

## A Novel Non-enzymatic Biosensor Based on Ti-Metallic Glass Thin Film: The Blood Glucose Oxidation Approach

### Abstract

**Background:** Material selection is a key issue for the fabrication of non-enzymatic electrode in glucose biosensors. Metallic glass (MG) as an advanced innovative material can provides many basic structural requirements of electrodes. A novel non-enzymatic biosensor based on  $Ti_{57}Cu_{28}\{Zr_{0.95}Hf_{0.05}\}_xSi_{15-x}$  MG (Ti-MG) thin film was introduced for glucose oxidation. **Methods:** The Ti-MG thin film was deposited on the carbon substrate of screen-printed carbon electrode (SPCE), and the Ti-MG modified SPCE was fabricated as Ti-MG/SPCE. The morphology and structure of the Ti-MG thin film were characterized by field emission scanning electron microscope and X-ray diffraction. Electrochemical evaluations were studied by electrochemical impedance spectroscopy and cyclic voltammetry. **Results:** The Ti-MG was sputtered on the carbon substrate in the form of a porous spongy thin film with 285 nm thickness and nanoparticles with average diameter size of 110 nm. The Ti-MG/SPCE showed low charge transfer resistance to the electron transfer and high electrocatalytic activity toward the oxidation of glucose in PBS (pH = 7.4) solution. This biosensor exhibited good analytical performance with a linear range from 2 to 8 mM glucose and sensitivity of  $0.017 \mu A mM^{-1}$ . **Conclusion:** The experimental results indicate that Ti-MG thin film has a high ability to electron transfer and glucose oxidation for the development of non-enzymatic glucose biosensors.

**Keywords:** Biosensor, glucose oxidation, non-enzymatic, thin film, Ti-metallic glass

Submitted: 13-Apr-19

Revision: 25-May-19

Accepted: 09-Oct-19

Published: 06-Feb-20

### Introduction

Diabetes is one of the epidemic diseases in the world, and it was estimated that there are 451 million (age 18–99 years) people with diabetes worldwide in 2017, which is expected to increase to 693 million by 2045.<sup>[1]</sup> To controlling of diabetes, blood sugar level detection is the most significant action in which the patient with diabetes should be carried out. Therefore, the development of diagnostic medical devices in this case, such as biosensors, is too important for blood glucose monitoring.<sup>[2]</sup> Glucose biosensor is an appropriate device to measure blood glucose concentration by converting detected physical or chemical reaction parameters to a measurable signal through special transducers.<sup>[3,4]</sup> Electrochemical biosensing methods such as amperometric, potentiometric, and conductometric due to high sensitivity, low detection limit, fast response time, and low fabrication cost have

been used widely more than other sensing methods such as piezoelectric, calorimetric, and optical.<sup>[5,6]</sup> In these biosensors, produced energy from analyte (glucose) reactions with a modified electrode surface (bioreceptor and biocatalyst) through electrochemical mechanisms was converted to a measurable electrical signal. The signal intensity of the generated electron current intensity measured to express glucose concentration quantitative in oxidation/reduction reaction.<sup>[7]</sup>

Currently, glucose biosensors were developed based on the following two types: enzymatic (biological materials) and non-enzymatic (nonbiological materials) electrodes.<sup>[8,9]</sup> The glucose enzymatic biosensors have three consecutive generations, which glucose oxidase enzyme is widely used in their fabrication.<sup>[10,11]</sup> The application of biological material such as enzymes, antibodies, and others in these enzymatic electrodes causes many limitations and drawbacks in their fabrication and applications.<sup>[12]</sup> In glucose non-enzymatic

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**How to cite this article:** Sarafbidabad M, Jazi HK, Rafienia M. A novel non-enzymatic biosensor based on Ti-metallic glass thin film: The blood glucose oxidation approach. *J Med Signals Sens* 2020;10:35-41.

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DOI: 10.4103/jmss.JMSS\_15\_19

### Quick Response Code:



biosensors, various nonbiological materials such as metals and metal compound, composites, and carbon micro- or nano-material have been proposed for non-enzymatic electrode fabrication due to their electrocatalytic properties and high sensitivity to glucose oxidation processes.<sup>[13,14]</sup> Materials selection and compositing them to substrate electrode are one of the most important priorities for improving the quality of non-enzymatic electrodes in glucose biosensors fabrication to the elimination of enzymatic electrode limitations.

