Biosensor-Integrated Drug Delivery Systems in Diabetes

Subjects: Medicine, General & Internal

Contributor: Ronny Priefer, Iwona Cicha, Patrícia Severino, Eliana B. Souto, Sona Jain

One of the most recognized diseases worldwide is diabetes. There are currently almost half a billion individuals globally with this disease and this is expected to crest three quarters of a billion by the end of the decade. Traditionally, diabetes is broken into three categories: Type 1 (previously referred to as juvenile); Type 2 (occasion defined as adult onset), and gestational diabetes. Gestational diabetes occurs in ~2–10% of pregnant women with roughly 50% of these cases leading to the mother developing T2D after giving birth. Generally, 5–10% of cases of diabetes are of the T1D form with the remaining 90–95% having T2D. The need to monitor blood glucose, whether for T1D or T2D, is vital for the health and welfare of those afflicted with these diseases. Equally, if not more important, is the need to administer the necessary drug once the knowledge of one's blood glucose is determined. It is this key second part that has led to significant efforts and ultimate successes in bringing closed-loop systems for diabetes management to market.

Keywords: biosensors ; biomedical applications ; Diabetes

1. Urine-Glucose Testing

Between the 1920s and 1960s, a patient's urine was the only means by which to gauge one's blood glucose. This required taking a few drops of urine and mixing in with Benedict's solution to yield a bright red precipitate as an indicator that there was glucose in the sample (**Figure 1**) [1].

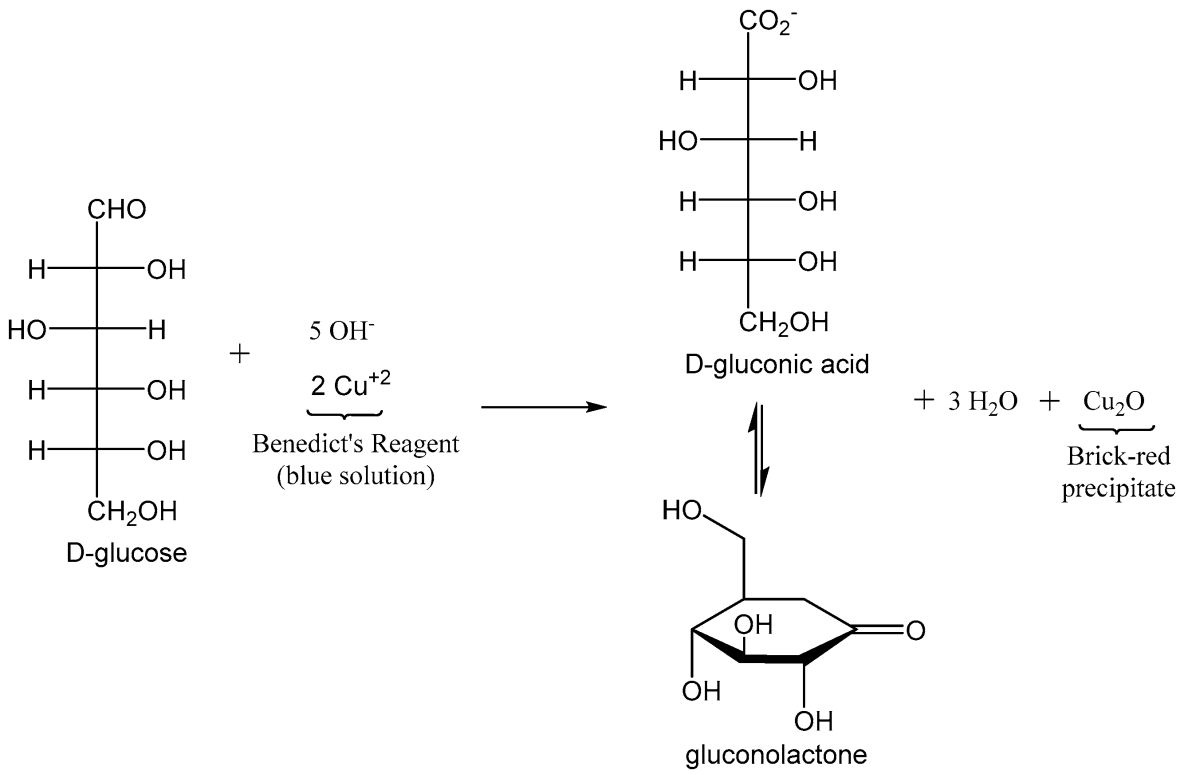

Figure 1. Benedict's reaction for urine glucose testing.

