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Study on detection methods for glucose in biological samples

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Abstract
As a main source of energy, glucose plays a critical role in normal human metabolism. Abnormal change of glucose will contribute to some diseases such as diabetes. Therefore, the sensitive determination of glucose becomes increasingly significant in the field of clinical disease diagnosis and the research of physiological functions. A number of analytical methods have been developed to provide fast, sensitive, selective and reliable quantification in complex biological samples. In this article the studies of detection methods for glucose in recent years are reviewed.

Keywords: glucose; diabetes; determination; detection; sensor

Introduction
Glucose is an important fuel source to generate the universal energy molecule ATP, which plays a crucial role in life processes [1, 2]. The concentration of it in extracellular fluid of central nervous system controlled the brain activity, which is closely linked to brain energy metabolism and synaptic transmission [3]. Moreover, glucose concentration in human blood and urine is used as a clinical indicator of diabetes [4]. Clearly, the development of a reliable cost effective glucose biosensor plays a leading role in the field of medical diagnostics and biotechnology. Many strategies have been reported for the determination of glucose in biological samples. In this paper, the attributes of different analytical technique for the determination of glucose in recent years are reviewed.

2. Analytical Methods
2.1. Colorimetric method: Colorimetry has commonly been used for routine analysis due to its simplicity, low-cost and practicability. It does not require any expensive or sophisticated instruments and the color changes can be even directly observed by the naked eye [5, 6]. Recently, some colorimetric systems have been set up to detect various kinds of substances such as DNA, biologically relevant molecules, metal ions, viruses and micro-organisms and so on [7, 8].

Lim *et al*. [9] used gold nanoparticles self-assembled with a specifically synthesized thiol-derivatized mannose to develop a novel colorimetric bioassay for glucose in human serum. The addition of Con a containing four binding sites induced the aggregation of mannose-stabilized gold nanoparticles via specific mannose–Con A interactions, which led to a red shift of the surface plasmon absorption band centered at 520 nm. The presence of glucose in the solution hindered the Con A-induced aggregation of the mannose-stabilized gold nanoparticles, which resulted in a decrease of the surface plasmon absorption band shift. The linear concentration range was 500–4000μg/mL within 10 min and the detection limit was 363μg/mL. The present bioassay could be successfully applied for the determination of human blood glucose levels for the diagnosis of diabetes without the use of enzymes.

Dutta *et al*. [10] developed a simple, highly selective and inexpensive colorimetric method for the detection of glucose based on a new peroxidase substrate 3,5-DTBC and peroxidase catalytic activity of prussian blue (PB) modified Fe_2O_3 nanoparticles. The PB-Fe_2O_3 nanostructure showed typical Michaelis–Menten kinetics and good affinity to the peroxidase substrate 3,5-DTBC. As a novel mimic peroxidase, the PB-Fe_2O_3 NPs exhibited several advantages over other peroxidase nano-mimetics such as stability, dispersibility, non-toxicity, magnetic separability and high catalytic efficiency. Finally, with the method, human blood glucose level could be monitored conveniently.

2.2. HPLC method: High-performance liquid chromatography (HPLC) is a powerful tool that enables the separation of complex mixtures into individual components, and is a highly sensitive and reproducible analytical technique. In recent years, HPLC has been combined with many sensitive detection techniques and has experienced continuous improvement of stationary phases, which have improved its sensitivity and specificity. HPLC is currently widely used for the analysis of drugs and dosage forms with respect to quality control, quantitative determination of active ingredients and impurities, monitoring drug blood concentration in patients, and bioequivalence assessment [11-13].

Chen *et al*. [14] established a candidate reference method for the determination of glucose in human serum based on HPLC method. D-galactose as the internal standard was added to the serum samples, and glucose standard was also added to equilibrate. The samples were treated with anhydrous ethanol to remove proteins by precipitation. Glucose and galactose reacted with 1-phenyl-3-methyl-5-pyrazolone in serum under weakly alkaline condition and the derivatives were analyzed by HPLC. The established HPLC method for serum glucose determination in this study was accurate precise and practicable, and may be used as candidate reference method for determination of glucose in serum.