Among innovative materials that can be selected for this purpose, metallic glasses (MGs) are advanced materials that extensive research is conducted on their disciplines as biosensors or bioelectrodes.<sup>[15]</sup> MG (also known as amorphous metal) is a bulk metallic material (BMG), usually as an alloy, with disordered atomic-scale structure.<sup>[16,17]</sup> The good electronic, electrochemical, thermal, mechanical, and magnetic properties of MGs make them as a favorable option for developing modern nanocomposites in electronic and electrochemical applications with high chemical and physical resistance such as electrocatalysis devices and current sensors.<sup>[18]</sup> Today, the different MG alloys based on Fe,<sup>[19]</sup> Pt,<sup>[20]</sup> and Pd<sup>[21]</sup> have been developed for therapeutic and diagnostic applications such as fabrication of non-enzymatic electrode in glucose biosensors. Sagasti *et al.* used Fe-based MG for biological and chemical detection purposes.<sup>[19]</sup> The obtained results let us assume that this alloy is suitable for developing sensors with chemical or biological detection purposes. Furthermore, Kinser *et al.* were exhibited that Pt-BMG has electrical properties conducive which can be processed to produce nonrandom topography at the nanoscale for biosensor electrode applications.<sup>[20]</sup> Electrochemical measurements suggest that biocompatible Pt-BMG electrode enhances signal and sensitivity in glucose biosensors. In other research, Pd-based MG was utilized for developing non-enzymatic electrochemical glucose sensors by Zeng *et al.*<sup>[21]</sup> The results of this research indicate that Pd-based MG has electrochemical catalytic activity toward the oxidation of glucose. Hence, MG is promising materials for enzyme-free electrochemical glucose biosensor.

For justification of the electrocatalytic mechanism on the surface of non-enzymatic electrodes, Pletcher and Burke have been presented two main models, namely the chemisorption model<sup>[22]</sup> and incipient hydrous oxide adatom mediator (IHOAM),<sup>[23]</sup> respectively. The generated various signals and redox reaction peaks will amplify due to chain MG/glucose reactions on the MG surface.<sup>[18]</sup> Therefore, adding active metal elements available in MG on the surface electrodes improves the electron transfer capability due to the properties mentioned above and can accelerate slow electrochemical reactions during an electrocatalytic process as a bioreceptor of glucose.<sup>[24,25]</sup> The research done on electrocatalytic properties of MGs demonstrated

that the MG has excellent electrocatalytic properties and presents extensive potential applications in many industries that are affiliated with catalysis materials.<sup>[26]</sup> The researchers indicated that  $Ti_{41.3}Cu_{43.7}Hf_{13.9}Si_{1.1}$  BMG has a better electrochemical performance in NaCl and Hank's solutions and good mechanical properties compared with pure Ti and Ti-6Al-4V alloy. Hence, the Ti-MG alloy has a high potential for electrochemical and biomedical applications.<sup>[27]</sup> In another study, Gong *et al.* showed that the significant improvement of sensitivity in the Coriolis flow meter using the  $Ti_{50}Cu_{25}Ni_{15}Zr_5Sn_5$  BMG sensing pipe allows the possibility of the use of the Ti-based BMG in various industries such as fossil fuel, chemical, environmental, semiconductor, and medical science fields.<sup>[28]</sup> Hence, Ti-MG nanostructures can be a promising material for modification and fabrication of non-enzymatic electrodes to glucose sensing due to the electrocatalytic properties mentioned above.

In this paper, Ti-MG thin film was sputtered on the carbon substrate, and a commercial electrode was fabricated by new material and method. We investigated the novel Ti-MG thin film to study blood glucose oxidation and develop non-enzymatic electrodes in glucose biosensors.

## Materials and Methods

### Materials and apparatus

Ti, Cu, Si pure powder (Alfa Aesar, USA), and Zr-Hf sponge (ZPP, Iran) were mixed according to  $Ti_{57}Cu_{28}\{Zr_{0.95} - Hf_{0.05}\}_xSi_{15-x}$  MG stoichiometric for creating target pellets. Glucose ( $C_6H_{12}O_6$ , 99.5% purity) was purchased from Merck, Germany, to prepare the glucose solutions. Sodium hydrogen phosphate salt ( $Na_2HPO_4$ , 98% purity, Sigma-Aldrich, USA) was used to prepare the 0.1 M phosphate buffered saline (PBS) solution as a supporting electrolyte. All measurements were performed at room temperature (average 25°C), and all other reagents were of analytical grade. High-quality deionized water is used throughout the experiments.