Beyond the lack of practicality of this approach, which was improved on with the "dipstix" [2], it was still only a proxy for blood glucose levels. Currently, there are a number of urine-glucose tests available commercially. However, the technology has its limitations, primarily, it is still simply a proxy for blood glucose. A recent report highlighted this issue, whereby the urine-glucose test was only 14% selective and even failed to identify ~16% of participants with diabetes [3]. A

benefit that should not be overlooked with urine-glucose testing is the lack of potential infections that have been reported, albeit minimally, with blood glucose [4]. In developing countries, where blood transmitted pathogenic disease is more prevalent, the cost associated with the lancets themselves are a significant hurdle.

2. Blood Glucose Testing

In 1964, Dextrostix, by the Ames-Miles Laboratories, was developed as the first blood glucose test strip [5]. Similar to its predecessor, this approach utilized a colorimetric change, albeit enzymatically. Taken from Clinistix, which was developed in the 1940s, this double sequential enzymatic reaction proceeded by the initial conversion of glucose to gluconic acid (which is in equilibrium with gluconolactone) by glucose oxidase, which also yielded hydrogen peroxide [5]. The hydrogen peroxide acted as a reagent in the oxidation of *o*-toluidine, which was facilitated by peroxidase. The major advance with Dextrostix was the ability to trap the red blood cells by a semipermeable membrane to prevent interference. For its time, it was a revolutionary technology. However, by today's standards, it would be considered somewhat archaic. In addition to requiring 1 min and a relatively large blood sample (30 µL), the results were gauged by the patient's interpretation of a colorimetric change [5]. Fortunately, over the past decades, significant advances within nanotechnology have allowed for the self-monitoring of blood glucose to become a more manageable, less invasive, and expeditious process.

The most instrumental advancement with regard to blood glucose monitoring was the nanotechnology approach for both the creation of enzyme-based circuitry and the miniaturization of the necessary electrodes for the detection of an electrochemical oxidation/reduction potential. Unlike Dextrostix, the majority of today's blood glucose detection devices employ a single enzymatic reaction. With just a single drop of blood, the glucose held within is reacted with a nanolayer of glucose oxidase that is complexed with its redox cofactor, flavin adenine dinucleotide (FAD) [6][7]. In this process, the glucose is oxidized to gluconolactone while the glucose oxidase-flavin adenine dinucleotide (GO_x-FAD^+) is reduced to GO_x-$FADH_2$. Upon the regeneration of GO_x-FAD^+ by the reaction with O_2, also held within the blood, hydrogen peroxide (H_2O_2) is produced. The aforementioned nanolayer of GO_x-FAD^+ is coated on a silver working electrode surface. Thus, when the generated H_2O_2 is oxidized to $2H^+$ and O_2, the corresponding amperometric signal can be correlated with the initial glucose concentration [6][7]. Although this first-generation electrochemical detection technology still dominates the blood glucose monitoring industry, three new generation of devices have been developed (**Figure 2**) [5].

