



Review

The evolution of commercialized glucose sensors in China

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ABSTRACT

The glucose monitor with a screen-printed carbon sensor has been in commercial production since 1994. In last 15 years, around 10 companies have been involved in manufacturing and marketing the meters and glucose test strips and are being strong competitors of the companies which import these products. Comparison of early stage glucose meters and glucose test strips with latest fabrications showed a large increase in production volume and improved functional features. It also showed technological development of glucose monitors including circuit improvement, as more integrated computer processor units (CPU) are now being used. The technology of mass-production of disposable screen-printed test strips has been widely used in local industries mainly for the production of blood glucose test strips. The opportunities and challenges in local diabetes market are discussed in this paper.

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1. Introduction

According to the mid of 2006 report from Ministry of Health, nearly 40 million people suffer from diabetes in China (Chin CDC). Since diabetic patients need to control their blood glucose levels carefully, the importance of self-monitoring of blood glucose has been widely recognized as an effective method of measuring blood sugar not only in clinics but also at home and in the working place. The first research on amperometric determination of blood glucose using a redox couple-mediated, glucose oxidase (GOx)-catalyzed reaction was demonstrated by Williams et al. (1970). But this study did not lead to the rapid application of amperometry in self-monitoring blood glucose in the home.

The first electrochemical blood glucose monitor for self-monitoring diabetic patients was pen-sized and was launched in 1987 as ExacTech by Medisense Inc. Many studies on the development of blood glucose sensors have been carried out since the 1980s (Cass et al., 1984; Newman et al., 1992; Wang et al., 1995; Cui et al., 2000; Gao et al., 2005; Newman and Turner, 2005; Heller and Feldman, 2008).

With regard to the huge local requirement of millions of diabetes suffers, the production of glucose sensors and test meters is still growing fast and many of the methods being developed have been based on electrochemical techniques such as the use of carbon electrodes, and are particularly attractive for this have been based on the use of electrochemical techniques such as carbon electrodes are particularly attractive for this application due to their high sensitivity, selectivity, small size and low cost (Hu, 1989). Screen-printing of carbon ink for the fabrication of electrochemical sensors has realized commercial success in glucose sensing field. In 1993, Hu was the first to use screen-printing tech-

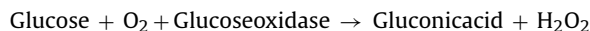
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nology for the mass production of extremely inexpensive, highly reproducible and reliable single-use glucose sensors in China. From this point on printing technology in the production of disposable low-cost enzyme sensors for the amperometric determination of blood glucose has been widespread growth in this country. Several hundreds of basic research papers have been published in China on electrochemical glucose sensors since 1990s (Dong et al., 1991; Hu and Turner, 1991; Jin et al., 1994; Zhang and Rechnize, 1994). Because of this large number of publications, a full review of the literature, even of the most recent advances, is difficult to achieve. Nevertheless this paper intends to acquaint the reader with the fundamentals of the electrochemistry of glucose and provide a perspective of the evolution of the electrochemical glucose assay and monitors in China where 40 million people suffer from diabetes.

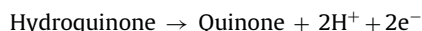
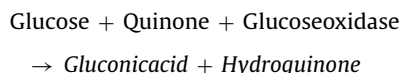
2. Mediator-modified SPCEs

Rapid and low interference analysis of blood sugar is of great interest in the diagnosis of diabetes. A large number of the disposable enzyme sensors used in the analysis of glucose are based on electrochemical determination of enzyme-generated hydrogen peroxide as shown in the following reaction:

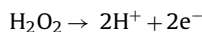
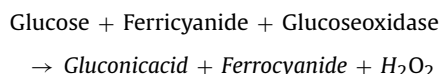


In this reaction, oxidation and reduction of H_2O_2 generally requires a high potential at the bare metal electrodes, which implies a large interference. For this reason, most of the portable glucose testing systems with glucose sensors use mediators that enable the reduction at low potential, thereby decreasing the electrochemical interference. Due to the simple technological processing and low cost, graphite products are preferred to be the base material for screen-printed carbon electrodes for glucose determination (Hu and Ge, 1999). Different carbon inks obtained from Acheson, DuPont, Gwent and Ercon have been compared for the production of base electrodes in glucose test strips. Fig. 1 shows the cyclic voltammograms of the ferri/ferrocyanide redox couple at the commercial carbon strip electrodes screen-printed with the four carbon inks mentioned above. Of the commercial sensors, On-Call-Plus using DuPont carbon ink yielded a best reversibility as Fig. 1(a) but the other commercial electrodes were also found to be effective. Fig. 1(c) and (d) shows the effect of commercial electrodes from Yicheng and Jinque which showed high peaks at the 400 and 300 mV, respectively, and were designed using silver as the conducting tracks.