The screen-printed carbon electrode (SPCE, ref. 150, DropSens, Spain) was used to base a commercial electrode as a base triple electrode system with listed physical and electrochemical cell properties [Table 1]. Radiofrequency sputtering (RF sputtering, Edwards Auto 500 Magnetron, BOC, England) technique was utilized for deposition Ti-MG nanoparticles on the bare SPCE. An electrochemical system analyzer (PGSTAT302N, Autolab, Eco Chemie, Utrecht, Netherlands) was used for electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) measurements. The phase structures were investigated by X-ray diffraction (XRD, Philips, X'pert-MPD,  $CuK\alpha$  at 40 kV and the Breg-Brentano geometry). The field emission scanning electron microscopy (FESEM, Nov, NanoSEM230-FEI, 230 kV) was utilized to study of surface morphological characterization.

## Preparation of the Ti-MG/SPCE

One of the most important steps in the fabrication of a non-enzymatic electrode is the selection of a suitable deposition method, which has a direct connection with electrodes performance and efficiency. There are several methods for thin film deposition on the surface electrode. Among these methods, sputtering is a very efficient method. Sputtering is a physical vapor deposition (PVD) method for thin-film (micro- to nano-size) deposition. In this research, the Ti-MG thin film was deposited on the carbon surface of bare SPCE by RF sputtering technique and the Ti-MG modified SPCE denoted as Ti-MG/SPCE. The thin film sputtering system consists of vacuum chamber, vacuum pump, power supply, gas inlet, and cathode and anode poles for putting up target and substrate, respectively. The sputtering mechanism in PVD methods includes vaporization of the target material, transfer the vapor from the target to the substrate, and formation of a thin film on the substrate. RF sputtering is done in a vacuum pump and is formed a bright arc or plasma by the controlled entry of argon inert gas (99.999%) into the chamber. In this process, energized ions with energy of 50–1000 eV hit the target and subsequently separate its surface atoms by gas ionization between the target and substrate and then applying a negative potential to target. These atoms or molecules accelerate in argon plasma and lead to the formation of a thin film on the surface substrate.

The Ti-MG/SPCE was fabricated by Edwards Auto 500 Magnetron sputtering system. First, the  $Ti_{57}Cu_{28}\{Zr_{0.95}-Hf_{0.05}\}_xSi_{15-x}$  MG powder was converted to a pill with a 3" diameter and 6 mm thickness by a mold. The bare SPCE as substrate was covered by a perforated circle's masks with 4 mm diameter, which this circle fits with working electrode diameter in bare SPCE. Then, the prepared pill from the previous step (target) was placed on the magnetron at 8 cm distance with the substrate and warhead put on it. In this state, the sputtering process is done accordance with the parameters listed in Table 2. Accordingly, Ti-MG nanoparticles in the form of a thin film were deposited on the carbon (working electrode) surface of bare SPCE, and Ti-MG/SPCE was obtained during the mechanism described above. This technique is an economical and easy method to deposition of nanoparticles on the surface electrode for the preparation of samples.

## Results and Discussion

### Surface morphology

The structural characterization and surface morphology of Ti-MG thin film were investigated by FESEM. Figure 1 shows the FESEM image and particle size distribution histogram of Ti-MG thin film deposited on the carbon surface at the Ti-MG/SPCE. The FESEM image indicates that the Ti-MG nanoparticles were sputtered on the carbon substrate in the form of a porous spongy thin film with 285 nm thickness

**Table 1: Physical and electrochemical properties of SPCE (ref. 150)**

Electrode parts	Materials
Working electrode	Carbon (4 mm diameter)
Auxiliary electrode	Pt
Reference electrode	Ag
Substrate	Ceramic (L33 × W10 × H0.5 mm)
Electric contacts	Ag

Pt – Platinum; Ag – Silver

**Table 2: Radio frequency sputtering parameters**

Parameters	Condition
Target	Ti-MG powder
Substrate	SPCE
Power (W)	230
Temperature (°C)	28
Deposition rate (nm/s)	0.3
Deposition time (min)	15
Deposition thickness (nm)	300
Base pressure (Pa)	0.85
Working pressure (Pa)	1
Target voltage (V)	310
Target-electrodes distance (cm)	8

SPCE – Screen-printed carbon electrode; Ti-MG – Ti-metallic glass

contains rounded and bright particles [Figure 1a]. A particle size distribution histogram determined from the FESEM image indicates that these particles are in the range of 38–206 nm with an average diameter size of 110 nm [Figure 1b]. It seems that with the continuing RF sputtering process, deposited nanoparticles were formed a sponge-shaped Ti-MG thin film and with the end of this process, dew-like nanoparticles were formed on the thin film surface.

