# Optic Based Techniques for Monitoring Diabetics

**Hannaneh Monirinasab and Farzaneh Fathi**

**Abstract**  The development of a well-organized, label-free, and non-invasive diagnosis approach for diabetes is one of the major health concerns. Recently, glucose monitoring as a biomarker for diabetics using optical phenomena in blood or human fluids has attracted more attention. These optic-based sensing approaches include surface plasmon resonance (SPR) and localized SPR (LSPR) based methods and also recently developed photonic crystals (PCs) based structures for biomarker detection. These optic-based detection methods have brought a considerable revolution in the diagnosis of biological molecules due to their ability to detect the very trivial refractive index change near the gold surface. SPR which is an important optic-based sensing method happens when a polarized light hits a prism covered by a gold layer of the sensor surface. In SPR analysis, any minor mass variations and refractive index shifting close the gold layer can be sensed by angle changes of SPR peaks. In the detection of biomolecules, PC-based inverse opal (IO) structures are one of the templates for a label-free sensing system. PCs-based biosensors with their nano and 3 dimensional ordered microporous organizations are reliable, cheap, and robust materials that reveal a reversible change in the structural color and reflection optical spectra by changing glucose concentrations. In this chapter, current manufacturing techniques related to the application of SPR, LSPR, and PC biosensors for the detection of diabetic biomarkers like glucose, insulin, etc. were discussed.

**Keywords** Diabetic biomarker · Optic · Biosensor · Surface plasmon resonance · Photonic crystal

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# 1   Introduction

A biosensor is defined as a transducer that transforms a bimolecular binding event using by capturing on the bio-receptor surface to a readable physical quantity which led to the discovery of biomolecules related targets like small molecules, proteins, DNA, cancer biomarkers, cells, viruses, bacteria, microorganisms, organelles, etc. [1, 2]. The Bioreceptor element covering the surface is a bio-recognition molecule such as antigens, DNA, antibodies, cell, or aptamer that can selectively attach to target molecules in the samples during test. Depending on the transduction mechanism and system for response transduction, biosensors can be involved in the optical, electrochemical, thermal, and piezoelectric or magnetic [3]. In general, biomarkers in biological samples, including blood, serum, urine, saliva, and tears, indicate the initial sign of disease can be detected using developed sensitive and selective biosensors. [4, 5]. Biosensors with a specific platform for non-invasive biomarker capturing and potency of sensor surface modification by nanomaterials result in more selective responses and high sensitivity that make them valuable and label-free diagnostic instruments for clinical analysis [6–8].

Optical based biosensor is completed by using the interaction of the optical field with an analyte as a detection element which can be classified into two general types: label-free and label-based form [9]. When the detected response is produced directly by the interaction of the analyte biomaterial with the transducer, it is a label-free form [10]. But, the label-based sensing method includes using a label and optical signal enhancer like gold nanoparticles fluorescent or luminescent labels [11]. Glucose, the main biomarker in diabetes, was detected using enzymatic and non-enzymatic electrochemical and optical methods [12–16]. For example, using the $CeO2@CuO$ nanostructure, a modified screen-printed electrode was developed for the non-enzymatic detection of glucose [12]. Surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR) as an optically based detection method, with the ability to detect the very trivial refractive index (RI) change in gold sensor surface, have brought a considerable alteration in the diagnosis of biological molecules [17–19]. In LSPR based biosensors, the various shape of LSPR arrays like the triangle or rhombic structures on the substrate of LSPR biosensors led to show larger peak wavelength shift and enhancement of the sensitivity through stimulation of electromagnetic radiation [20, 21]. Moreover, the gold nanostructures used in the LSPR-based technique can exhibit a distinctive ultraviolet–visible (UV) absorption band [22]. Peak wavelength changes are caused by mass absorption and refractive index change on the silver and gold nanoarrays with various shapes or sizes [23]. Also, photonic crystal (PC) based IOs structures are templates for sensitive and non-invasive detection systems [24]. IO-based materials with their 3-dimensional nano-porous organizations have found useful optical sensing uses in detecting biomolecules like glucose [25]. In this chapter, the latest manufacturing methods and the main challenges of applying SPR, LSPR, SPR imaging, and PC biosensors to detect diabetic biomarkers like glucose, insulin, etc. are discussed.

