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Wearable Glucose Monitoring and Implantable Drug Delivery Systems for Diabetes Management

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The global cost of diabetes care exceeds $1 trillion each year with more than $327 billion being spent in the United States alone. Despite some of the advances in diabetes care including continuous glucose monitoring systems and insulin pumps, the technology associated with managing diabetes has largely remained unchanged over the past several decades. With the rise of wearable electronics and novel functional materials, the field is well-poised for the next generation of closed-loop diabetes care. Wearable glucose sensors implanted within diverse platforms including skin or on-tooth tattoos, skin-mounted patches, eyeglasses, contact lenses, fabrics, mouthguards, and pacifiers have enabled noninvasive, unobtrusive, and real-time analysis of glucose excursions in ambulatory care settings. These wearable glucose sensors can be integrated with implantable drug delivery systems, including an insulin pump, glucose responsive insulin release implant, and islets transplantation, to form self-regulating closed-loop systems. This review article encompasses the emerging trends and latest innovations of wearable glucose monitoring and implantable insulin delivery technologies for diabetes management with a focus on their advanced materials and construction. Perspectives on the current unmet challenges of these strategies are also discussed to motivate future technological development toward improved patient care in diabetes management.

1. Introduction

Diabetes is an incurable chronic disease resulting from a deficiency in the production (Type I) or the resistance of insulin (Type II), which has become a leading cause of human deaths worldwide, accounting for ≈11.3% according to the International Diabetes Federation.[1] It is estimated that the number of diabetic adults will rapidly increase worldwide by 54%, from 285 million in 2010 to 439 million in 2030, due to multiple factors such as obesity, aging, ethnicity, lifestyle, socioeconomic status, education, and urbanization.[2–8] The quality of life for people with diabetes is significantly affected by chronic hyperglycemia and glucose toxicity, which may also lead to serious microvascular and macrovascular complications such as cardiovascular disease, blindness, neuropathy, and nephropathy.[9] Currently, the most effective defense against the progression of diabetes is to develop a personalized management plan via frequent monitoring and evaluation of glucose levels throughout the day (i.e., at least four times a day and twice a day for type I and type II diabetes, respectively). This enables diabetic patients to adjust appropriate mealtime insulin dosing, thereby reducing the risk of complications.[10]

Figure 1 presents the historical development of glucose monitoring and insulin delivery technologies over the past decades. Since the first launch in 1974, point-of-care blood tests using a portable finger-pricking kit (typically using an enzyme-based glucometer and disposable strips) have been most widely used for self-monitoring of blood glucose levels despite their limitation related to multiple intervals, time constraints, pain, and inconvenience.[11–13] Since the late 1990s, implantable continuous glucose monitoring (CGM) devices have been used in clinics to quantify blood glucose, allowing for retrospective analysis and hypo/hyperglycemia detection and prediction.[14,15] However, these approaches are invasive and also require periodic recalibration to adjust sensor drift, via finger-pricking blood testing. Maintaining the measurement accuracy of the implanted devices remains challenging because they are largely affected by time-dependent biofouling growth.[16,17] Therefore, there is an increasing demand for a new device enabling more reliable, less invasive, and continuous monitoring of glucose levels in diabetics.

Wearable (i.e., on-body) glucose sensors are under development through the innovation of mechanically deformable and electrochemically active materials.[18–21] These sensors are capable of unobtrusively interfacing with various human body parts, allowing for long-term in situ assessment of glucose concentrations from body fluids including tear, saliva, interstitial fluid

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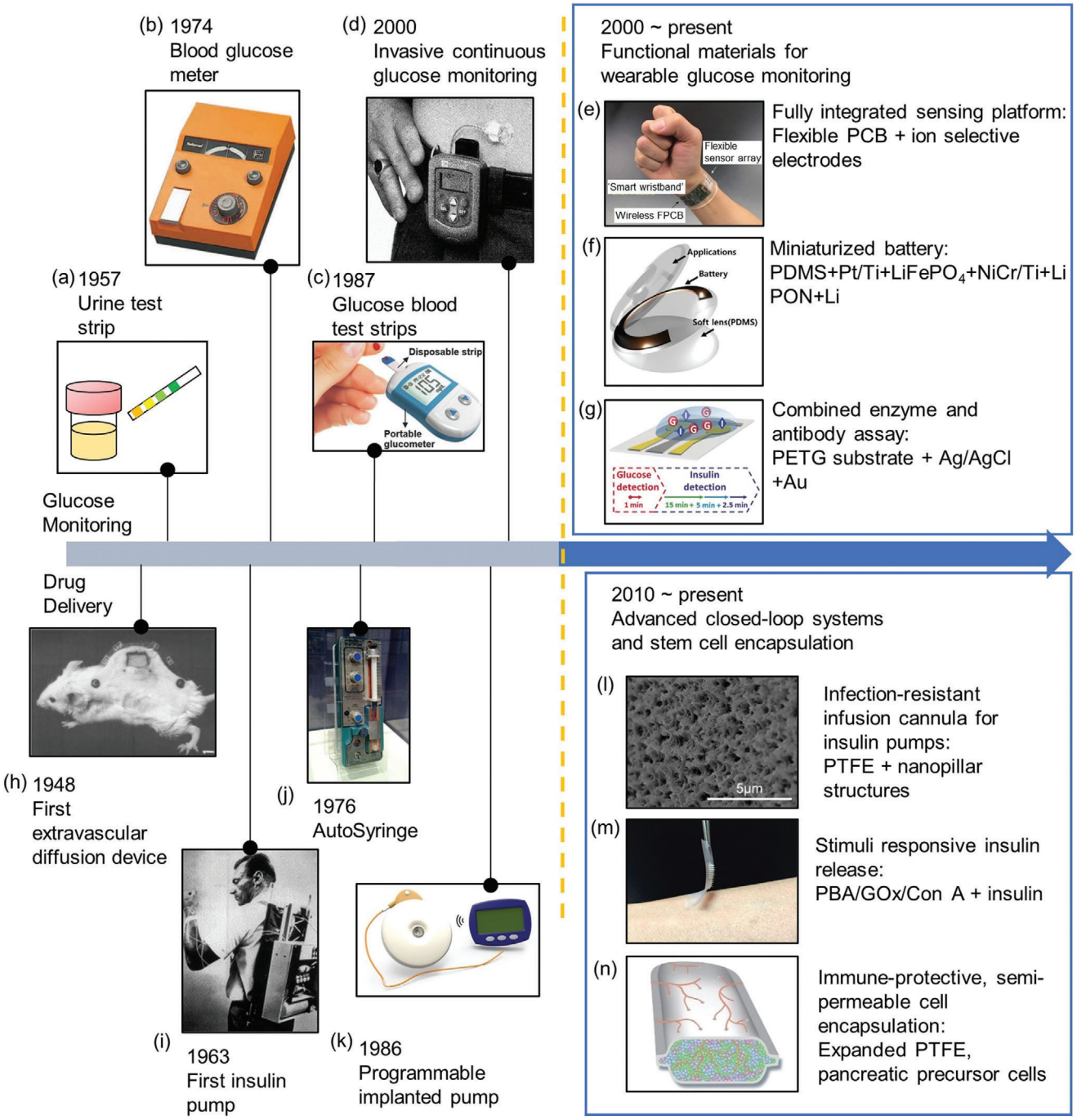