To study atomic and molecular structure at the Ti-MG/SPCE, the XRD patterns of Ti-MG thin film are shown in Figure 2. In this diffractometry analysis, peaks with different angles and intensities are related to a specific crystalline plane. The results show an obvious peak at  $2\theta = 41.6^\circ$  that is assigned to Ti-MG. In this case, mixtures of metal and amorphous grade particles are dispersed on the carbon matrix.

In the Ti-MG/SPCE,  $Ti_{57}Cu_{28}\{Zr_{0.95}-Hf_{0.05}\}_xSi_{15-x}$  MG nanoparticles are sensitive to glucose absorption by creating nanoelectrochemical cells due to their specific electrocatalytic property and glucose molecule size with 1.5 nm diameter.<sup>[18]</sup> The surface morphology results show that Ti-MG nanoparticles deposited on carbon substrate using RF sputtering technique are in the form of a thin film which composes randomize nanoparticles assembly with nanothickness size and amorphous structure. This nanoporous thin film provides a suitable substrate surface (superior surface area) for contact with available biochemical molecules in a buffer solution such as PBS by deposited Ti-MG nanoparticles.



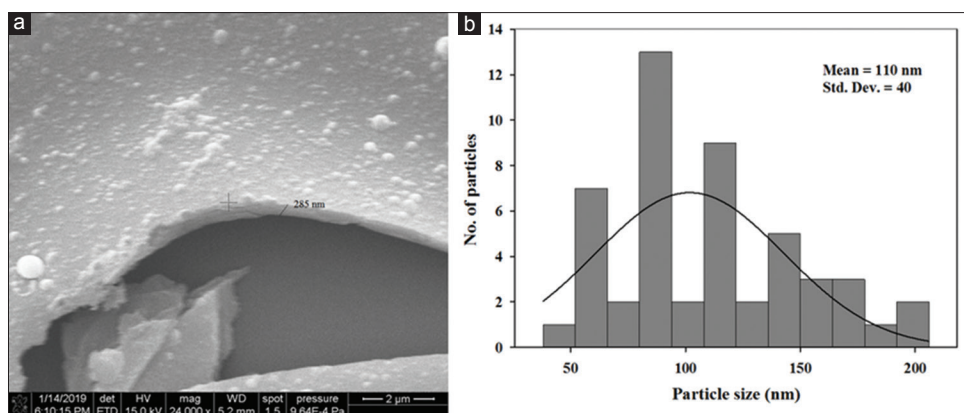


Figure 1: (a) Field emission scanning electron microscope image and (b) particle size distribution histogram of Ti-metallic glass thin film

### Electron transfer behavior

The electrochemical behavior of electrodes was investigated by EIS to study electron transfer. In this analysis, the charge transfer resistance ( $R_{ct}$ ) was measured that its amount is proportional to the radius of the semicircle in the Nyquist plot, while minimum  $R_{ct}$  value leads to the best kinetics of electron transfers. The Nyquist plots of bare SPCE and Ti-MG/SPCE in 0.1 M  $[\text{Fe}(\text{CN})_6]^{3-/4}$  electrolyte solution containing 0.1 M KCl are shown in Figure 3. The  $R_{ct}$  value in the bare SPCE is 263  $\Omega$ , while this value in the Ti-MG/SPCE decreased to 182  $\Omega$ . The EIS results show that the Ti-MG/SPCE has a lower  $R_{ct}$  compared with the bare SPCE. Therefore, the internal resistance of Ti-MG/SPCE is lower than bare SPCE and confirms that electron transfer is facilitated in the Ti-MG/SPCE surface, and the Ti-MG thin film acts as an electron mediator. The reason for the electron diffusion and transfer in the Ti-MG thin film is related to their good conductivity and also the created thin-film features from the deposition method. The obtained result shows that electrode surface modification by Ti-MG thin film does not limit the kinetics of electron transfer.