# 2 SPR Method for Detection of Diabetic Biomarkers

## 2.1 Glucose

In SPR analysis, any minor mass variations and refractive index shifting close to the gold sensor surface can be sensed by an SPR curves shift of the modified gold surface (Fig. 1a) [26, 27]. Using SPR based assay, low mass, and contrition of analyte (such as glucose) which is the most challenging factor in clinical sample detection, gold chip surface modification led to developing a sensitive method to improve SPR based sensing system. Measurement of glucose concentration in blood and urine is an important index for diabetes diagnosis, monitoring, and treatment. Surface Plasmon Resonance (SPR) is a new technique for glucose sensing, and it can be different in method or optical fiber type and shape. Tilted fiber Bragg grating
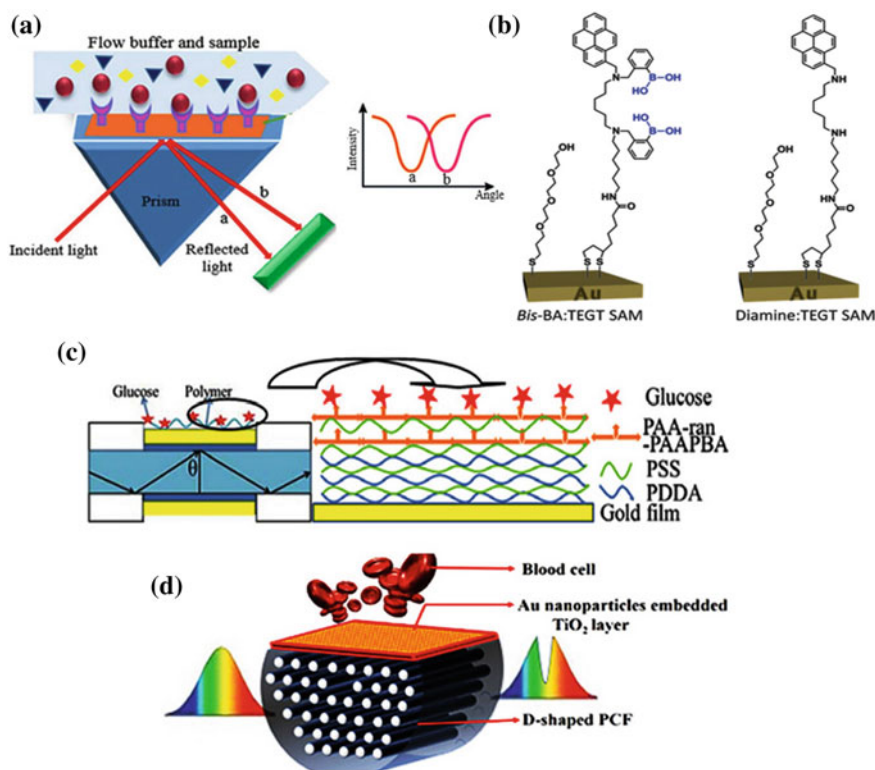


**Fig. 1** **a** Representative image of SPR system. Reprinted with permission from [19]. **b** Tri (ethylene glycol)-terminated thiol (TEGT) self-assembly on the gold chip surface. Reprinted with permission from [33]. **c** schematic diagram of borate polymer immobilization. Reprinted with permission from [32]. **d** Detection of glucose range by developed D-shaped PC fiber. Reprinted with permission from [34]

(TFBG) is a new generation of optical fiber cladding by thin metal such as Ag and is utilized as glucose and $H_2O_2$ sensors [28]. Besides blood and urine, Transdermal extraction of interstitial fluid (ISF) can be minimally invasive blood glucose monitoring, further glucose/galactose-binding (GGB) protein modified SPR chip can sense glucose.[29] Glucose SPR sensors are based on two categories: enzymatic and non-enzymatic. P-mercaptophenylboronic acid (PMBA) modified Au chips is the non-enzymatic model for glucose detection. PMBA-Au chip and Au nanoparticle and 2-aminoethanethiol (AET) can amplify SPR signal and detect low constriction of glucose [30]. Molecularly Imprinted Hydrogels (MIHs) and Molecularly Imprinted Polymerization (MIPs) are other non-enzymatic chip modifications with recognition sites and biomimetic templates for the target analyte, as a result, they can bind analytes selectively in complex physiological fluids like urine. The sensitivity of MIHs and MIPs is lower than protein-based; however, it is enough for urine glucose detection at the physiologically level (1–20 mg/ml). Poly (allylamine hydrochloride) (PAA.HCl) into D-glucose 6-phosphate monobarium salt (GPS-Ba) is MIH chip modifications example used for polar glucose detection, and it can connect glucose non-covalently - hydrogen binding [31]. Boronic acid (BA) is low cytotoxicity and immunogenicity compound which forms cyclic boronate esters with diols (ex: glucose) in basic aqueous media. The sensing surface is fabricated by a self-assembled monolayer (SAM) of bis-BA derivative and tri (ethylene glycol)-terminated thiol (TEGT). TEGT can decrease non-specific protein adsorptions (Fig. 1b). Another form of boronic acid is poly (acrylamide-ran-3-acrylamidophenylboronic acid) (PAA-PAAPBA) polymer used to modify the surface of the Au sensor and carry it out as a glucose sensor (Fig. 1c). These sensors have a superior affinity, sensitivity, and stability [32, 33].

As mentioned previously, there are two categories for designing SPR-base glucose sensors: enzymatic and non-enzymatic. Various methods have investigated glucose detection by enzymatic sensors. The glucose oxidase (GOx) enzyme converts glucose to $H_2O_2$ and gluconic acid. GOx-based assays are well established. The covalent binding of GOx on Au or Ag surface makes it stable and reliable [35]. Zinc oxide (ZnO) is appropriate for attachment of GOx on Au surface in SPR measurements. GOx/ZnO/Au/prism system can detect 0-300 mg/dl glucose. Enzyme-based sensors are expensive and have low stability compared to non- enzyme ones [36]. In SPR biosensor-based photonic crystal fiber (PCF), we can monitor air holes' size and shapes, such as sensing layer thickness and the length of air holes to the pitch of D-shaped PCF. PCF sensors require to load and deliver the analyte samples frequently. To solve this challenge DPCF sensor was designed. DPCF sensor can detect glucose in range of 0–100 g/l with 0.83 nm/ (g/L) sensitivity in presence of hemoglobin (Fig. 1d) [34]. In this method, detection of blood glucose level was conducted by Au nanoparticle-$TiO_2$ surface in hemoglobin presence.