Figure 1. Representative conventional and recent advanced technologies for glucose diagnosis and therapy. a) Urine test for glucose level using test strip.b) Blood glucose meter. Reproduced with permission.[211] Copyright 2012, Taylor & Francis. c) Blood glucose test with test strips. Reproduced with permission.[22] Copyright 2018, John Wiley and Sons. d) Subcutaneous continuous glucose sensor. Reproduced with permission.[212] Copyright 2000, Mary Ann Liebert. e) Fully integrated flexible glucose sensor. Reproduced with permission.[18] Copyright 2016, Springer Nature. f) Smart contact lens for glucose sensing Reproduced with permission.[213] Copyright 2018, Elsevier. g) Tattoo-based wearable glucose sensor. Reproduced with permission.[214] Copyright 2019, John Wiley and Sons. h) The first extravascular diffusion device. Adapted with permission.[215] Copyright 1949, Oxford Academic. i) The first insulin pump designed by Arnold Kadish. Reproduced with permission.[216] Copyright 2010, John Wiley & Sons. k) A programmable implantable insulin pump. l) SEM image of the surface of the oxygen plasma etched PTFE.[152] Copyright 2020, American Chemical Society. m) Glucose responsive insulin releasing microneedles patch. Adapted with permission.[217] Copyright 2015, National Academy of Sciences. n) Stem cells differentiated into islet cells delivered in a device platform (PEC-QT, ViaCyte, Inc., San Diego, CA, USA). Reproduced with permission (source: viacyte.com).

Table 1. The active materials, basic configurations, and working principles of latest wearable glucose sensors according to their target body fluids.

Target biofluid	Platform	Method	Active material	Ref.
ISF	Tattoo	Electrochemical, reverse iontophoresis	GO_X, PB, PI, Au, PMMA	[85]
	Skin-mounted device	Electrochemical, reverse iontophoresis	Hydrogel, Pt nanoparticle–graphene hybrid	[89]
		Electrochemical, microneedle	GO_X, PP	[90]
		Optical, microfluidics	GO_X	[49]
Sweat	Skin-mounted device	Electrochemical microfluidics, biofuel cell	Nafion, chitosan, GO_X	[100]
		Electrochemical, microneedle	GO_X, graphene, Au	[203]
	Fabrics	Electrochemical	rGO-PU, Au	[101]
Saliva	Mouthguard	Electrochemical	GOD PMEHB	[105]
	On-tooth device	RLC resonance	Silk film, PNIPAM hydrogel	[54]
	Pacifier	Electrochemical	GO_X, PB, Chitosan	[108]
Tear	Eyeglasses	Electrochemical, microfluidics	GO_X, PB	[63]
	Contact lens	Optical, microfluidics, RLC resonance, wireless power transfer	GOD/POD, Graphene/Ag NW, AgNF	[53,55,111]

(ISF), and sweat. These body fluids contain various levels of glucose concentrations (e.g., 0.05–5 × 10^{-3} M in tear; 0.008–1.77 × 10^{-3} M in saliva; 1.99–22.2 × 10^{-3} M in ISF; 0.01–1.11 × 10^{-3} M in sweat).[22] However, the correlation of these measurements against blood glucose concentrations (e.g., 2–40 × 10^{-3} M in the blood) can vary widely between people, which poses a roadblock for wide clinical utility.[22] These sensors are compatible with the integration of miniaturized wireless powering and data communication units enabling real-time data analysis and reporting to caregivers through an encrypted server. Ideally, these sensors could be also coupled to an implantable insulin delivery system for timely dosing by autonomous insulin release in response to sensing feedback. This system would compensate for the pharmacokinetic delay by conventional insulin infusion, thereby prolonging the duration of euglycemia within a targeted glucose range (typically 3.9–10 mmol•L^{-1}) and reducing the incidence of hypoglycemia.[23–25] Currently available candidates for these implantable insulin delivery systems include 1) insulin pumps that can adjust insulin dosage based on glucose readings received from glucose sensors (computational closed-loop), 2) glucose-responsive materials that can release insulin upon elevated glucose levels (responsive closed-loop), and 3) transplanted islets that can secrete insulin via metabolic exchange (biological closed-loop).[26] While the potential benefit of this closed-loop system for diabetes is enormous, many challenges regarding its biosafety, therapeutic efficacy, and patient compliance remain.

Herein, we review the latest technologies of wearable glucose sensors and implantable insulin delivery systems for diabetes management. In each section, we discuss the active materials, basic configurations, and working principles of these devices according to their target body fluids, as summarized in **Table 1**. In the conclusion, we also discuss the unmet clinical challenges and future opportunities to motivate further technological development toward improved patient care in diabetes management.

2. Wearable Glucose Sensors

Wearable glucose sensors that enable the minimal-to-noninvasive continuous monitoring of glucose concentration from non-blood biofluids have emerged as a next-generation solution for diabetes management. **Figure 2** presents a schematic diagram to illustrate the basic platforms and sensing mechanisms of current wearable glucose sensors tailored for the assessment of body fluids including tear, saliva, ISF, and sweat. Abundant combinations of these components have provided multiple paths for the extraction, collection, and analysis of these body fluids in a continuous manner. In this section, we introduce the latest enabling technologies for wearable glucose monitoring devices.

2.1. Enabling Technologies for Wearable Glucose Sensors

2.1.1. Glucose Sensing Mechanisms

Various glucose-sensing mechanisms have been developed relying on electrochemical, optical, and electromagnetic principles. The electrochemical sensing mechanism involves either enzymatic or non-enzymatic reactions, which has been most widely used due to its simple construction and quantitative output.[22,27] For the enzymatic glucose sensing, enzyme (i.e., glucose oxidase, GO_x) oxidizes glucose to yield gluconic acid and hydrogen peroxide via the following equation:[22]

$$Glucose + H_2O + O_2 \xrightarrow{GO_x} Gluconic\ acid + H_2O_2 \quad (1)$$

In this GO_x enzyme-based glucose sensing, the redox reaction of glucose in the presence of a catalyst can generate a steady change in electrical current at a fixed potential (a.k.a. amperometric sensing).[28,29] To further improve the performance of amperometric sensing, recent studies have focused on increasing the surface area of recording electrodes,[30,31] stabilizing the immobilized enzyme layer on electrodes,[32,33] and selecting the appropriate electrocatalytic mediator.[34,35] Nonetheless, challenges remain in maintaining the enzymatic activities against environmental conditions (e.g., pH, humidity, and chemicals).[36] Alternatively, non-enzymatic glucose sensing has been utilized to eliminate the need for catalysts or molecular recognition