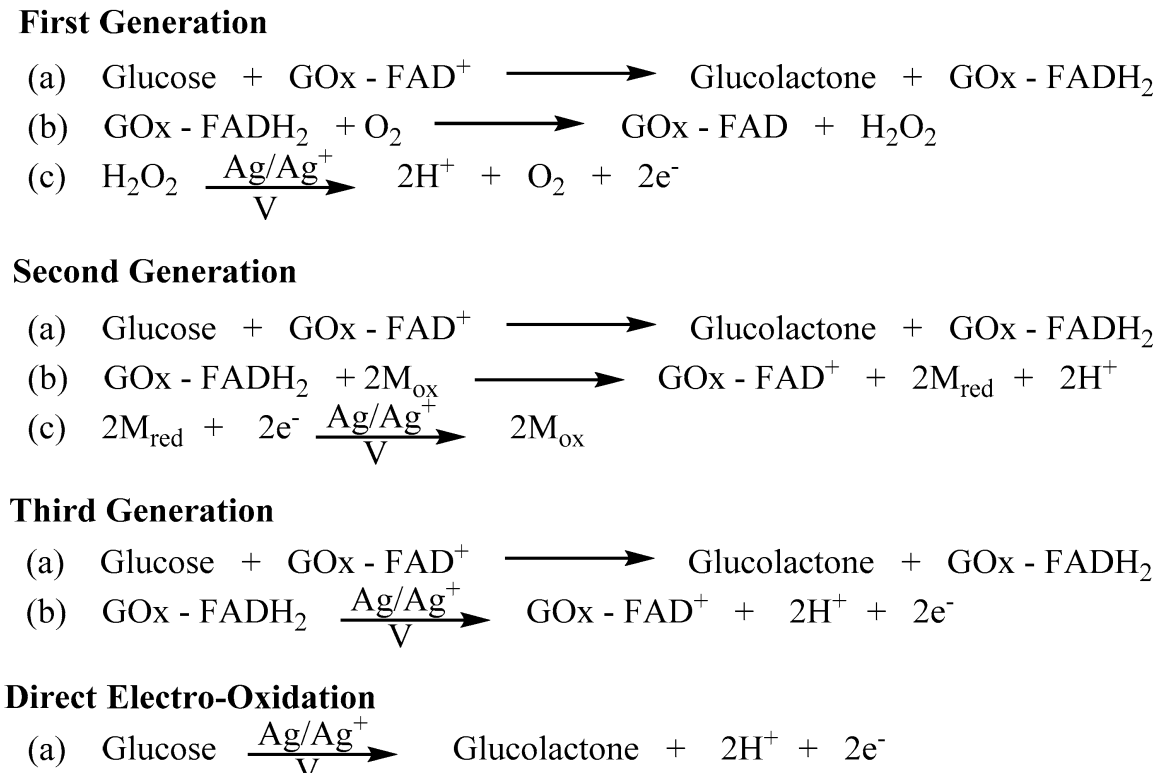

Figure 2. The steps involved in all generations of glucose monitoring via amperometric biosensors.

The second- and third-generation of the electrochemical detection of blood glucose both employ the same nanolayer of GO_x-FAD^+ for the conversion of glucose to gluconolactone with the production of GO_x-$FADH_2$. For second-generation devices, instead of employing the natural co-substrate of molecular oxygen for the production of H_2O_2, these employ an impregnated artificial metal mediator [8][9][10][11]. Thus, in the oxidation of GO_x-$FADH_2$ back to GO_x-FAD^+, the metal mediator is reduced. It is this reduced metal that when oxidized back by the silver working electrode yields a quantifiable

amperometric signal [8][9][10][11]. With third-generation electrochemical glucose detectors, the metal mediator has been completely removed. Herein, the nanolayer has been covalently or electrochemically bound to the silver working electrode [12][13]. Thus, the conversion of GO_x-$FADH_2$ back to GO_x-FAD^+ can be accomplished by direct electron transfer. Unlike the prior two generation devices, this approach measures reduction as opposed to the oxidation potential. Various other enzymatic approaches have also been evaluated that have employed either glucose [14][15][16] or quinoprotein-based glucose dehydrogenases [17][18][19] in the aforementioned generations. Typically, these utilize mediators such as nicotinamide adenine dinucleotide (NAD^+) and quinones.

The final electrochemical glucose detection technology, known as direct electro-oxidation (rarely referred to as fourth generation) is a non-enzymatic approach. Nanostructured electrodes, whether platinum–lead alloy nanowires [20], gold nanoparticles [21], platinum nanoforests [22], or general alloy nanostructures [23] such as those containing gold, palladium, rhodium, lead, or platinum work by simply measuring the electro-oxidation of glucose to gluconolactone. The advantage of this approach is that the incredible high surface area of these nanostructures allows for the remarkable electro-catalytic activity.

These fantastic advancements in the realm of nanotechnology have been translated from the aforementioned self-monitoring of blood glucose (SMBC) [24] to the newer continuous glucose monitors (CGMs) [25]. It was the development and adoption of CGMs, the first of which was by Metronic in 1999, that led to the closed-loop system finally being introduced into the market. However, it took almost two decades before an all-in-one device was actually approved. A primary concern with CGMs has been the “lag-time” related to the fact that these devices detected glucose changes in interstitial fluid as opposed to directly within the blood. This lag-time could be anywhere between 4 and 27 min. Regardless, it is the nano-sensing of CGMs coupled with traditional administration, whether insulin or glucagon, via an incorporated syringe-like injector system that has brought about these novel closed-loop delivery systems [4]. These devices are of great assistance in the health and wellness of the diabetic community. However, whether SMBC, CGM, or closed-loop systems all still have the major limitation of being invasive in nature and, although rare, a potential site of infection [4]. Thus, significant work has been underway to develop non-invasive approaches to monitor glucose levels, with many utilizing some nanotechnology in the hopes of also linking developing less-invasive closed-loop delivery systems.