The first enzymatic carbon screen-printed glucose sensor using Acheson inks was developed by Hu in early of 1994 (Hu and Ge, 1999). In this sensor, glucose oxidase was adsorbed onto the surface of the carbon electrode and benzoquinone was used as a mediator. The reactions at the electrode are as follows:



The first blood glucose testing system was launched in China in 1994 and was based on the results mentioned above. Later, Hu and Zhang used ferricyanide as the mediator because ferricyanide is more soluble and sensitive than benzoquinone in the water phase. This reaction is as follows:



Initial cyclic voltammetric investigations of ferricyanide adsorbed onto a carbon-based electrode showed promising results for the electro-catalytic oxidation of glucose and glucose oxidase. (Zhang et al., 1999; Hu and Ge, 1999). In response to the growing market demand, researchers undertook studies to find new mediators with fast reaction times and lower interference. Yicheng recently tested SPCEs with hexaamineruthenium(III) chloride mediator as the electron shuttle. The company found that the use of this mediator could eliminate interference from other oxidizable species in the blood, providing improved analytical results in the determination of blood glucose and leading to a precise test strip which required only a 0.5 μl sample of blood and produced the results in 5 s (Yicheng Bioelectronics Ltd., www.yichengbioelectronics.com.cn.2007/) (Chinese).

Another mediator osmium (II)-poly-pyridine was also used in the construction of screen-printed carbon-based electrodes, and was used mixed with the enzyme glucose oxidase to form a solution which was dispensed onto the SPCEs creating a thin layer after drying at 55 °C for 5 min. A company in Guilin has shown that the test strip containing the osmium mediator could be successfully applied to the analysis of blood glucose in clinical practice. (Guilin Zhonghui Technology Co., Ltd., www.glzhkj.cn2007/) (Chinese)

3. Glucose enzyme-modified SPCEs

Glucose oxidase is an oxygen-dependent enzyme which has long been used in the production of glucose sensors. However, there are some problems associated with the use of this enzyme for glucose monitoring. As the enzyme uses oxygen as an electron acceptor, there is a competition between the artificial mediator and oxygen mediations. Thus, if the blood oxygen level is high, measurement of blood glucose may appear lower than the true value. For this reason, some other enzymes such as pyrroloquinoline-quinone-dependent glucose dehydrogenase (PQQ-GDH) have been used in the construction of disposable glucose test strips. In this system the blood oxygen level does not affect reaction, as the enzyme does not use oxygen as an electron acceptor. The PQQ-GDH enzyme is also superior in its reaction speed to glucose oxidase.

According to the recent research and substantiated in some cases, the pyrroloquinoline-quinone-dependent glucose dehydrogenase (PQQ-GDH) is not sufficiently substrate specific as it also reacts with maltose, galactose and maltotriose (Tsujiura et al., 2006; Tamadaka and Soda, 2007). This enzyme profile has led to a report of errors in the results when the PQQ-GDH enzyme glucose test strip was used to monitor blood glucose in diabetic patients. Recently, the enzyme called flavin adenine dinucleotide-dependent glucose dehydrogenase (FAD-GDH) (Amano Company Report, 2007, www.amano.com.jp/) was shown to have thermostability and high substrate specificity. This FAD-dependent glucose dehydrogenase would therefore be superior to other glucose oxidoreductase tested to date in the construction of an O_2 -insensitive amperometric glucose sensor. The two enzymes mentioned above have been of great interest to local companies and have been used for pilot scale production of glucose sensors (Hu, in press).

Fig. 2 shows the measurement of blood glucose at a concentration of 400 mg/dl using FADGDH/ferricyanide-modified glucose test strips and an operating potential of 300 mV. The current peak was reached in about 0.7 s.

In order to improve the properties of the disposable glucose sensors use glucose oxidase and glucose dehydrogenase, new materials and improved screen-printing techniques have been developed in recent years. Hu demonstrated the procedure of fabricating a disposable amperometric glucose sensor using water-based enzyme

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