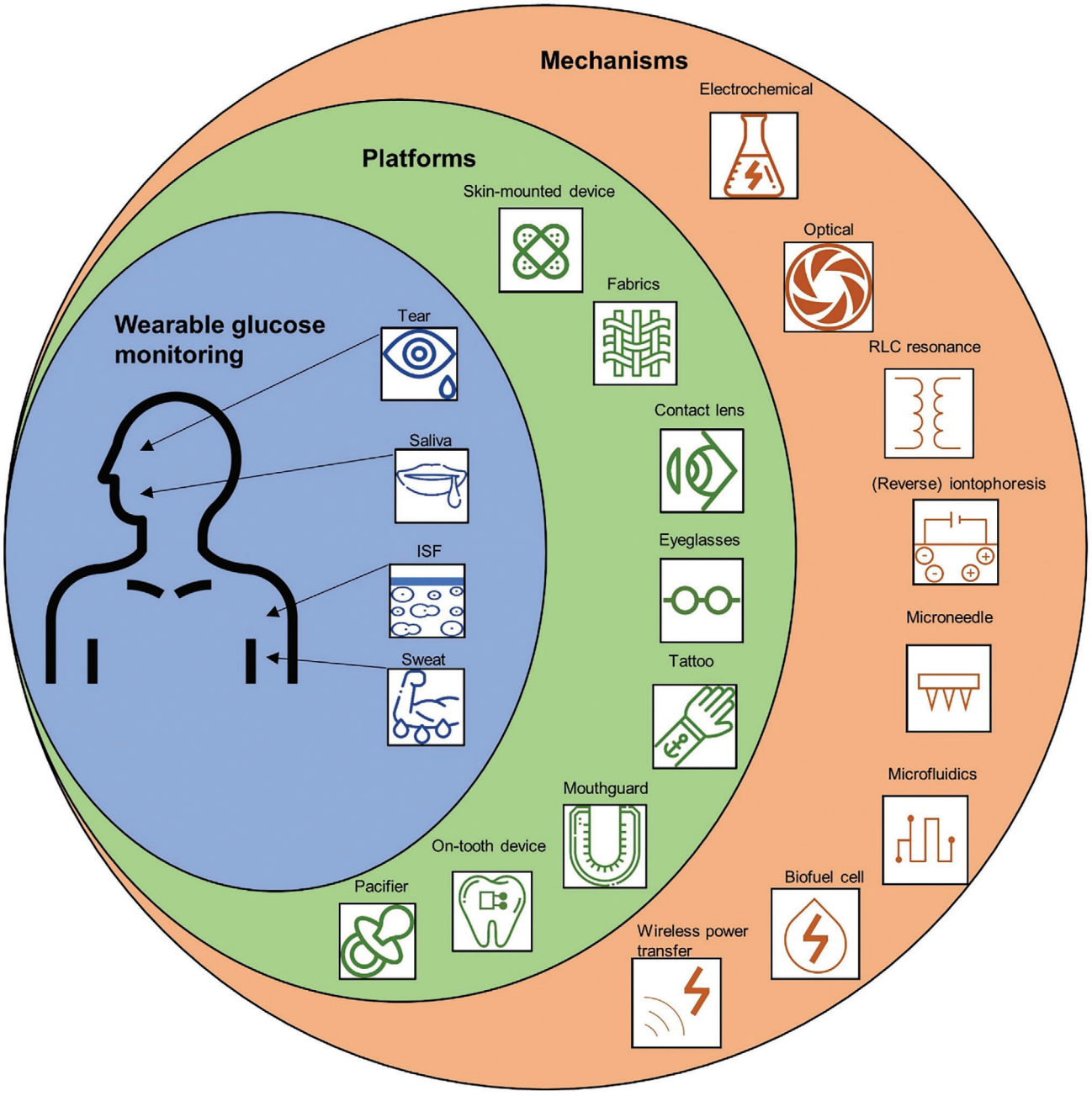

Figure 2. Schematic diagram for the basic platforms and sensing mechanisms of wearable glucose sensors for the assessment of body fluids including tear, saliva, ISF, and sweat.

elements.[37–40] This sensing mechanism relies on the binding of glucose molecules to non-enzymatic electrodes (based on metal, metal oxide, or carbon nanomaterials) that can change their electrochemical environment to catalyze the oxidation of glucose molecules.[38,39] Nanostructured non-enzymatic electrodes have been developed to provide a substantially large surface area for further increased sensitivity up to 97.9 mA mM^{-1} cm^{-2}.[40–42] Nevertheless, the selectivity of this sensing mechanism remains limited due to the interference from erroneous sources such as uric acid, ascorbic acid, dopamine, β-Nicotinamide adenine dinucleotide, Mg^{2+}, Ca^{2+}, L-cysteine, NaCl, lactose, sucrose, maltose, and mannose.[43,44] Moreover, the difficulty of catalyzing the oxidation of glucose against the daily variation of body temperature has impeded the application of this sensing mechanism in practice.[45]

Optical glucose sensing occurs through the combined use of a light source, a photodetector, and an optical transducer that converts the detected changes in light intensity in response to glucose concentration into a measurable electrical signal.[46] Conventional optical glucose sensors typically rely on the implementation of either Raman spectroscopy, optical coherence tomography, or infrared spectroscopy, which are bulky

and expensive instrumentation.[45] Recent technological developments have enabled the advent of wearable optical glucose sensors using either colorimetric or fluorescent assays that allow for the quantifiable evaluation of glucose concentration.[47–49] The colorimetric and fluorescent assays are designed to analyze the optical wavelength of excitation light using a digital image and a fluorescent microscope, respectively.[47,50] The colorimetric glucose sensors are extremely cost-effective (i.e., disposable), but they are typically limited to a single time point measurement due to irreversible color change. The quantitative analysis of glucose concentration is only available through the combined use of a digital imaging technique to eliminate the effect of brightness and color temperature from various light sources.[50]

A series resistance-inductance-capacitance (RLC) resonance circuit has been also used for glucose sensing in which the impedance spectrum of this circuit is correlated to glucose concentration.[51,52] Specifically, the fluctuation of glucose concentration changes the electrical property (i.e., dielectric constant) of the blood, leading to a detectable shift in the resonance frequency of this circuit that can be wirelessly captured by a receiver antenna.[53] The impedance of this circuit can also be coupled with the transducer, enabling near-field wireless powering.[54] This circuit has been widely applied to glucose sensing at the corneal surface (i.e., tear) and in the intraoral space (i.e., saliva) due to its capability for both wireless powering and data communications.[55,56] However, the sensing results are easily affected by the temperature and posture of the wearer and the amount of tear and saliva.

2.1.2. Sampling Methods for Body Fluids

A timely sampling of body fluids is crucial to enabling accurate glucose monitoring for tight glycemic control.[57,58] Recently, several effective methods for the minimal-to-noninvasive extraction of body fluids have been enabled through the development of advanced wearable systems.[59–61] Tears are continuously renewed by the lachrymal gland with a range of 0.6 to 1.1 μL min^{-1}.[62] The daily dynamics of tear glucose concentration paralleled the glucose concentration indicate a significant association between the glucose concentration in tear and blood ($P < 0.001$).[63] The natural secretion of tears and blinking provide a fresh sample of tears for glucose analysis throughout the day. Also, the interference from impurities in tears is relatively small, in comparison to other types of body fluids, such as sweat. Tears can be directly captured at the corneal surface for CGM by using a contact lens- or eyeglasses-type sensor.[64,65]