3. Non-Invasive Glucose Testing

Although by definition urine glucose testing is non-invasive, it has been socially deemed untidy and is a relatively unpopular approach for diabetes management [26]. Currently, numerous novel, albeit not yet marketed approaches have been attempted that are looked at through the skin, tears, and even the breath for the monitoring of blood glucose. For through-skin approaches, near-infrared [27][28], mid-infrared [29][30], thermal emission spectroscopy [31][32], ultrasound [33][34], metabolic heat conformation [35][36], electromagnetic [37][38], mm-wave radar [39][40], and microwave sensing [41] have all been attempted with various degrees of success. More recently, tears have become an active area of research due to the fact that the leakage of glucose directly into tear fluid is known to occur either from the interstitial fluid or epithelial cells [42]. Thus, attempts utilizing the aforementioned nanotechnology enzymatic detection approaches have been evaluated in addition to some unique methods such as optical polarimetry [42][43] and retina pigmentation regeneration [44].

For breath detection, glucose is not the chemical that is being quantified. Instead, due to the propensity of individuals that have diabetes to undergo ketoacidosis, there is an inherent elevated level of ketones within the body, specifically acetone. Thus, researchers have utilized traditional technologies such as gas-chromatography, mass spectrometry, and/or combinations thereof to detect this volatile organic compound (VOC). Chitosan-based sensors have been developed for the detection of low concentrations of acetone, down to 0.1 ppm [45]. Unfortunately, the impediments of this technology are its (1) variability with humidity; (2) lengthy processing steps of making the film sensor, which included hydrofluoric acid, surface oxidation at temperatures > 1000 °C, photolithography and so on; and (3) lack of selectivity to only acetone, as it also detected another volatile breath organic, methanol. Others have utilized Si-doped WO_3 nanoparticle films [46]. This approach gives accurate and precise results, but variability in relative humidity, need to analyze at 400 °C as well as some response to ethanol are all limitations that need to be overcome. Similar successes with thin-walled SnO_2 functionalized with Pt nanoparticles have been reported [47], however, the high temperature requirements as well as the lack of selectivity (also detects toluene) have hindered its further development. Others have examined Pt-functionalized WO_3 nano-hemitubes that require 300 °C and lack selectivity (H_2S and toluene are also detected, albeit not to the intensity of acetone) [48]. Fe_2O_3 doped with Pt as semiconductors has shown success, however, a >200 °C temperature was needed, leading to a decrease in its long-term stability [49]. More recently, cavity enhanced absorption spectroscopy (CEAS) has gained significant attention [50]. However, this type of device tends to be 1–2 feet in length, requires a vacuum pump, and is currently not economical. Applied Nanodetectors is attempting to launch a product to detect the breath acetone levels using a headspace VOC analysis [51].

Recently, a unique approach employed the layer-by-layer self-assembly of multilayers utilizing the pseudo-polyelectrolyte, poly (4-vinylbenzeneboronic acid) (PVBBA) with the weak polyelectrolyte, poly (allylamine hydrochloride) (PAH) to create nanofilms for the detection of breath acetone [51]. The PVBBA/PAH nanofilms are coated on UV-transmitting poly(methyl methacrylate) (UVT-PMMA) at different assembly pH and layer numbers. The slides are subjected to a light emitting diode with a peak wavelength of ~300 nm and detected via a UV-photosensor with an integrated transimpedance amplifier. Upon the exposure of a 10-layered PAH/PVBBA coated UVT-PMMA slide to acetone vapor, crosslinking occurred via a Petasis reaction. These results suggest that it may be possible to quantify this reaction and therefore obtain accurate acetone concentrations. Indeed, clinical studies have shown that this nanotechnology may be a viable approach to bring the first non-invasive diabetes monitor to market [52].