Iniesta *et al*. [15] developed a simple, rapid, sensitive and selective procedure based on the combination of HPLC-UV-Vis and HPLC-MS for the determination of a set of 13 analytes present in a commercially available IVF medium using small sample volumes. HPLC-MS allowed the glucose–sodium adduct to be measured accurately and the working and linear ranges achieved were 0.028–0.389 mmol L^{-1} with a detection limit of 13 mM. The use of HPLC-UV-Vis allowed the chromatographic separation of 8 amino acids. Development of the analytical approach provided determination and quantification of a set of 13 analytes from a very complex sample. The novelty of the combination of techniques relied on a screening tool and a strategy to the future evaluation and an improved assessment of human embryo viability.

2.3. ECL method: Electrochemiluminescence (ECL) is a light emission that arises from the high-energy electron transfer reaction between electrogenerated species. As a valuable detection method, ECL has attracted great interest in analytical chemistry owing to its distinct advantages of simplicity, rapidity, sensitivity, controllability and low background, and has been extensively used for different analytical purposes such as squamous cell carcinoma antigen, glucose, cell tumor and so on. ECL is also a commendable model for investigating the mechanism of electron transfer [16-18].

Ye *et al*. [19] developed a highly sensitive ECL biosensor for glucose detection by immobilizing glucose oxidase (GOD) on a glassy carbon electrode (GCE) modified with C60 embedded in tetraoctylammonium bromide ($TOAB^+$) film. C60 was a promising electron transfer mediator between GOD and GCE surface. Meanwhile, C60 had excellent catalytic performance to directly enhance the ECL intensity of luminol. In addition, the introduction of C60 and $TOAB^+$ could immobilize more enzymes effectively onto the electrode so that they could enhance the sensitivity and detection limit of ECL biosensor. Under the optimum condition, the developed glucose biosensor exhibited the linear response range from 500 nM to 13 mM with a detection limit of 166.7 nM. The biosensor offers an alternative analytical method with excellent properties of high selectivity, long-term stability and outstanding reproducibility.

Liu *et al*. [20] developed a novel facile signal-off ECL biosensor for the determination of glucose based on the integration of chitosan, CdTe quantum dots (CdTe QDs) and Au nanoparticles (Au NPs) on the glassy carbon electrode. Upon the addition of glucose, the Au NPs catalyzed glucose to produce gluconic acid and hydrogen peroxide based on the consumption of dissolved oxygen, which resulted in a quenching effect on the ECL emission. Therefore, the determination of glucose could be achieved by monitoring the signal-off ECL biosensor. Under the optimum conditions, the ECL intensity of CdTe QDs and the concentration of glucose had a good linear relationship in the range of 0.01-10mmol L^{-1}. The detection limit for glucose was 5.28μmol^{-1}. The biosensor showed good sensitivity, selectivity, reproducibility and stability, which had been employed for the detection of glucose in human serum samples with satisfactory results.

2.4. Fluorescence method: In recent years, fluorescence measurements have received more attention owing to their operational simplicity, high sensitivity, good reproducibility and real-time detection. A series of fluorescence probes have been designed for the detection of biomolecules and metal ions. For example, gold nanoclusters (AuNCs), which exhibit molecule-like properties including discrete electronic states and size-dependent luminescence have received great attention. Fluorescent silicon nanoparticles (SiNPs), which have a zero-dimensional silicon-based nanostructure, have been widely used in biology, owing to their good biocompatibility, low cytotoxicity, and antiphotobleaching capability. Colloidal quantum dots (QDs) which exhibit broad absorption profiles and narrow emission with high quantum yields and allow the chemical modification of functional groups on their surfaces make QDs naturally suitable for serving as fluorescent platforms for sensing and imaging in biology [21-23].

Gao *et al*. [24] utilized the instinct peroxidase-like property of Fe_3O_4 magnetic nanoparticles (MNPs) to establish a new fluorometric method for determination of hydrogen peroxide and glucose. In the presence of Fe_3O_4 MNPs as peroxidase mimetic catalyst, H_2O_2 was decomposed into radical that could quench the fluorescence of CdTe QDs more efficiently and rapidly. Then the oxidization of glucose by glucose oxidase was coupled with the fluorescence quenching of CdTe QDs by H_2O_2 producer with Fe_3O_4 MNPs catalyst, which could be used to detect glucose. Under the optimal reaction conditions, a linear correlation was established between fluorescence intensity ratio I_0/I and concentration of glucose from 1.6×10^{-6} to 1.6×10^{-4} mol/L with a detection limit of 1.0×10^{-6} mol/L. The proposed method was applied to the determination of glucose in human serum samples with satisfactory results.