Sweat is one of the easily accessible body fluids because the sweat glands are widely distributed across the entire body with a high density of more than 100 glands cm^{-2}. A strong correlation between sweat and blood glucose concentration was suggested with a high correlation coefficient of 0.75.[66] Sweat is extracted through microscale pores on the epidermal layer which can be easily captured and collected in a non-invasive manner. However, the extraction of sweat is tedious due to the low secretion volume and fast evaporation of sweat and typically requires exercise or sauna bathing that may be prohibitive for diabetic patients with mobility difficulties.[67] Moreover, the increased body temperature following exercise or sauna bathing can affect blood glucose levels, which may result in inaccurate measurement results.[68] To overcome these challenges, transdermal extraction of glucose by exploiting iontophoresis has been used by applying an electrical current to migrate pilocarpine across the skin, which induces localized high sweat rate (354 nL min^{-1}•cm^{-2}).[69] This iontophoretic sampling method enables the on-demand induction of sweat in an electronically controlled fashion, but several side effects including tingling sensation, blistering, and skin irritation remain to be addressed.[70,71] The most recent approaches have been focused on controllably guiding and collecting sweat into a reservoir via microfluidic channels in a manner that minimizes the evaporation and contamination of sweat.[50,72–74] These microfluidic channels are embedded within a thin, lightweight, and stretchable patch that is capable of intimately interfacing with the skin, allowing for the high-fidelity collection of sweat in ambulatory care settings. The direct collection of sweat on the skin through the microfluidic channels can minimize the risk of sample contamination, which may cause by 1) the mixture of newly collected and old sweat, 2) other contaminants such as oil and residual dirt on the skin, and 3) other chemicals on the surrounding skin or from the environment.[75]

Glucose concentration in ISF also provides a high degree of linear correlation with blood glucose concentration ($R^2 > 0.90$).[76] ISF can be extracted through the skin by using a vertically ordered array of microneedle with sharp tips that can pierce the stratum corneum of the skin with minimal tissue damages during the injection.[77,78] The length of these microneedles is typically limited to 1 mm to avoid the risk of invading blood vessels or nerve endings.[79] Nonetheless, the sampling method using microneedles is invasive and may pose a risk of bacterial infection, which often requires the in situ analysis of ISF with a wearable (i.e., on-skin) glucose sensor to reduce the sampling time.[59,80] Similar to the iontophoretic extraction of sweat, glucose can be also electrically induced from ISF to the outermost surface of the skin via reverse iontophoresis by applying a potential difference across two electrodes.[81,82] During the sampling process, the reverse iontophoretic current can induce the electroosmotic flow of body ions (e.g., Na^+), leading to the extraction of neutral molecules (e.g., glucose) to the cathode where the human skin is negatively charged at physiological pH.[83]

Saliva is also considered an attractive body fluid for glucose monitoring due to the easy access to saliva samples and good correlation between saliva glucose and blood glucose levels.[84] A statistically significant correlation was found between saliva glucose and blood glucose.[85] The saliva glucose concentration is ≈1/100 of the blood glucose concentration.[86] No needles or other devices are needed for the collection and stimulation of saliva because the natural secretion of saliva (0.3–0.4 mL•min^{-1}) can provide enough amount for glucose analysis.[87] Several miniaturized sensors have been developed to collect saliva directly from the intraoral cavity, allowing for CGM.[88–90] Detailed discussions about these sensors are shown in the following chapter.

2.2. State-of-the-art in Wearable Glucose Sensors

2.2.1. ISF-Based Wearable Glucose Sensors

Figure 3a shows an example of the latest ISF-based wearable glucose sensor in which reverse iontophoresis electrodes and recording electrodes are integrated into a skin-mounted tattoo

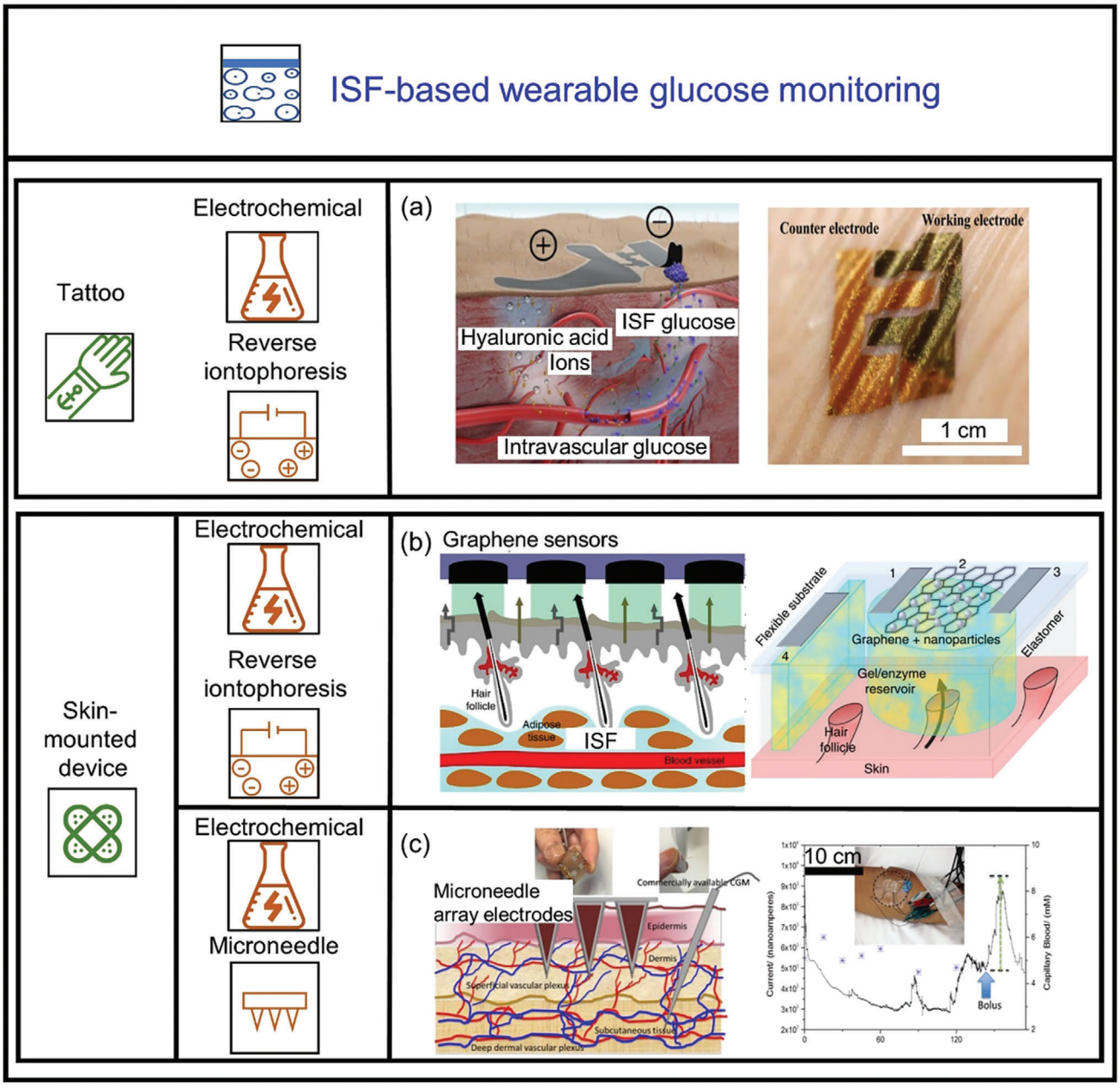

Figure 3. ISF-based wearable glucose monitoring. a) Tattoo-like ultrathin ISF glucose sensor based on reverse iontophoresis method for the extraction of ISF. Reproduced with permission.[91] Copyright 2017, AAAS. b) Skin-mounted ISF glucose sensor with a path-selective pixel array for reproducible ISF extraction. Reproduced with permission.[95] Copyright 2018, Springer Nature. c) Skin-mounted ISF glucose sensor with an epoxy microneedle array, along with the result of continuous monitoring of glucose concentration. Reproduced with permission.[96] Copyright 2016, Springer Nature.