For the direct discovery of glucose molecules, triple mutant bacterial glucose/galactose-binding protein was reported. This modification was accomplished by changing lysine to arginine and adding serine at the glucose-specific coupling site. Then modified GGBP was immobilized on Au surface as glucose-specific binding properties in SPR measurement with a dissociation constant of 0.5 mM [37]. To measure glucose high-resolution circular birefringence (CB) properties, we can use

the Surface plasmon resonance prism coupler sensor. This device enables the sense of CB properties with a resolution of up to $8.9 \times 10 - 7RIU$ for refractive indices in the 1.3–1.4. This SPR prism coupler contains a half-ball glass lens, a gold/chromium (Au-Cr) isotropic soft platform, and a $Ta_2O_5$ anisotropic layer and CB sample. When the concentration of glucose and refractive index change SPR sensor can sense [38]. Kretschmann-based SPR sensor with nano-laminated Au-Cr soft layer for measuring glucose refractive indices is a sensitive and user-friendly method. Refractive index changing of various glucose concentrations is analyzed at 670 and 785 nm optical wavelength. Minimum limit of detection (LOD) of Au-Cr K-SPRis 4 mmol/L. The developed biosensor can be implemented as a sample detector in lab-on-chip and point-of-care devices [39].

## 2.2 Insulin

Insulin is an important hormone that normalizes carbohydrate metabolism, and detecting it in human serum can be useful for medical diagnostics and checking patients with different forms of diabetes. Using SPR biosensor for insulin sensing is possible [40]. For example, Au NPs captured in hydroxyl/thiol-functionalized fourth-generation polyamidoamine (G4-PAMAM) dendrimers can enhance the surface density and insulin immobilization [41]. Type 1 diabetic patients are described by autoimmune aggression against pancreatic beta cells such as Proinsulin Autoantibodies (PAA). PAA is the preclinical marker, and SPR based sensor for serum detection can be designed by two types of PAA antigen: the genuine unmodified proinsulin (PI) and the recombinant chimeric thioredoxinproinsulin (TrxPI) [42]. Also, retinol-binding protein 4 (RBP4) is another diabetes marker that has a key role in obesity-induced insulin resistance and type 2 diabetes. Au surface with a single-stranded DNA (ssDNA) aptamers modification has a high affinity to RBP4 in SPR measurement [43].

## 2.3 Glycated Hemoglobin (HbA1c)

Over a long period in diabetic patients, hemoglobin protein has been glycosylated by glucose. HbA1C is accepted as a good biochemical marker of diabetes diagnostic. As mentioned, Glucose part, 4-vinylphenyl boronic acid (VPBA), and phenylboronate are boronic acid derivatives and are used for HbA1C detection [44, 45]. Aptamers are small, single-stranded DNA or RNA (ssDNA or ssRNA) emerging molecules and can bind to a specific target such as antibodies; thus, they have therapeutic and diagnostic applications as HbA1c, insulin, and Retinol binding protein 4 sensing. The application of aptamers is one of the most common modifications on the SPR Au chip for biomarker detection. In this work, the authors show that the amount of salt and the pH value can significantly affect the affinity between the aptamer and

HbA1c protein [46]. They exhibited that the pH value of 6 is the best condition for detecting HbA1c, with high sensitivity and a low LOD (2.55 nM). In this pH range, the aptamer and glycated hemoglobin have negative and positive charges, respectively, making the promoted interaction by electrostatic attraction and showing the enhanced SPR response compared with the other pH values. Utilized of fused deposition modeling (FDM) 3D printing and the HbA1c aptamers monolayer for developing high-sensitivity and rapid angle-scanning SPR can be interesting and attractive point-of-care device for HbA1c detection in diabetic patients [47]. In diabetic patients, non-enzymatic glycation reactions accelerate between glucose and proteins and form advanced glycation end products (AGEs), which have a key role in diabetic complications. An AGE generated from HbA1c is N-(carboxymethyl)valine (CMV). Thus CMV-Hb assay in nephropathy can be useful for diagnosing diabetes [48].

## 2.4   Glutamic Acid Decarboxylase (GAD)

SPR sensors play a key role in pre-diabetic markers detection. Glutamic acid decarboxylase (GAD) is an enzyme that converses glutamate to GABA. GAD synthesis is increased in the pancreas Beta-cell in high glucose concentration. As a result, GAD autoantibodies (Anti-GAD) presence is the main pre-diabetic marker used in type I diabetes mellitus prediction and diagnosis. SPR sensor for Anti-GAD antibody detection was designed by self-assembled monolayers (SAMs). The type of SAMs indicates different behaviors. 3-mercaptopropionic acid (3-MPA) and 11-mercaptoundecanoic acid (11-MUA) are the most common thiol compound used as SAMs. 3-MPA acts as a spacer between MUA and gold chip also reduces steric hindrance. The evidence ratio of MUA to MPA and the type of terminal group (hydroxyl or carboxyl) in mixed SMAs affect the sensitivity of sensors. Non-specific adsorption in the hydroxyl group is less than carboxyl. Biotin-GDA was immobilized on MUA-Streptavidin modified chip. Biotin–streptavidin can reduce non-specific binding. Heterogeneous lengths are activated better than homogeneous lengths by NHS/EDC also Streptavidin and Biotin-GDA immobilization is more. Based on evidence 10:1 ratio of 3-MPOH to 11-MUA SAM has high sensitivity as an anti-GAD sensor [49, 50].