Just as SMBC led to CGMs, which has allowed for the delivery of the vital insulin drug directly into the body on-demand [25], it is the desire within the non-invasive biotechnology industry to duplicate this pathway. A future where one could simply breathe, blink, or sweat to obtain a reading of one's glucose levels that when sent to a receiver to administer the correct type and amount of drug is a future worth working toward.

References

1. Swidorski, D. Diabetes History. 2014. Available online: https://www.defeatdiabetes.org/diabetes-history/ (accessed on 3 May 2022).
2. American Diabetes Association. Severe Hypoglycemia Predicts Mortality in Diabetes. Available online: https://care.diabetesjournals.org/content/35/9/1814 (accessed on 3 May 2022).
3. Storey, H.L.; van Pelt, M.H.; Bun, S.; Daily, F.; Neogi, T.; Thompson, M.; McGuire, H.; Weigl, B.H. Diagnostic accuracy of self-administered urine glucose test strips as a diabetes screening tool in a low-resource setting in Cambodia. BMJ Open 2018, 8, e019924.
4. Patel, B.; Priefer, R. Infections associated with diabetic-care devices. Diabetes Metab. Syndr. 2021, 15, 519–524.
5. Vaddiraju, S.; Burgess, D.J.; Tomazos, I.; Jain, F.C.; Papadimitrakopoulos, F. Technologies for continuous glucose monitoring: Current problems and future promises. JDST 2010, 4, 1540–1562.
6. Vaddiraju, S.; Burgess, D.; Jain, F.; Papadimitrakopoulos, F. The role of H2O2 outer diffusion on the performance of implantable glucose sensors. Biosens. Bioelectron. 2009, 24, 1557–1562.
7. Vaddiraju, S.; Singh, H.; Burgess, D.J.; Jain, F.C.; Papadimitrakopoulos, F. Enhanced glucose sensor linearity using poly (vinyl alcohol) hydrogels. JDST 2009, 3, 863–874.
8. Degani, Y.; Heller, A. Direct electrical communication between chemically modified enzymes and metal electrodes. I. Electron transfer from glucose oxidase to metal electrodes via electron relays, bound covalently to the enzyme. J. Phys. Chem. 1987, 91, 1285–1289.
9. Pishko, M.V.; Katakis, I.; Lindquist, S.E.; Ye, L.; Gregg, B.A.; Heller, A. Direct electrical communication between graphite electrodes and surface adsorbed glucose oxidase/redox polymer complexes. Angew. Chem. Int. Ed. Engl. 1990, 29, 82–84.
10. Dong, S.; Wang, B.; Liu, B. Amperometric glucose sensor with ferrocene as an electron transfer mediator. Biosens. Bioelectron. 1992, 7, 215–222.
11. Joshi, P.P.; Merchant, S.A.; Wang, Y.; Schmidtke, D.W. Amperometric biosensors based on redox polymer− carbon nanotube− enzyme composites. Anal. Chem. 2005, 77, 3183–3188.
12. Vaddiraju, S.; Tomazos, I.; Burgess, D.J.; Jain, F.C.; Papadimitrakopoulos, F. Emerging synergy between nanotechnology and implantable biosensors: A review. Biosens. Bioelectron. 2010, 25, 1553–1565.
13. Wang, J. Glucose biosensors: 40 years of advances and challenges. Electroanalysis 2001, 13, 983–988.
14. Gorton, L.; Bremle, G.; Csöregi, E.; Jönsson-Pettersson, G.; Persson, B. Amperometric glucose sensors based on immobilized glucose-oxidizing enzymes and chemically modified electrodes. Anal. Chim. Acta 1991, 249, 43–54.
15. Mizutani, F.; Yabuki, S.; Katsura, T. Amperometric enzyme electrode with the use of dehydrogenase and NAD (P) H oxidase. Sens. Actuators B Chem. 1993, 14, 574–575.
16. Skoog, M.; Johansson, G. Internal supply of coenzyme to an amperometric glucose biosensor based on a chemically modified electrode. Biosens. Bioelectron. 1991, 6, 407–412.
17. Laurinavicius, V.; Kurtinaitiene, B.; Liauksminas, V.; Ramanavicius, A.; Meskys, R.; Rudomanskis, R.; Skotheim, T.; Boguslavsky, L. Oxygen insensitive glucose biosensor based on PQQ-dependent glucose dehydrogenase. Anal. Lett.

1999, 32, 299–316.