to absorb ISF and subsequently detect the glucose concentration, respectively.[91] In this work, electrochemical twin channels (ETC) were established to promote the transportation of intravascular blood glucose to the skin surface. The intravascular blood glucose obtained through the ETC was highly correlated with the real blood glucose level. This glucose sensor was multilayered with "sand dune" nanostructures with a total thickness of ≈3 µm. The ultrathin nature of this sensor promoted its highly conformal contact to the dermal ridges for improved fidelity in the collection of glucose. Another notable work enabled the simultaneous sampling of both ISF and sweat at the cathode and anode through the application of reverse iontophoresis and iontophoresis at once.[92]

Recent works have also demonstrated the ISF-based wearable glucose sensors enabled by the discriminated extraction of glucose using an electroosmotic flow (i.e., iontophoresis) that tends to follow the low-resistance, preferential pathways associated primarily with follicles.[93,94] The extracted glucose potentially undergoes a dilution when it is extracted from a relatively large area of skin (> 3 cm^2). Figure 3b presents a potential solution to avoid this dilution issue using a path-selective miniaturized pixel array

platform to fix the area and volume of the pixels to extract ISF.[95] The dilution factor of the extracted glucose was constant and independent of follicular density, thereby eliminating the variability of glucose concentrations in ISF by a quantized readout.

The quantification of glucose in ISF can also be achieved by integrating these wearable sensors with microneedle arrays. Figure 3c presents an example of an ISF-based wearable glucose sensor integrated with epoxy-based microneedle arrays that were metalized with platinum and functionalized with GOx with electropolymerized phenols.[96] The fully integrated sensor was attached to the forearm of a wearer for CGM with a reproducible response to variable glucose concentrations in the physiological range (0–30 mM), compared to those obtained with a commercial capillary blood glucometer. The correlation of the measured glucose concentration in ISF and blood was verified, along with the time lag of glucose change in ISF.

Despite great success, several challenges remain in these ISF-based wearable glucose sensors. The time delay of glucose fluctuation compared to blood glucose concentration leads to potential medical issues in time-sensitive cases, such as hyperglycemia and hypoglycemia. The delay is caused by the time needed for the uptake of ISF and the slow diffusion of glucose from blood vessels to ISF. Skin irritation is another challenge upon the extraction and collection of ISF, especially with a large current that is often required for the reverse iontophoresis process. There have been several attempts to lower the current.[97,98] Also, RI technology is susceptible to sweat because the sweat gland was reported to be a transport pathway in iontophoresis.[82,99,100]

2.2.2. Sweat-Based Wearable Glucose Sensors

Several sweat-based glucose sensors have been demonstrated within a number of wearable substrates including patches, tattoos, and fabrics. **Figure 4a** presents an example of a colorimetric sweat-based wearable glucose patch allowing for the measurement of sweat loss and multiple analytes in sweat.[50] Microfluidic channels equipped with capillary bursting valves were embedded within this sensor, providing the capability to sequentially fill individual micro-reservoirs with sweat where colorimetric assays are located. The colorimetric responses of the assays to the concentrations of each analyte in sweat provided spectral information for the color reference markers in which their absolute colors were extracted from digital images. Recently, a ratiometric fluorescence sensor was also applied for wearable glucose monitoring.[101] In this work, glucose-sensitive ratiometric fluorescence nanohybrids exhibited a mixture of red fluorescence color from porous silicon and blue fluorescence color from carbon quantum dots with a ratio of their intensities under UV. The glucose-sensitive ratiometric fluorescence nanohybrids. Such ratio was determined by the production of hydrogen peroxide (H_2O_2) upon the oxidation of glucose and thus could quantify the glucose concentration.

Another notable strategy for the development of a battery-free wearable glucose sensor involves the use of a sweat-based biofuel cell to serve as a power supply.[102] In addition to utilizing glucose directly for the bio battery, lactate in sweat has also been an attractive candidate for the biofuel cell.[103–106] Figure 4b presents the most recent example in which a fully perspiration-powered electronic skin was used to harvest energy from lactate in sweat and to perform continuous monitoring of multiple biomarkers, such as glucose.[107] A stable current was generated to power electrical loads as the flowing redox reaction takes place. The lactate oxidase immobilized bioanodes catalyze the lactic acid to pyruvate and Pt alloy nanoparticle-decorated cathodes that reduce oxygen to water.

An emerging trend is to establish a closed-loop system that integrates these wearable glucose sensors with drug delivery units toward autonomous feedback therapy. Figure 4c presents the recent development of a graphene-based glucose sensor integrated with a therapeutic unit enabling transcutaneous drug delivery through the use of temperature-responsive, biodegradable microneedles coated with a phase-change material.[108] Continuously measured glucose concentrations in sweat were compared with blood glucose data obtained from a commercial glucose meter. Upon programmed thermal actuation, a testbed drug (Metformin) was released into the bloodstream through the microneedles in which the release rate was controlled by multichannel thermal actuators. The entire device layer is thin and flexible to establish a conformal contact to the skin, promoting the efficacy in glucose sensing and drug delivery. The orchestrated monitoring of glucose and physiological cues with sweat control and transcutaneous drug delivery showed a possibility for closed-loop management of diabetes. More discussions about the closed-loop systems are shown in Section 3.2.2.

Figure 4d shows a sweat-based wearable glucose sensor embedded within a fabric platform with facile sewing.[109] High electrocatalytic activity of the sensor was reported through the synergetic effects between the Au nanoparticles and reduced graphene oxide-polyurethane (rGO/PU) wherein the large surface area of the nanoscale Au wrinkles provides significantly enhanced sensitivity (140 $\mu A \bullet mM^{-1} \bullet cm^{-2}$). Continuous monitoring of glucose concentration in sweat was demonstrated on human subjects along with control measurements using commercial glucose assay and meter.