## 2.5   Acetone Vapor

In diabetic patients, exhaled breath acetone positively correlates with blood glucose and is non-invasive monitoring. However, the concentration of acetone vapor is low and conventional devices for its detection are chromatography-mass spectrometry (GC–MS) and selective ion flow tube mass spectrometry. SPR based sensors can be the superior device for acetone vapor sensing due to its sensitivity and real-time measurement. Chitosan-PEG polymer, p-Toluene sulfonic acid doped polyaniline

(PANI), chitosan, and reduced graphene oxide (RGO) based SPR sensors are soupier materials for acetone vapor sensors [51, 52]. In Chitosan-PEG polymer SPR based biosensor, acetone vapor was detected in the range of 0.5–5 ppm with high sensitivity, selectivity, and linearity.

# 3 SPR Imaging (SPRi)

Surface Plasmon Resonance imaging (SPRi) is another type of label-free optical detection and monitoring of biomolecular events which follows the same principles of SPR. However, it uses images from the CCD camera and different detection methods. Magnetic nanoparticles (MNP) can covalently conjugate to insulin antibody (Abinsulin). Quantum dots to achieve enhanced SPR responses can be a good idea. Activated carboxyl CdSe/ZnS quantum dots (QD800) and insulin aptamers are immobilized on the modified cysteamine-PAMAM dendrimer SPR Au chip. After diluted and mixed Abinsulin-MNP, serum insulin is monitored level of insulin by aptamer-insulin-antibody sandwich microarray (Fig. 2a) [53]. SPRi technique and multiplex chips can measure the combination of hormones. A mixed SAM of thiolated polyethylene glycol (CH3O-PEG-SH) and 16-mercaptohexadecanoic acid (MHDA) are utilized as a biosensor to detect the diabetic biomarker.[54]. Furthermore, by Advanced glycation end products (AGEs) antibody–Protein G-modified gold surface is detected AGEs [55].
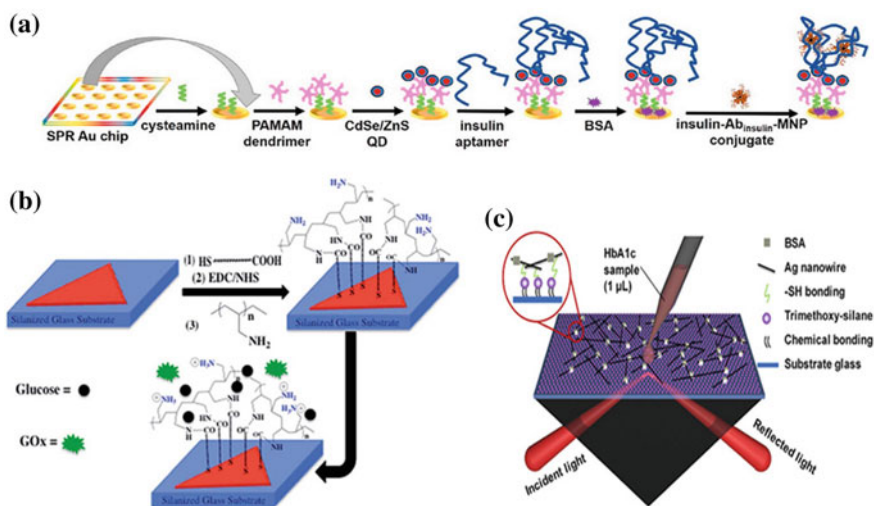


**Fig. 2** Scheme of **a** SPR microarray aptamer-based biosensor for insulin detection. Reprinted with permission from [53], **b** glucose biosensor by polymer-modified gold nano-prisms. Reprinted with permission from [56], **c** plasmonic Ag nanowires for the on-chip detection of HbA1c protein. Reprinted with permission from [60]