### Electrocatalytic performance

The electrocatalytic activity depends on redox reactions (oxidation/reduction) in electrodes surface and glucose in the electrolyte solution. The electrocatalytic performance of electrodes toward glucose oxidation was analyzed by CV. Figure 4 shows the cyclic voltammograms of bare SPCE and Ti-MG/SPCE in the absence (dot line) and presence (solid line) 1 mM glucose in 0.1 M PBS solution at a scan rate of 50  $\text{mVs}^{-1}$ . Figure 4a shows that there are no obvious redox peaks in bare SPCE. However, this electrode exhibit a background current difference with and without glucose ( $\Delta I_{\text{NoGl/Gl}}$ ). Figure 4b shows that the Ti-MG/SPCE has a wide  $\Delta I_{\text{NoGl/Gl}}$ , and also, the anodic and cathodic peaks current in the presence of glucose at 0.30 V and 0.21 V, respectively. In the absence of glucose, neither the bare SPCE nor the Ti-MG/SC modified electrode shows oxidation peaks current. In the presence of glucose, only

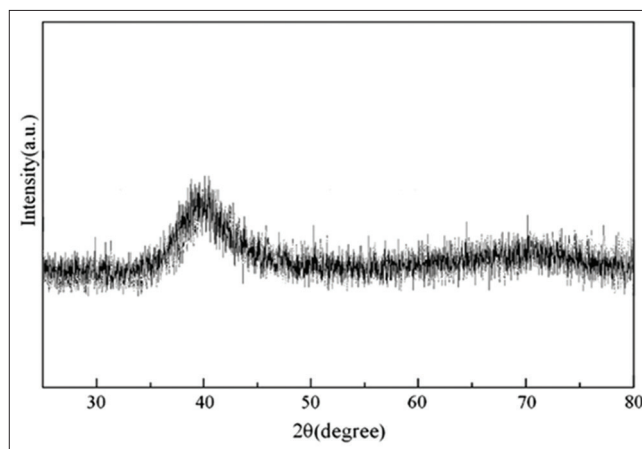


Figure 2: X-ray diffraction patterns of Ti-metallic glass thin film

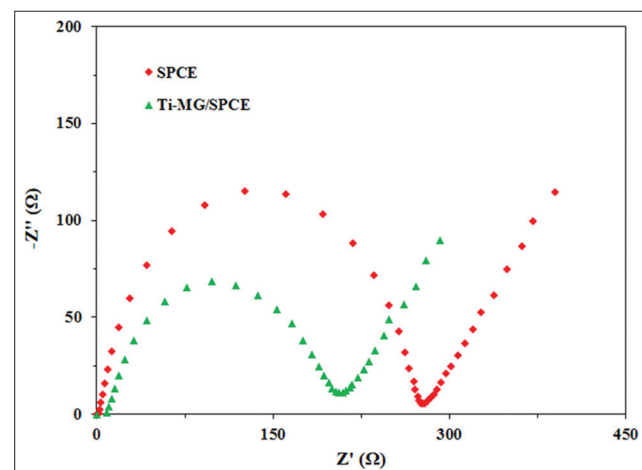
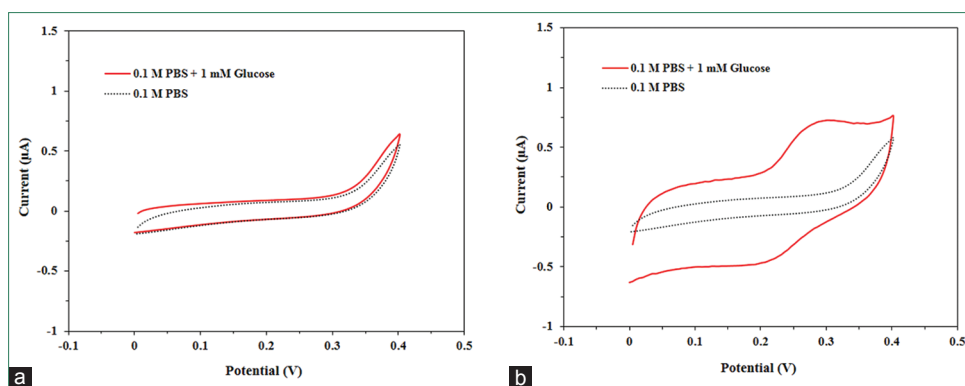


Figure 3: Electrochemical impedance spectroscopy of bare screen-printed carbon electrode and Ti-metallic glass/screen-printed carbon electrode in 0.1 M  $[\text{Fe}(\text{CN})_6]^{3-/4}$  solution at the potential of 0.18 V and frequency range of 10 kHz – 100 mHz