A key challenge for these sweat-based wearable glucose sensors is overcoming the low and variant secretion rate of sweat, which hampers the collection of enough sweat samples for reliable analysis. The secretion rate of sweat was reported to be as low as 1 $nL \bullet min^{-1} \bullet mm^{-2}$ with variant rates.[110,111]

2.2.3. Saliva-Based Wearable Glucose Sensors

Saliva-based glucose sensors can be easily integrated onto the mouthguard for non-invasive continuous monitoring of glucose levels.[90,112] **Figure 5a** shows a saliva-based glucose sensor built upon a mouthguard that also incorporates a wireless measurement system.[113] This sensor was able to quantify the glucose concentration in saliva in a range of 1.75–10 000 $\mu mol \bullet L^{-1}$, covering human salivary sugar concentration of 20—200 $\mu mol \bullet L^{-1}$. This sensor was integrated with a cellulose acetate membrane to reject the interference from salivary components, such as ascorbic acid and uric acid, which could be interfered with the output current.[90] Recently, the colorimetric quantification of salivary glucose was also demonstrated using a paper-based microfluidic device embedded within a mouthguard.[89] Figure 5b shows a further miniaturized saliva-based glucose sensor enabling the

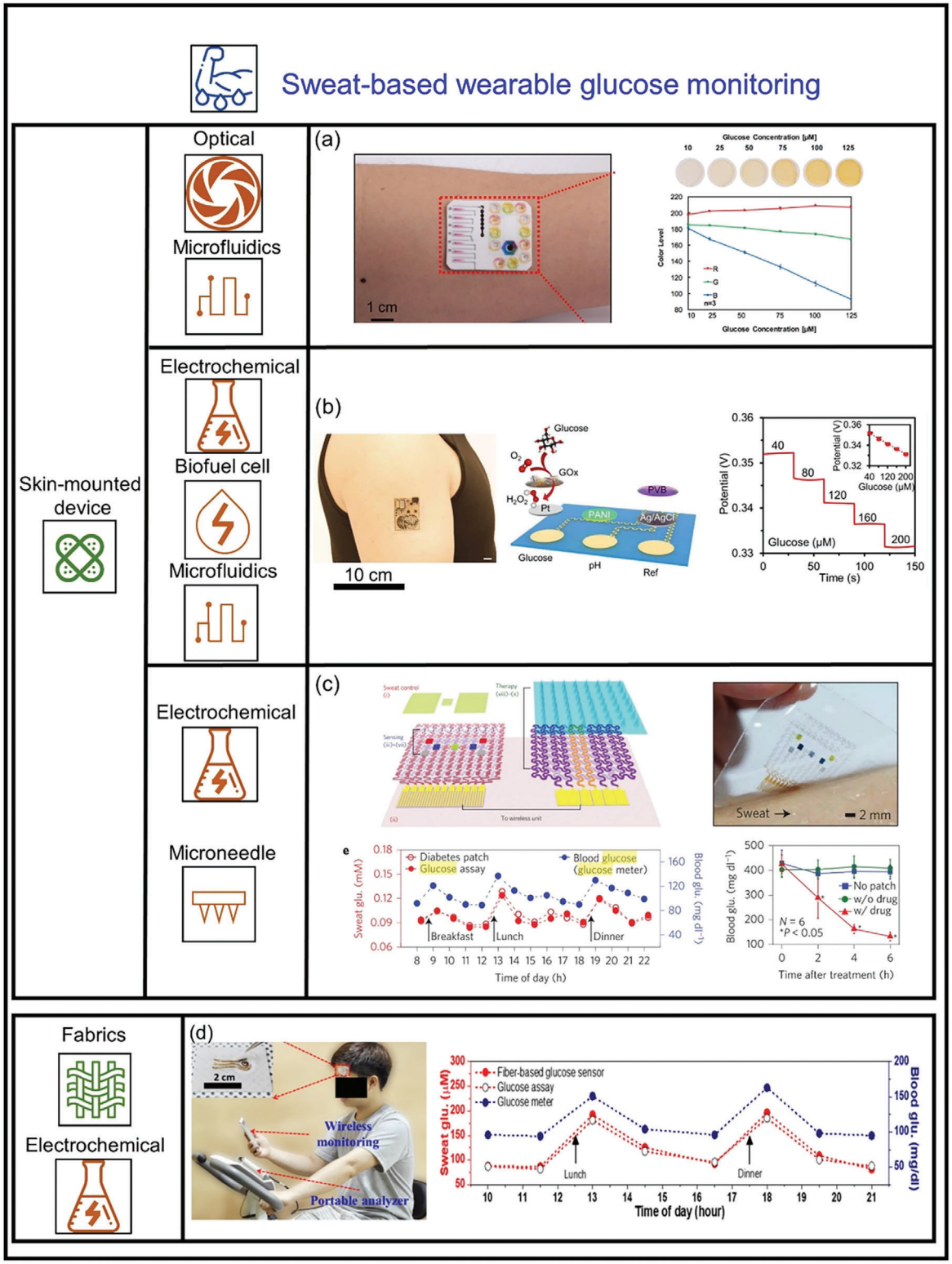

Figure 4. Sweat-based glucose monitoring. a) Colorimetric sweat-based glucose sensor patch, along with the measurement results of glucose concentration by color levels of red, green, and blue colors. Reproduced with permission.[50] Copyright 2019, American Chemical Society. b) Sweat-based biofuel cell for glucose sensing, along with the potential data at different glucose concentrations. Reproduced with permission.[107] Copyright 2020, AAAS. c) Skin-mounted closed-loop patch for glucose sensing and drug delivery with microneedles. Reproduced with permission.[108] Copyright 2016, Springer Nature. d) Sweat-based glucose sensor integrated into a fabric, along with representative measurement results. Reproduced with permission.[109] Copyright 2019, American Chemical Society.