# 4  Localized SPR (LSPR)

In LSPR, locally coherent oscillation of electrons at the surface of metallic structures due to creating surface plasmon resonance (SPR) by nanoparticles (NPs) or nanorods (NRs). LSPR sensitivity is higher than bulk SPR and can multi detection array with low sample volume. LSPR doesn't have bulk SPR obstacles such as steric hindrance and nonspecific proteins adsorption. The LSPR behavior is a sensitive function of nanoparticle shape, size, material, and surrounding medium refractive index. LSPR shift occurs by pH reduction; as a result, poly(allylamine) or gold NRs size changing in the presence of glucose oxidase (GOx) and glucose reaction, finally can sensing glucose and $H_2O_2$ (Fig. 2b) [56, 57]. Three-dimensional (3D) glucose-bismuth selenide ($Bi_2Se_3$) nanostructures and Gold nanoparticles (Au NPs)—thermo-active redox reaction of chloroauric acid (HAuCl4) are another method in Glucose sensing by LSPR [58, 59]. As mentioned previously, $HbA_1c$ is the most important factor in diabetes monitoring; silver nanowire-based LSPR chip indicates good potential for detecting $HbA_1c$ level in the blood (Fig. 2c) [60, 61]. For developing a non-enzymatic glucose sensor based on LSPR, Au nanorods on Ni foam surface can be chosen, Au NRs as plasmon catalysts, and Ni foam due to its high conductivity [62].
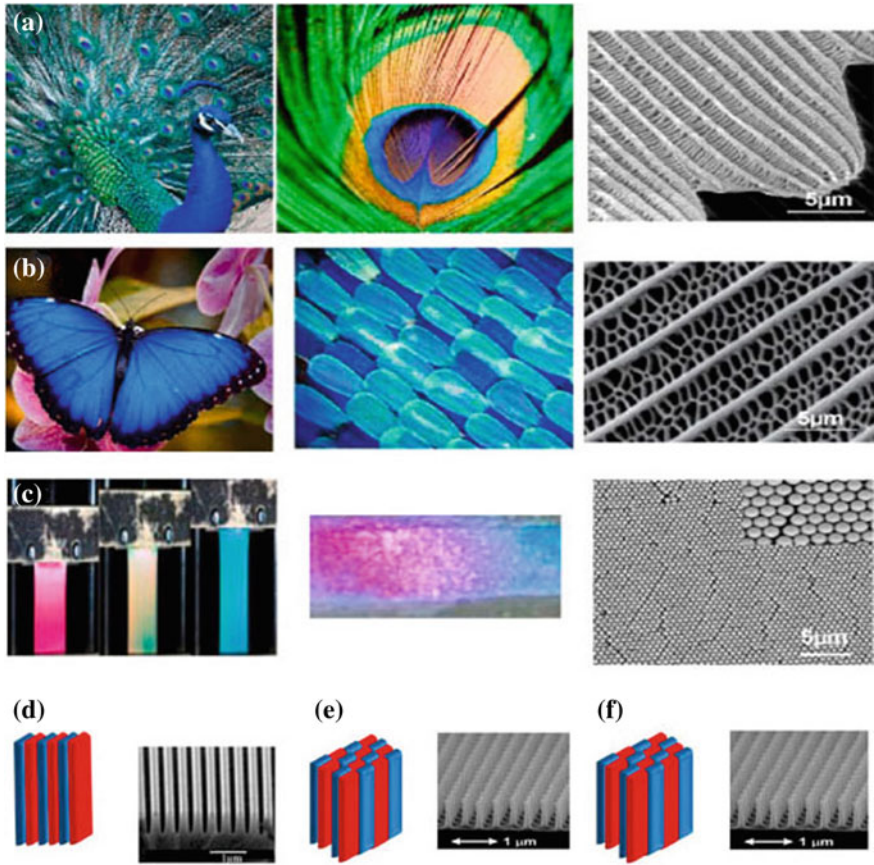
# 5  Photonic Crystals (PCs)

Photonic crystals (PCs) materials with having a spatially periodic dielectric arrangement make the circulation of photons similar to the periodic potential in semiconductors, which leads to the flow of electrons [63, 64]. The similarity of the potential periodicity of the semiconductor materials is like that of dielectric constant periodicity in PCs structures [65]. Recently the use of advanced PCs materials with distinctive optical and physical properties has been found more attention in biomedical applications like biosensors and imaging [66].

## 5.1  Brief Overview of PCs Physics

PCs were first completed in the late 80 s and then recognized in a directed mode arrangement in the 90s [67]. In nature, PCs exist in the wings of butterflies, peacock feathers, and opal gemstones, and a common characteristic between them is their rainbow color [68, 69]. This observed color of them dose not related to any absorption or pigment. Still, it is due to the interaction of light with the periodic or random construction of these natural material designs [69]. PCs are arrangements with a periodic variation of the RI in 1, 2, or 3 dimensions, and their working system is equivalent to that of electrons in crystalline structures (Fig. 3). A photonic bandgap (PBG) in PCs arrays occurs when the light cannot spread within the polarization

**Fig. 3** Natural PCs (photonic crystals): **a** peacock feathers, **b** butterfly wing, **c** PCs opal films. Schematic picture of PCs arrays, **d** 1dimensional, **e** 2dimensional, **f** 3dimensional, with correlated scanning electron microscopy images. Reprinted with permission from [73]

directions of PC martials [70]. Like an electrical band-gap, the PBG is produced by a matrix or a crystal arrangement. A complete PBG is an individual character only observed in PCs where light propagation is banned in all directions [70]. For a more and deeper understanding of the PC structures and their optic behavior, several complete review papers and textbooks are accessible [71, 72].

## *5.2 PCs Biosensors*

Stimulus-responsive hydrogel polymers introduced as filling materials in the 3-dimensional PC arrays could act as an optical detection system for various biological

markers [74]. Changing the hydrogel material volume of PCs structures in reaction to stimuli would be transformed to the reflected wavelength spectra. Phenylboronic acid (PBA) modified hydrogels are well identified as glucose-responsive hydrogels because of having a good affinity to diol-molecules like sugars [75]. The absorption of glucose molecules by attached PBA in the hydrogel matrix structures makes volumetric changes, leading to the hydrogel being the desired agent for glucose monitoring [76]. Using PC hydrogel arrays, the visual detection of glucose was done [76]. In designated biosensors, polystyrene colloidal structures are fixed in a PBA modified hydrogel surface to diffract light for sensitive detection on the hydrogel surface region (Fig. 4a). The volumetric variation of the hydrogel structures during glucose detection led to the Debye diffraction disk length change. This biosensor has the positive points of the fast fabrication of the PCs arrangements and the easy way of Debye ring diffraction display with more selectivity for glucose than other sugar molecules like fructose and galactose [76]. In developing of glucose biosensor based on PC hydrogels, this material displayed major sensitivity for glucose in lab devices, the element arrangement of the PCs altered from 917 to 824 nm (93 nm) within 3 min as the glucose amount improved from 0 to 10 mM, and the physical color of the PC s arrays transformed from red–orange, to green, and lastly, to cyan [77]. With a homebuilt portable optical instrument, this inexpensive smart bio-sensing system can offer a more suitable and well-organized approach for urine glucose discovery in medical analysis and point-of-care sensing. In another work developed by Chen et al., polystyrene microspheres were first self-assembled and this two-dimensional (2D) platform was then covered by a 4-boronobenzaldehyde-modified poly(vinyl alcohol) hydrogel (Fig. 4b) [78]. The developed biosensor was able to label-free and real-time detection of glucose in tears which covers both tears' and blood' physiological ranges. The physical color could move from red through yellow to green in this biosensor with increasing glucose range from 0 to 20 mM [78].