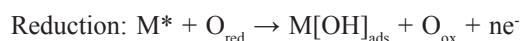
a negligible increase of background current was observed for the bare SPCE, while a wide background current with an anodic and cathodic peak current for the Ti-MG/SPCE. The obtained results of Figure 4 show that the Ti-MG/SPCE has a higher  $\Delta I_{\text{NoGl/Gl}}$  and or in other words,



**Figure 4: Cyclic voltammograms of (a) bare screen-printed carbon electrode and (b) Ti-metallic glass/screen-printed carbon electrode in the absence (dot line) and presence (solid line) of 1 mM glucose in 0.1 M PBS solution at a scan rate of 50 mVs<sup>-1</sup>**

a much larger current signal with wider background current along, and also a redox peaks current pair in the presence glucose compared with bare SPCE.

The superior electrocatalytic parameters in the Ti-MG/SPCE indicate increase energy level and reaction kinetics into glucose oxidation. It can be concluded that deposited Ti-MG thin film on the conductive carbon (graphite) surface can catalyze the electro-oxidation of glucose in accordance with the following argument. In the non-enzymatic biosensor, according to the IHOAM model and the following glucose oxidation mechanism, the first M\* (adatom or reductive metal absorption site) underwent a premonolayer oxidation step and formed an incipient hydrous oxide layer of reactive as OH<sub>ads</sub>. In the redox reactions, this layer acted as mediators and inhibitors in oxidation and reduction processes, respectively. Then, after adsorption of glucose on transient active metals surface, glucose was bonded to M[OH]<sub>ads</sub> (oxidative absorbed hydroxide radical) and oxidizes by it. Eventually, glucose oxidation by redox reactions causes produce electron in the electrode surface.<sup>[24,25]</sup>



The Ti-MG thin film is a combination of metal elements that creates an active surface-fluid interface with a low lattice coordination number. This means that the number of stable and define atoms or ions in the closest site around an atom is very low. Short-range order and randomize situation in Ti<sub>57</sub>Cu<sub>28</sub>{Zr<sub>0.95</sub>-Hf<sub>0.05</sub>}<sub>x</sub>Si<sub>15-x</sub> MG structure<sup>[29]</sup> causing increasing the number of the atomic sites of Ti, Cu, Zr, and Hf in the surface and subsequently increasing selective adsorption OH. Metal elements of Ti-MG thin film are transition metal with good oxidizing properties, that it can as an active metal atom (M\* = Ti, Cu, Zr, and Hf) oxidize glucose due to the above model.<sup>[23]</sup> Therefore, it can be concluded that deposited Ti-MG thin film by sputtering RF with memorizing this structure has the ability to produce hydrogenated oxide layer and facilitates continue the

process of glucose oxidation. The high energy amorphous structure of the Ti-MG-modified electrode has a special effect on the glucose redox reactions that leads to increase background current and create a redox peaks pair in the presence glucose [Figure 4]. The amorphous surfaces at discontinuous areas and edges are more reactive due to its direct exposure to the solution compared with their bulk counterparts and undergo premonolayer oxidation. It can be inferred that unbalanced conditions in the production of these reactive thin films make them a high entropy structure. This considerable energy level increase kinetics reaction is used to react with very high speed in the face of a reactive environment. For this reason, the tendency for glucose oxidation in the amorphous thin film is very high. The Ti-MG nanoparticles have a dynamic special effect on glucose oxidation reactions and can easily connect to glucose nanobiomolecules and produce electron by oxidation reaction on the modified surface electrodes. These produced electrons are transferred to carbon substrate. The repeated this cycle and releasing electrons cause the produce current signals and formation of oxidation peaks current.

### Glucose sensing

The Ti-MG/SPCE is a good candidate for electrochemical detection of glucose due to efficient electrocatalytic performance in Ti-MG thin film. Figure 5 shows cyclic voltammograms of the Ti-MG/SPCE to different concentrations of 2, 4, 6, and 8 mM glucose in 0.1 M PBS solution at a scan rate of 50 mVs<sup>-1</sup>. The results show an increase in glucose concentration from 2 to 8 mM, anodic peak currents regularly, and logically increases from 0.9 to 1.0 µA. This indicates the high impact of the electrode toward glucose concentration which shows its ability for glucose sensing. To evaluate the analytical performance, the calibration plot of the Ti-MG/SPCE is shown in Figure 6. The biosensor exhibited a linear relationship in the range of 2 to 8 mM ( $I_p/\mu\text{A} = 0.017 C_{\text{glucose}}/\text{mM} + 0.98$ ,  $R^2 = 0.9797$ ) with a sensitivity of 0.017 µA mM<sup>-1</sup>. Analytical performance of biosensor based on Ti-MG thin film is compared with other published