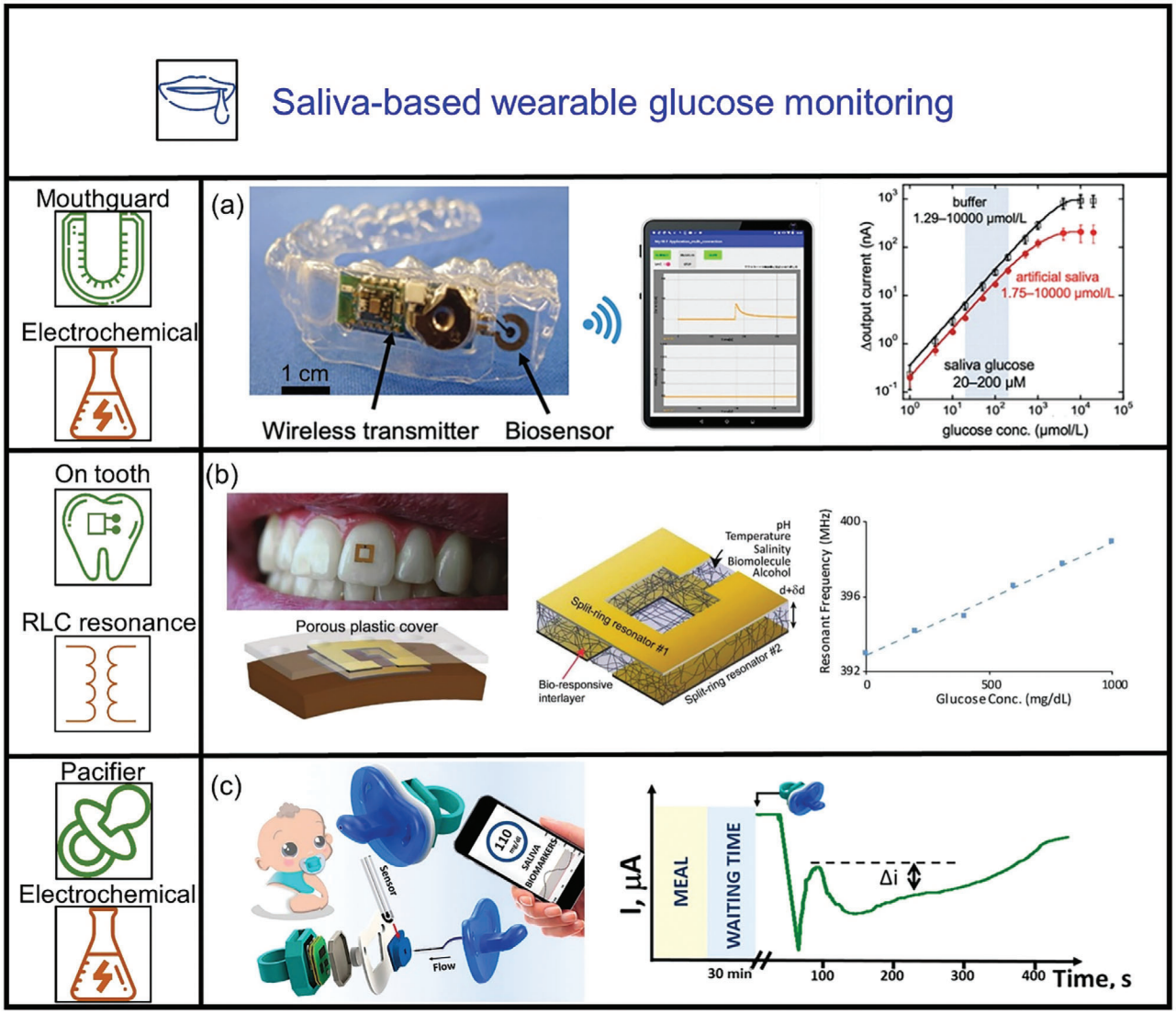

Figure 5. Saliva-based wearable glucose monitoring. a) Mouthguard-based glucose sensor with a wireless communication module, along with representative measurement results. Reproduced with permission.[113] Copyright 2020, American Chemical Society. b) On-tooth glucose sensor sandwiched between resonators and a bio-responsive interlayer material, along with the calibration of resonance frequency to glucose concentration. Reproduced with permission.[55] Copyright 2018, John Wiley and Sons. c) Pacifier-based glucose sensor, along with the continuously measured current variation induced by the change of glucose concentrations after meal. Reproduced with permission.[116] Copyright 2019, American Chemical Society.

on-tooth monitoring of salivary glucose between the consumed foods in a less obtrusive manner.[55] This sensor consists of a broadside-coupled, split ring resonator (BC-SRR) geometry (composed of two stacked, reverse-facing SRRs), and a bio-responsive interlayer sandwiched by the SRRs. The increased salivary glucose concentration induced the reduction of the effective permittivity of the saliva, and thus increasing the resonant frequency of this sensor.

The glucose deregulation in certain patient groups, such as newborns, can cause harmful effects.[114,115] Platforms for newborns require better wearing comfort and user experience. The pacifier is an attractive platform specifically for babies to wear because of its biocompatible non-toxic materials that are designed for long-term exposure inside the mouth. Figure 5c shows an example of the saliva-based glucose sensor built upon a pacifier using a screen-printing technique.[116] The fluctuations of salivary glucose after meals were measured by output current at the electrodes inserted in a chamber of the pacifier.

The key challenge for these saliva-based glucose sensors is overcoming the interferences caused by impurities in saliva from ingested foods, digested metabolites, or/and bleeding gums. To compensate for this impurity issue, filtering of large biomolecules mixed in the saliva has been often used in conventional (i.e., non-wearable) saliva-based glucose sensing and may also need to be integrated with wearable devices.[117,118] The concentration difference of saliva induced by masticatory or gustatory during food intake is another challenging problem.[119] Another challenge may include discomfort from the long-term wearing of the mouthguard or on-tooth devices.[55]

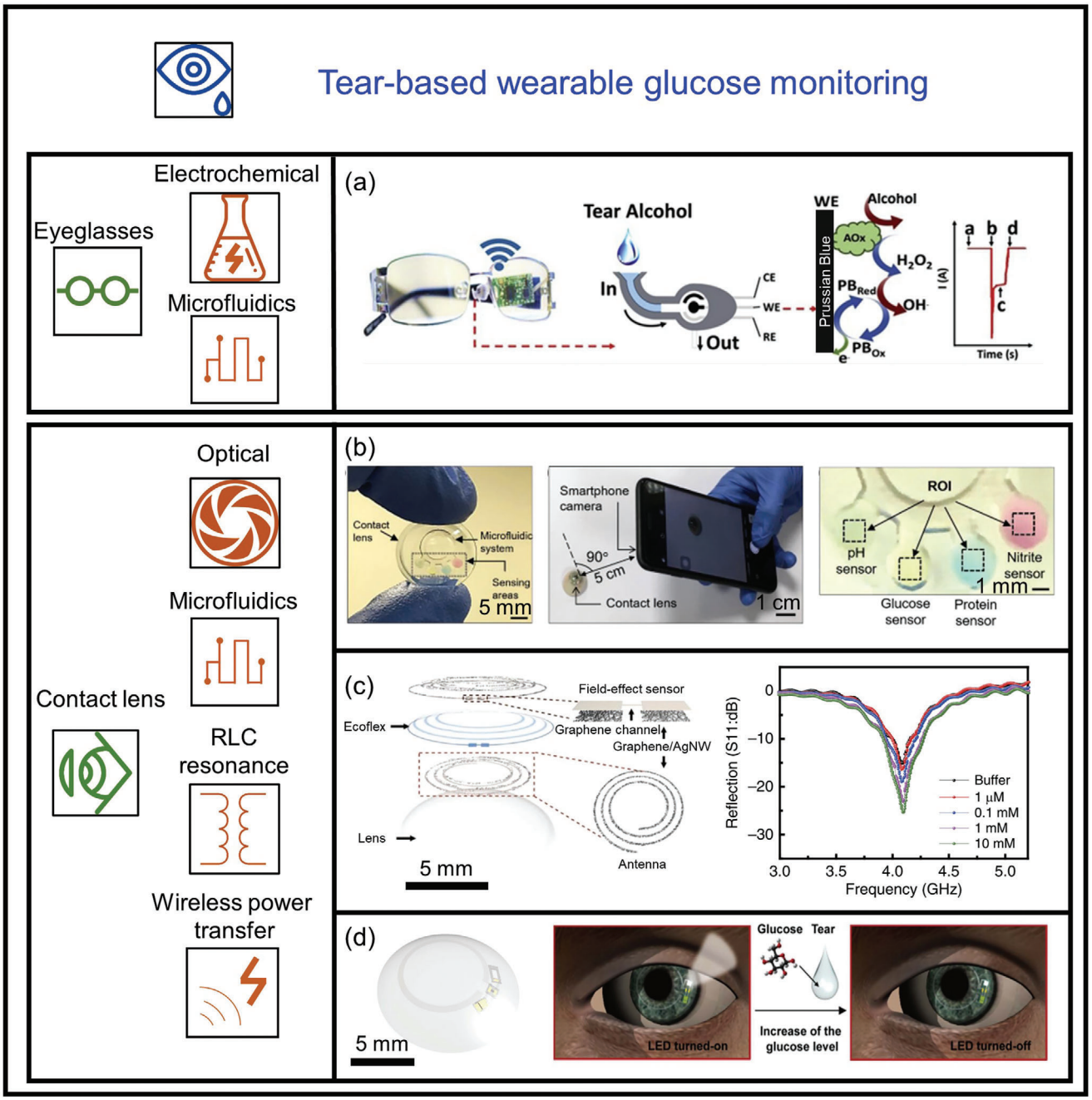

Figure 6. Tear-based wearable glucose sensor. a) Eyeglasses-based tear glucose sensor. Reproduced with permission.[65] Copyright 2019, Elsevier. b) Colorimetric contact lens-based glucose sensor with microfluidic channel for tear collection. Reproduced with permission.[120] Copyright 2020, Elsevier. c) Contact lens-based glucose sensor with RLC resonance circuits, along with the reflection at different glucose concentration. Reproduced with permission.[56] Copyright 2017, Springer Nature. d) Contact-based glucose sensor with wireless power transfer technology. Reproduced with permission.[54] Copyright 2018, AAAS.