Photonic crystal fibers (PCF) show a very significant character in biosensors due to having flexible, sensitive, and bulky refractive index contrast [82]. The PCF-mediated biosensors recently are acceptably designed and found to propose very high sensitivity in the detection of biomarkers [83, 84]. A triangular lattice structure of PCF-based biosensor for monitoring glucose concentration was developed by Thenmozhi et al. in 2017[80]. By finite element technique, PCF structures are detected glucose with an average sensitivity of 19,135.70 nm/RIU, showing a blue-shift and increasing the RI of filling analyte. In this biosensor, glucose sensitivity material has flowed on PCF structures' central air cavity, which connects to six liquid core sections. With satisfying phase-matching conditions, the liquid-core mode pairs to defect mode wholly and shows loss peak used to sense glucose amounts (Fig. 4c) [80].

Also, by applying the PCF structures and Raman spectroscopy, the development of glucose biosensors was done [85]. Due to the natural minor Raman scattering cross-section of glucose, Raman spectroscopy was not applicable for detecting this molecule. But quantitative glucose Raman detection in the range of 0–25 mM is possible using the very sensitive liquid-filled PCF platform [85]. Using PC structures naked-eye glucose detection and real-time monitoring of diabetes
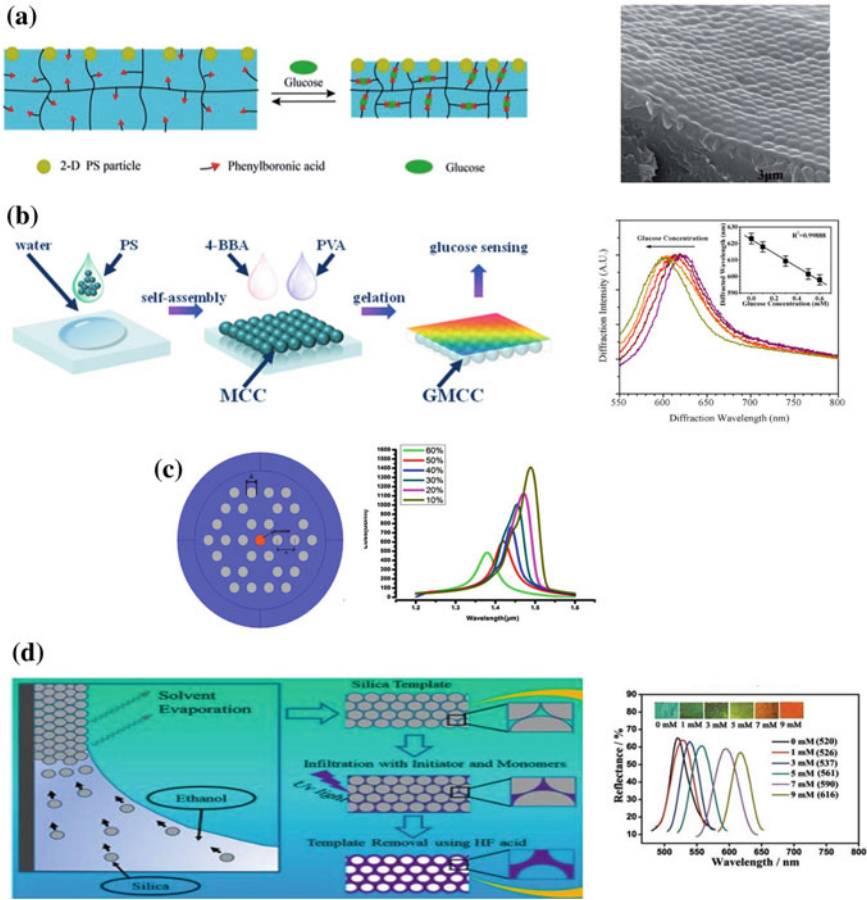
**Fig. 4** Schematic image of the **a** 2-D PC hydrogel response to glucose and related SEM image of PC hydrogel film. Reprinted with permission from [79], **b** PC hydrogel sensor and biosensor response to glucose in the diffraction wavelength. Reprinted with permission from [78], **c** Cross-section of developed glucose PCF biosensor and related optical response of different glucose samples. Reprinted with permission from [80], **d** synthesis process of hydrogel IOs and optical signals of PCs in different glucose solutions. Reprinted with permission from [81]

is possible and displays hopeful use in the sense of diabetes mellitus. A vertical convective self-assembly technique prepared pCs arrays for this purpose with a novel kind of polymer microsphere including methyl methacrylate (MMA), N-isopropylacrylamide (NIPA), and 3-acrylamidophenylboronic acid (AAPBA) [86]. Developed opal closest-packing PCs structures with high solidity, periodically-ordered arrangements, and desired physical color exhibitions a redshift near 75 nm in wavelength and decreased reflection intensity during glucose molecules detection [86].