18. Loew, N.; Scheller, F.W.; Wollenberger, U. Characterization of Self-Assembling of Glucose Dehydrogenase in Mono- and Multilayers on Gold Electrodes. Electroanalysis 2004, 16, 1149–1154.
19. HabermuÈller, K.; Ramanavicius, A.; Laurinavicius, V.; Schuhmann, W. An oxygen-insensitive reagentless glucose biosensor based on osmium-complex modified polypyrrole. Electroanalysis 2000, 12, 1383–1389.
20. Wang, J.; Thomas, D.F.; Chen, A. Nonenzymatic electrochemical glucose sensor based on nanoporous PtPb networks. Anal. Chem. 2008, 80, 997–1004.
21. Zhou, Y.-G.; Yang, S.; Qian, Q.-Y.; Xia, X.-H. Gold nanoparticles integrated in a nanotube array for electrochemical detection of glucose. Electrochem. Commun. 2009, 11, 216–219.
22. Yuan, J.; Wang, K.; Xia, X. Highly ordered platinum-nanotubule arrays for amperometric glucose sensing. Adv. Funct. Mater. 2005, 15, 803–809.
23. Myung, Y.; Jang, D.M.; Cho, Y.J.; Kim, H.S.; Park, J.; Kim, J.-U.; Choi, Y.; Lee, C.J. Nonenzymatic amperometric glucose sensing of platinum, copper sulfide, and tin oxide nanoparticle-carbon nanotube hybrid nanostructures. J. Phys. Chem. C. 2009, 113, 1251–1259.
24. Clarke, S.; Foster, J. A history of blood glucose meters and their role in self-monitoring of diabetes mellitus. Br. J. Biomed. Sci. 2012, 69, 83–93.
25. Olczuk, D.; Priefer, R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. Diabetes Metab. Syndr. 2018, 12, 181–187.
26. Bolla, A.S.; Priefer, R. Blood glucose monitoring-an overview of current and future non-invasive devices. Diabetes Metab. Syndr. 2020, 14, 739–751.
27. Zhang, R.; Liu, S.; Jin, H.; Luo, Y.; Zheng, Z.; Gao, F.; Zheng, Y. Noninvasive Electromagnetic Wave Sensing of Glucose. Sensors 2019, 19, 1151.
28. Boatemaa, M.A.; Doss, S. Non-invasive glucose estimation based on near infrared laser diode spectroscopy. Asian J. Biomed. Pharmaceut. Sci. 2017, 1, 22–28.
29. Pleitez, M.A.; Lieblein, T.; Bauer, A.; Hertzberg, O.; von Lilienfeld-Toal, H.; Mäntele, W. In vivo noninvasive monitoring of glucose concentration in human epidermis by mid-infrared pulsed photoacoustic spectroscopy. Anal. Chem. 2013, 85, 1013–1020.
30. Yeh, Y.-C.; Yang, S.; Zhao, F.; Schmidt, D.J. Noninvasive Glucose Monitoring by Mid-infrared Self-emission Method. In Proceedings of the 7th International Conference on Biomedical Electronics and Devices (BIODEVICES 2014), Eeseo, France, 3–6 March 2014; pp. 107–111.
31. Abd Salam, N.A.B.; bin Mohd Saad, W.H.; Manap, Z.B.; Salehuddin, F. The evolution of non-invasive blood glucose monitoring system for personal application. JTEC 2016, 8, 59–65.
32. Nawaz, A.; Øhlckers, P.; Sælid, S.; Jacobsen, M.; Nadeem Akram, M. Review: Non-invasive continuous blood glucose measurement techniques. J. Bioinform. Diabetes 2016, 1, 1–27.
33. Harman-Boehm, I.; Gal, A.; Raykhman, A.M.; Naidis, E.; Mayzel, Y. Noninvasive glucose monitoring: Increasing accuracy by combination of multi-technology and multi-sensors. JDST 2010, 4, 583–595.
34. Srivastava, A.; Chowdhury, M.K.; Sharma, S.; Sharma, N. Measurement of glucose by using modulating ultrasound with optical technique in normal and diabetic human blood serum. In Proceedings of the 2014 International Conference on Advances in Engineering & Technology Research (ICAETR-2014), Unnao, India, 1–2 August 2014; pp. 1–5.
35. Kit, S.Y.H.; Kassim, N.M. Non-invasive blood glucose measurement using temperature-based approach. J. Teknol. 2013, 64.
36. Cho, O.K.; Kim, Y.O.; Mitsumaki, H.; Kuwa, K. Noninvasive measurement of glucose by metabolic heat conformation method. Clin. Chem. 2004, 50, 1894–1898.
37. Park, J.-H.; Kim, C.-S.; Choi, B.-C.; Ham, K.-Y. The correlation of the complex dielectric constant and blood glucose at low frequency. Biosens. Bioelectron. 2003, 19, 321–324.
38. So, C.-F.; Choi, K.-S.; Wong, T.K.; Chung, J.W. Recent advances in noninvasive glucose monitoring. Med. Devices 2012, 5, 45.
39. Omer, A.E.; Shaker, G.; Safavi-Naeini, S.; Murray, K.; Hughson, R. Glucose Levels Detection Using mm-Wave Radar. IEEE Sens. Lett. 2018, 2, 1–4.
40. Cano-Garcia, H.; Saha, S.; Sotiriou, I.; Kosmas, P.; Gouzouasis, I.; Kallos, E. Millimeter-Wave Sensing of Diabetes-Relevant Glucose Concentration Changes in Pigs. J. Infrared. Millim Terahertz Waves 2018, 39, 761–772.