Tashkhourian *et al*. [25] designed a nanosensor for the enzymatic determination of glucose based on the fluorescence enhancement of silver nanoparticles (AgNPs). This enhancement was the result of the glucose oxidase-catalyzed oxidation of glucose. The experimental results showed that the increase of the AgNP fluorescence was linearly proportional to the concentration of glucose within its concentration ranges of 2.50×10^{-5}-7.50×10^{-3} M and 7.50×10^{-3}-7.50×10^{-2} M with a detection limit of 5.53×10^{-7} M under the optimized experimental conditions. To evaluate the applicability of the nanobiosensor, determination of glucose in real samples was performed according to the developed procedure.

2.5. Electrochemical Method: Since the early 70s electrochemistry has been used as a powerful analytical technique for monitoring electroactive species in living organisms. In the past decades, numerous glucose electrochemical biosensors have been developed for the sensitive and selective determination of blood glucose level in diabetic patients owing to their simplicity, high sensitivity and low cost. Particularly, glucose oxidase and glucose dehydrogenase based enzymatic glucose biosensors have been used for the selective and sensitive determination of glucose. However, the enzyme immobilization and its stability on the electrode surface is still important task to fabricate the biosensors because of their poor electrical communication between the active site of the enzyme and the electrode. To solve these issues, some nonenzymatic glucose biosensors have been developed due to their long term stability, high sensitivity and low cost. At present, electrochemical glucose biosensors have reached remarkable features in sensitivity and reproducibility [26-28].

Mahmoud *et al*. [29] reported for the first time the fabrication of hierarchical porous CuO micro-/nanostructures with flower- and hollow sphere-like morphology via a facile hydrothermal method for sensitive and selective determination of ascorbic acid and glucose, respectively. Moreover, such unique properties of macro-/mesoporous CuO with defined dimensions and topologies offered minimized diffusive resistance for the dispersion of active sites. The best performance of the glucose and ascorbic sensor could be obtained at +0.55 V in 0.1 M sodium hydroxide solution. The as-prepared CuO modified screen-printed electrodes exhibited a fast electroactive response with high sensitivity within a wide concentration range of glucose and ascorbic acid in real samples. Significantly, the anion dependent approach might be used to control effectively the expansion and features of other metal oxide micro-/nanostructures.

Balouch *et al*. [30] reported a simple, economic, and efficient approach for synthesis of cobalt oxide nanostructures by a low-temperature aqueous chemical growth method, which exhibited high electrocatalytic activity towards the oxidation of glucose in alkaline solution. This enabled development of a highly sensitive, stable and reproducible non-enzymatic glucose sensor. The developed sensor demonstrated high anti-interference capability against common interferents such as dopamine, ascorbic acid and uric acid. Furthermore, the applicability of the developed sensor for the determination of glucose from human blood serum provides an alternative approach for the routine glucose analysis.

2.6. Other methods: In addition to these main approaches mentioned above for glucose detection, still a few special techniques with high sensitivity have been applied. Peng *et al*. [31] developed a new glucose sensor based on up-converting fluorescence resonance energy transfer the results suggested that the technique could be a promising alternative for detecting biomolecules in complex biological sample matrixes for diagnostic purposes. Torul *et al*. [32] presented a paper membrane-based surface-enhanced Raman scattering (SERS) platform for the determination of blood glucose level using a nitrocellulose membrane as substrate paper, and the microfluidic channel was simply constructed by wax-printing method. The developed paper-based microfluidic SERS platform has been found to be suitable for the detection of glucose in blood samples without any pretreatment procedure.

3. Conclusions

Glucose is the most significant energy source in human metabolism processes. The deviation of concentration of glucose can be harmful to human health, so it is important to determinate glucose concentration accurately in blood, urine and other biological samples. This review has highlighted the significant developments in rapid and alternative techniques for the detection of glucose in recent years. Currently, multiplexed detection and in situ detection are especially important, because glucose never work alone, but instead function within a network of several components in vivo. Although numerous designs for glucose detection have been reported, developing more efficient and practicable methods still remains necessary.

Acknowledgments

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