Also naked-eye glucose detection with a range of 3–20 m M is observable by changing the color PCs arrays from brilliant blue to bright green. For non-invasive detection of glucose, a PCs-based biosensor was developed by embedding colloidal microspheres within a polymer system of a polyacrylamide-poly(ethylene glycol) hydrogel with drooping phenylboronic acid molecules [24]. Phenylboronic acid was used as the molecular recognition factor to detect physiologic pH ranges. The improved PCs biosensor detected glucose in tear fluid with LOD of 1 µmol/L which was visible by shifting evident diffraction color in the visible spectral region from red to blue [24]. Inverse opal photonic crystal (IOPC) hydrogels commonly denote the polymer surface with the regular holes prepared using colloidal polymer microspheres as a template and to remove filling materials to prepare IOs nanostructures [25, 87]. IOs based biosensors can exhibit colorful signals with varying outer motivation, like pressure, humidity, pH, or thermal [88–91]. Recently, the IOPCs structures have been applied as a colorimetric biosensor for molecular recognition [92]. For example, IOs based films made from chitosan carbohydrate biopolymer could reversibly transfer their physical colors and absorbance peaks in reply to alcohols and phenols, which predicted the possible way to visually detect organic solvents [93, 94]. Glucose detection based on the IOs materials was done by Feng et al. (Fig. 4d) [89]. Using the natural structural color of IOs arrays, the developed hydrogel biosensor could be applied to detect carbohydrates with 1,2-cis-diol function and monitor diabetes without the need of complicated test tools [89]. An IO polymer membrane prepared from thermosensitive monomer and glucose-sensitive monomer was used for the colorimetric checking of glucose [95].

This system displays natural color based on Bragg diffraction rising from the 3-D organized arrays with periodicity in the visible light wavelength. The size of the hydrogel elements reversibly alters as the glucose amount differs in the divided holes of the IOs polymer layer surface [95].

PCs-based biosensors are reliable, cheap, and robust materials that expose a reversible alteration in the structural color and the intensity of the optical reflection peak with the variation in the glucose ranges. Using the colorimetric glucose-biosensing system, PC-based systems can detect the strong value of glucose amount around the threshold range for detecting diabetes mellitus. In Table 1, some examples of optical-based methods for detecting diabetic biomarkers were presented.

# 6   Conclusion

The development of optic-based sensing approaches includes SPR and LSPR based methods, and also photonic crystal-based structures have an important role in diabetics biomarker detection. These optic-based detection methods have brought a considerable revolution in diagnosing biological molecules due to their potency to detect the very trivial refractive index change on the gold surface. LSPR based biosensors for diabetic biomarker detection due to having different gold or silver nanoparticle structures produce sharp resonance absorbance bands in the visible

**Table 1** Some examples of optical-based biosensors for the detection of diabetic biomarkers

| Bio-sensing method | Detected biomarker | Immobilized molecules | Analytical performance parameters | Advantages | Ref |
|---|---|---|---|---|---|
| SPR | Glucose | p-mercaptophenylboronic acid and 2-aminoethanethiol | LOD = 80 nM | Amplified SPR response | [30] |
| SPR | Glucose | D-glucose 6-phosphate monobarium salt into allylamine hydrochloride | LOD = 0.12 mg/ml | Amplified SPR response | [31] |
| SPR | Glucose | Tri(ethylene glycol)-terminated thiol and bronic acid | LOD = 0.02 mg/ml | Low cytotoxicity and low immunogenicity | [33] |
| SPR | Glucose | GOx/ZnO/Au | LOD = 20 mM | High specificity good linearity beyond the physiological range | [36] |
| SPR | Glucose | Bacterial glucose/galactose-binding protein | LOD = 10 mM | Continuous glucose monitoring devices and direct glucose detection | [37] |
| SPR | Glucose $H_2O_2$ | Tilted fiber Bragg grating coated by silver /immobilized GOX | LOD $H_2O_2$ = 0.2 μm Linear range = 0–14 mM | High sensitivity miniaturized size remote operation | [28] |
| SPR | Glucose | Cr-Au and $Ta_2O_5$ layer | LOD = 3.72 mg/dl | Significant potential for non-invasive glucose sensing | [38] |
| SPR | Proinsulin autoantibodies | The genuine unmodified proinsulin recombinant chimeric thioredoxinproinsulin | childhood-onset diabetic patients = $67.12 \times 10^{-9}$ M Adults = $167.4 \times 10^{-9}$ M | Clinical use of SPR | [42] |

(continued)

**Table 1** (continued)

| Bio-sensing method | Detected biomarker | Immobilized molecules | Analytical performance parameters | Advantages | Ref |
|---|---|---|---|---|---|
| SPR | HbA$_1$C | 4-vinylphenyl boronic acid | LOD = 2.86 µg/ml | Sensitive boronic-based technique for targeting the sugars | [44] |
| SPR | Insulin | Bifunctional hydroxyl/thiol-functionalized polyamidoamine dendrimer encapsulated Au nanoparticle | LOD = 0.5 pM, linearity range = $5.25 \times 10^{-6}$ µM | High stability enhanced sensitivity significantly | [41] |
| SPR | HbA$_1$C | Aptamer | LOD = 2.55 nM | Sensitive technique accuracy and correctness of HbA1c measurement | [46] |
| SPR | HbA$_1$C | Phenylboronate monolayer | Linear range = 0.43–3.49 µg/ml | Quantification of HbA1c | [45] |
| SPR | HbA$_1$C | Aptamer | LOD = 1 nM Linear rang = 18–147 nM | Cheap, rapid-prototyping, high-sensitivity | [47] |
| SPR | Carboxymethyl valine - hemoglobin | Related monoclonal antibody | Linear rang = 10–40 pmol | Good marker in patients with diabetic nephropathy | [48] |
| SPR | Monoclonal anti-glutamic acid decarboxylase | 3-mercaptopropionic acid 11-mercaptoundecanoic acid | Linear range = 10–1000 nM | High sensitivity | [49] |