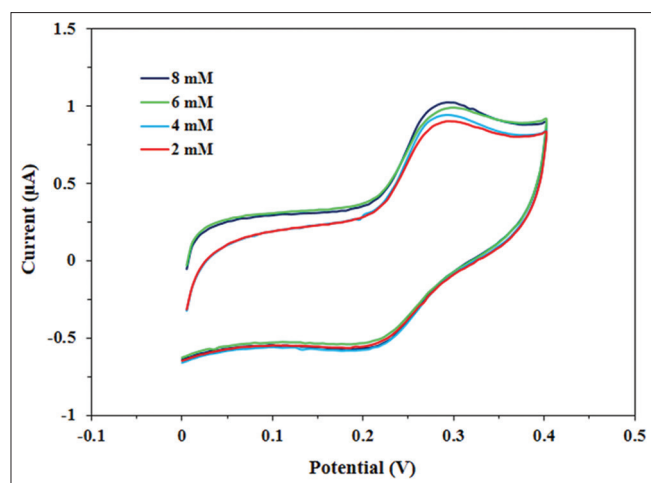


Figure 5: Cyclic voltammograms of the Ti-metallic glass/screen-printed carbon electrode to different concentrations of 2, 4, 6, and 8 mM glucose in 0.1 M PBS solution at a scan rate of 50 mVs<sup>-1</sup>

nonenzymatic biosensors based on MG mentioned in the third paragraph of the introduction. The Ti-MG/SPCE has good analytical parameters such as linear range and sensitivity in compared with other electrodes.

This desirable result is due to the synergetic and mutual effects of Ti-based MG nanoparticles and C substrate together. As already mentioned, carbon substrate and MG alloys have a good electrical conductivity that causing facilitates electron transfer in the electrode. Furthermore, MG nanoparticles with atomically dispersed elements have good electrocatalytic performance and provide a highly processable nanoscale that can be used for electrocatalysis and surface modification.<sup>[30]</sup> These results show that the Ti-MG thin film by providing desirable electrocatalytic activity and electron transfer improves glucose oxidation in samples biological.

## Conclusion

In this study, the Ti-MG/SPCE was fabricated for the development of blood glucose biosensors. The  $Ti_{57}Cu_{28}\{Zr_{0.95}-Hf_{0.05}\}_xSi_{15-x}$  MG nanoparticles deposited on the SPCE by the RF sputtering technique. This nanoparticle successfully entrusted on the carbon substrate in the form of the sponge-shaped thin film. The Ti-MG/SPCE exhibited low charge transfer resistance and high background current signal with good sensitivity toward glucose oxidation. Thus, the Ti-MG thin film as a novel nanoelectrocatalyst material has a high ability for glucose biosensing.

## Financial support and sponsorship

This study was funded by Biosensor Research Center, Isfahan University of Medical Sciences under grant number 296001.

## Conflicts of interest

There are no conflicts of interest.

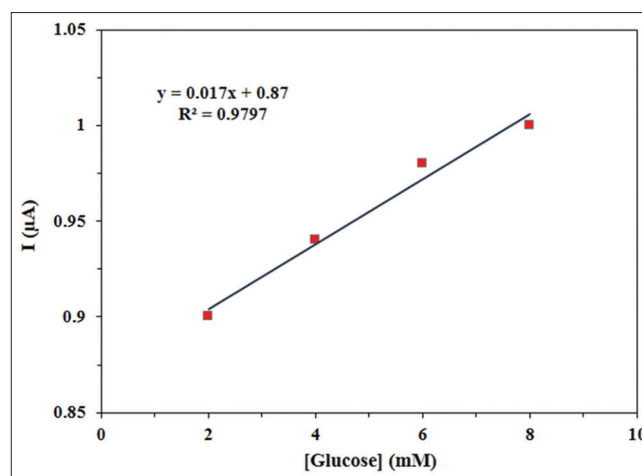


Figure 6: Calibration plot of Ti-metallic glass/screen-printed carbon electrode anodic peak current versus glucose concentration

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