM into a general healthcare meter for IVD in mHealth (Xiang and Lu, 2011, 2012a, 2012b; Su et al., 2012; Yan et al., 2013; Zhang et al., 2016). In this review, we summarize methods that have enabled the BGM for quantification of a wide range of targets, such as protein, small organic molecule, metal ion, nucleic acid molecules and enzyme activities.

2. The development of glucose meter

The BGM was first introduced around 1970 as a visual and semi-quantitative device where the glucose level was estimated by comparing the color of a glucose-specific reaction on a pad to a printed color chart. Although the first BGMs required multiple steps, large blood volume, and accurate timing, they were still able to assist people with diabetes to manage their glucose levels (Forman et al., 1972). Driven by the need for hundreds of millions of people with diabetes worldwide, the BGM has since evolved from the photometry-based detection used in the 70s to the current electrochemical-based detection using specific oxidoreductase reactions. The multistep process has been reduced to simply applying a blood droplet onto a strip; the time has reduced from ~2 min to a mere ~5 s; the volume required to conduct a test has reduced from 25 μL to as little as 0.3 μL; the physical size of the system has shrunk significantly; and the semi-quantitative device has become an accurate quantitative system (Heller and Feldman, 2008; Hones et al., 2008). The production cost for the glucose test strips has been lowered by screen printing, while other advanced techniques, such as laser ablation, have also been used for accurately controlling the dimensions of the electrodes (Hones et al., 2008). As a result of decades of research, development, engineering and marketing efforts, the current BGM is a low-cost, portable and accurate device.

Most of the today's BGMs rely on glucose oxidase (GOx) and glucose dehydrogenase (GDH) to generate the glucose-specific electrochemical signal (e.g., electrons). The two enzymes differ in their redox potentials (GOx at −48 mV versus SHE at pH 7.2 and GDH at 10.5 mV verse SHE at pH 7.0), stability, turnover rates, their affinity and selectivity for glucose (Sato et al., 2001; Kulys et al., 2006; Heller and Feldman, 2008; Yoo and Lee, 2010). Compared with GDH, GOx has a relatively higher selectivity for glucose, and can withstand greater extremes of pH, ionic strength, and temperature. However, the rate of glucose oxidation catalyzed by GOx is slower (5000 s^{-1}), compared to the rate of 11,800 s^{-1} catalyzed by GDH (Heller and Feldman, 2008). In addition, the GOx reaction requires dissolved oxygen as a substrate and thus the lack of oxygen can inhibit enzymatic activity. On the other hand, GHD reaction is oxygen independent, but it is not as glucose specific as GOx (Ferri et al., 2011). Two members of the GDH family (NAD-GDH and FAD-GDH) have been shown to possess both the glucose specificity of GOx and the oxygen independence of GDH (Boguslavsky et al., 1995; Tsujimura et al., 2006) and hence will be more likely to be widely used in the future.

After the glucose is oxidized, a mediator, such as ferrocene derivatives, hexacyanoferrate, and quinones, is commonly used to transfer the signal from the enzyme to the working electrode. The resulting current can be detected either coulometrically, where the total charge at a fixed time is measured (Heller and Feldman,

Table 1
Mediators used in commercial glucose test strips.

Brand	Mediator	Enzyme	Potential (vs. Ag/AgCl)	Bimolecular rate constant[a]	Reference
One Touch Ultra	Ferricyanide	GOx/GDH	300 mV	13.6 M^{-1} s^{-1}	Lee et al. (2005), Uematsu et al. (2012)
Arkray	Ruthenium hexamine	GDH	−200 mV (vs. SCE)	80 M^{-1} s^{-1}	Morris et al. (1992)
FreeStyle	$Os^{2+/3+}$ complex	GDH	−160 mV	N. A.	Heller and Feldman (2010)
Precision Xtra	Phenanthroline quinone[b]	GDH	200 mV	N. A.	Cardosi and Liu (2012)
Precision QID	Ferrocene[c]	GOx	600 mV	4.3×10^5 M^{-1} s^{-1}	Cunningham (2016)

N. A.: Not available.
[a] Electron transfer rate between the mediator and the respective enzyme.
[b] 1,10-Phenanthroline quinone.
[c] 1,1′-Dimethyl-3-(2-amino-1-hydroxyethyl) ferrocene.