(continued)

**Table 1** (continued)

| Bio-sensing method | Detected biomarker | Immobilized molecules | Analytical performance parameters | Advantages | Ref |
|---|---|---|---|---|---|
| SPR | Retinol binding protein 4 | A single-stranded DNA aptamer | LOD = 75 nM(1.58 ug/ml) | The high efficiency sensitivity compared to conventional antibody-based methods | [43] |
| SPR | Aceton vapor | Chitosan–polyethylene glycol | LOD = 0.96 ppb | Non-invasively monitor and screen for diabetes | [52] |
| SPR | Aceton vapor | p-Toluene sulfonic acid doped polyaniline, chitosan, and reduced graphene oxide | LOD = 0.88 ppb | Non-invasive monitoring | [51] |
| LSPR | Glucose | Thermo-active redox reaction of chlorauric acid and glucose | Linear rang = 2–250 $\mu$mol/l | Sensitive, effective, reliable, simple, and convenient | [58] |
| LSPR | Glucose | Bismuth selenide nanostructures | LOD = 6.1uM Linear range = 10–100 $\mu$M | Highly stable ultrasensitive non-enzymatic glucose sensor | [59] |
| LSPR | $HbA_1C$ | Silver nanowire-based chip | LOD = 3SB/m | Highly sensitive | [60] |
| LSPR | glucose | Au nanoparticles | Linear range = 5–20 mg/dl | Low-cost and real-time detection | [61] |
| Quantum dot-coupled-SPR | Insulin | Insulin Aptamer on PAMAM dendimer | LOD = 800 fm Linear dynamic range = 0.8–250 pM | High-throughput screening in clinical diagnostics- good sensitivity, specificity and reproducibility | [53] |

(continued)

**Table 1** (continued)

| Bio-sensing method | Detected biomarker | Immobilized molecules | Analytical performance parameters | Advantages | Ref |
|---|---|---|---|---|---|
| SPRi | Insulin, glucagon, and somatostatin | (CH3O-PEG-SH)/MHDA | LOD = 1 nM for insulin, 4 nM for glucagon, and 246 nM for somatostatin | Multiplex measurement | [54] |
| LSPR | Glucose | pH-responsive nanoplasmonic polymer poly(allylamine) | LOD = 25 μM | The simplicity of operation and excellent reproducibility ultrasensitive cost-effective detection | [56] |
| SPR | Glucose | GOX entrapped in gel on Silver and silicon film | Linear range = 0–260 mg/dl | High sensitivity and selectivity, stability, and short response time of the sensor | [96] |
| LSPR | Glucose | U-shaped fiber optic/ Au NPs/GOX | Linear range = 0–250 mg/dl | Enhanced sensitivity and its use as a point Sensor with very small amounts of blood for sensing | [97] |
| LSPR | Glucose | Au nanorods- modifed Ni foam | LOD = 14 μM | Sensitivity Non-enzymatic | [62] |

(continued)

**Table 1** (continued)

| Bio-sensing method | Detected biomarker | Immobilized molecules | Analytical performance parameters | Advantages | Ref |
|---|---|---|---|---|---|
| SPR based PCF | Glucose in presence of Hb | Au NP-TiO$_2$ | Linear range = 0–100 g/l | first DPCF glucose sensor to detect blood glucose with hemoglobin | [34] |
| LSPR | Glucose | Gold nanorods | Linear range = 0.1–1 mM | Simple colorimetric assay | [57] |
| SPRi | Advanced glycation end products | Cysteine-tagged, protein-G | LOD = 10 ng/ml | High sensitivity, label free detection, rapid response | [55] |
| PC | Glucose | – | LOD = 3–20 mM, | Naked-eye glucose detection | [86] |
| Hydrogel PC | Glucose | – | LOD = 150 mM | Visual glucose sensing | [76] |
| PCF | Glucose | – | LOD = 0–25 mM | High sensitivity, flexibility, reproducibility, low cost, small sampling volume | [85] |

*SPR* surface plasmon resonance; *LSPR* localized surface plasmon resonance; *PCF* photonic crystal fiber; *SPRi* surface plasmon resonance imaging; *PC* photonic crystal; *LOD* limit of detection; *GOx* Glucose oxidase; *HbA$_1$C* Glycated hemoglobin; *PAMAM* polyamidoamine; *CH$_3$O-PEG-SH* polyethylene glycol; *16-MHDA* mercaptohexadecanoic acid; *NPs* nanoparticles; *DPCF* D-shaped photonic crystal fiber.

light wavelength ranges, which is highly sensitive to the local refractive index near the surface of nanoarrays. In comparing SPR and LSPR based detection methods, SPR biosensors have a much higher refractive index sensitivity. Still, the sensitivity towards biomolecular binding interactions in LSPR sensor surfaces is more than that of SPR biosensors. This advantage of the LSPR biosensor makes it a valuable analytical approach for small biomarker discovery. Also, PC-based arrays, their nano and microporous 3D organizations, which are one of the templates for label-free sensing systems, have found attractive optical biosensor applications in detecting biomolecules like glucose. Introducing the biomarker detection based on PC arrays due to having large surface area and periodically ordered structures and specific reflective peaks makes them an effective platform for diabetic biomarker detection that can be applied to the clinical analysis. We believe that optical-based methods would have a hopeful future in biomedicine and clinical applications. However, main challenges are needed to develop large-scale and well-organized optical materials moving from laboratory toward industrial section.

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