41. Mohd Bahar, A.A.; Zakaria, Z.; Md Arshad, M.K.; Isa, A.A.M.; Dasril, Y.; Alahnomi, R.A. Real Time Microwave Biochemical Sensor Based on Circular SIW Approach for Aqueous Dielectric Detection. Sci. Rep. 2019, 9, 5467.
42. Cameron, B.D.; Gorde, H.W.; Satheesan, B.; Cote, G.L. The use of polarized laser light through the eye for noninvasive glucose monitoring. Diabetes Technol. Ther. 1999, 1, 135–143.
43. Purvinis, G.; Cameron, B.D.; Altrogge, D.M. Noninvasive polarimetric-based glucose monitoring: An in vivo study. JDST 2011, 5, 380–387.
44. Woods, J.; Smith, J.; Rice, M.; Routt, W.; Messerschmidt, R.; Ou, J. Non-Invasive Measurement of Blood Glucose Using Retinal Imaging. U.S. Patent 20050267343A1, 3 May 2022.
45. Nasution, T.I.; Nainggolan, I.; Hutagalung, S.D.; Ahmad, K.R.; Ahmad, Z.A. The sensing mechanism and detection of low concentration acetone using chitosan-based sensors. Sens. Actuators B Chem. 2013, 177, 522–528.
46. Righettoni, M.; Tricoli, A.; Pratsinis, S.E. Si: WO3 sensors for highly selective detection of acetone for easy diagnosis of diabetes by breath analysis. Anal. Chem. 2010, 82, 3581–3587.
47. Shin, J.; Choi, S.J.; Lee, I.; Youn, D.Y.; Park, C.O.; Lee, J.H.; Tuller, H.L.; Kim, I.D. Thin-wall assembled SnO2 fibers functionalized by catalytic Pt nanoparticles and their superior exhaled-breath-sensing properties for the diagnosis of diabetes. Adv. Funct. Mater. 2013, 23, 2357–2367.
48. Choi, S.-J.; Lee, I.; Jang, B.-H.; Youn, D.-Y.; Ryu, W.-H.; Park, C.O.; Kim, I.-D. Selective diagnosis of diabetes using Pt-functionalized WO3 hemitube networks as a sensing layer of acetone in exhaled breath. Anal. Chem. 2013, 85, 1792–1796.
49. Ryabtsev, S.; Shaposhnick, A.; Lukin, A.; Domashevskaya, E. Application of semiconductor gas sensors for medical diagnostics. Sens. Actuators B Chem. 1999, 59, 26–29.
50. Paldus, B.A.; Kachanov, A.A. An historical overview of cavity-enhanced methods. Can. J. Phys. 2005, 83, 975–999.
51. Ronny Priefer; Rust, M. Breath Acetone Monitor and Method of Detecting Breath Acetone. Utility Patent US9921209B2, 3 May 2022.
52. Zhang, J.; Jiang, X.; Wen, X.; Xu, Q.; Zeng, H.; Zhao, Y.; Liu, M.; Wang, Z.; Hu, X.; Wang, Y. Bio-responsive smart polymers and biomedical applications. JPhys 2019, 2, 032004.