2.2.4. Tear-Based Wearable Glucose Sensors

Figure 6a shows an example of a tear-based wearable glucose sensor mounted on eyeglasses.[65] A microfluidic device for tear collection was mounted on the eyeglasses nose-bridge pad, and the glucose concentration was measured by the electrochemical enzymatic method. This was the first platform that involves the use of eyeglasses for tear-based glucose monitoring without direct contact to the eye to minimize the risk of potential infections and impaired visions. However, an external stimulation to the eyes was required for the sampling of a relatively large volume of the tear (> 10 µL).

Contact lenses are naturally in touch with the cornea surface in a highly intimate manner, making them an ideal platform for

CGM in tear. Figure 6b shows an example of a colorimetric glucose sensor built upon a contact lens that incorporates microfluidic channels to collect tear.[120] The colorimetric assay within the microchannels responded to the change of the glucose concentration in the collected tear sample, displaying a detectable shift of refection peak in the visible spectrum. The precise readout was obtained by using a smartphone-MATLAB algorithm based on the nearest-neighbor model, which enabled semi-quantitative glucose monitoring without a power supply.

Figure 6c shows another example of a tear-based glucose sensor built upon a contact lens that incorporates a resonant RLC circuit.[56] The RLC circuit is stretchable and semi-transparent through the exclusive use of graphene-metal nanowires hybrid materials. When this circuit was operating at a radio frequency, the amplitudes of reflection indicated the glucose concentration in tear. With more glucose binding on the graphene, the reduced resistance enlarged the reflection. Power supply, associated circuitry and interconnect electrodes were not needed for this wireless sensing scheme that involves analyzing reflection coefficient from a near field electromagnetic coupling. Figure 6d shows another example of a fully integrated sensor that also incorporates a wireless power transfer circuit and display pixels, all in a single contact lens.[54] The antenna used for wireless power transfer received the radio frequency signals from an external transmitter to turn on a light-emitting diode to alarm the glucose level in tear beyond the threshold.

Despite great promises, many technical difficulties remain in the fabrication of these tear-based glucose sensors to meet the requirements of optical transparency, mechanical softness, and biocompatibility for securing the wearer's vision and on-eye safety. In addition, the cornea is exceptionally sensitive, and thereby the long-term continuous monitoring of glucose at the corneal surface is limited especially during sleep. Another challenge is that diabetics typically demand additional cautions on wearing contact lenses because any corneal injury would take longer to heal than normal conditions.[121] Also, a fundamental study on the correlation between the glucose concentrations in blood and tears is needed.[122] Due to these challenges, the project on a commercial smart contact lens for glucose monitoring developed by Google was terminated.[123]

3. Implantable Drug Delivery Systems

3.1. Current Technologies for Diabetes Treatment

Traditional diabetes treatments including oral non-insulin hypoglycemic drugs, insulin or insulin analog injections, and pancreas transplants have been available for decades (**Figure 7**). Recent advances in biomaterials and bioengineering have also fueled the development of novel drug delivery therapies for diabetes patients. These include genetic therapy, peptides drugs, oral-, nasal-, pulmonary-delivered insulin, and transplanted islets, many of which are undergoing clinical trials already.

For early-stage type II diabetes patients, oral non-insulin hypoglycemic drugs are often their first option. Although life-threatening side effects are rarely reported for these non-insulin drugs, they require daily dosage and strict adherence, which can reduce overall patient compliance. Moreover, these drugs can cause gastrointestinal tract irritation, diarrhea, loss of appetite, and cannot be taken by patients with liver or kidney problems.[124–126] The latest studies of non-insulin hypoglycemic drugs that highlight the opportunities and the limitations of using these compounds are well described elsewhere.[127–130]

For patients with type I diabetes and more advanced type II diabetes that cannot maintain normoglycemia via non-insulin medications and lifestyle change, injection or infusion of insulin is needed. Secreted from pancreatic β-cells, endogenous insulin is a protein hormone that is capable of regulating the blood glucose concentration within the range of 80–130 mg•dL^{-1}. Being incapable of generating endogenous insulin, patients with diabetes need exogenous insulin, such as animal insulin, recombinant human insulin, or insulin analogs.[126,131] The insulin can be injected subcutaneously via needles or pens, or continuously infused subcutaneously or intraperitoneally via pumps (more discussion in section 3.2). When combined with CGM devices, insulin pumps can adjust dosage using a built-in algorithm to establish a computational closed-looped system.

Lately, driven by the need to minimize invasiveness and maximize patient compliance, other insulin delivery methods in the forms of oral, transdermal, buccal, and pulmonary have been vigorously investigated.[132–135] These novel approaches need to overcome technical barriers such as physiological environments, enzymatic degradation, chemical instability, and limited absorption.[136] In section 3.3, we present various material approaches for target insulin delivery via either passive or active trigged release. We also further cover transdermal microneedles for insulin infusion, which has additional benefits such as long-term usage (e.g., weeks) and glucose monitor integrability. These novel materials respond to elevated glucose levels to release insulin and stop once normoglycemia is regained. Hence a responsive closed-looped system is formed.

For patients with late-stage diabetes with serious complications, pancreas or islet transplantation may be their only option. However, due to shortage of whole organ pancreas, cadaveric β-cells islets, as well as xenogeneic islets derived from human embryonic stem cells, induced pluripotent stem cell, and β-cells-mimetic genetically engineered cells, are being actively researched.[137–139] At the same time, the encapsulation of islets allows better control of the implantation rejection and immune response, and increases islet viability and their therapeutic value (more discussion in section 3.4).[140,141] When successfully implanted, islets are stimulated by glucose and secrete insulin via a natural metabolic process, thereby forming a biological closed-looped system.

3.2. Insulin Pumps

Insulin pumps are medical devices that continuously deliver insulin from a reservoir to diabetics. In general, there are three types of insulin pumps: 1) traditional insulin pumps, 2) insulin patch pumps, and 3) implantable insulin pumps, as shown in **Figure 8**. The traditional insulin pump includes a wearable main body, tubing, and an infusion cannula (Figure 8a). The main body houses an insulin reservoir, a pump mechanism, a power source, as well as necessary control, communication, and programming circuits to adjust insulin infusion rate. An infusion cannula is implanted subcutaneously with the detachable needle. The insulin

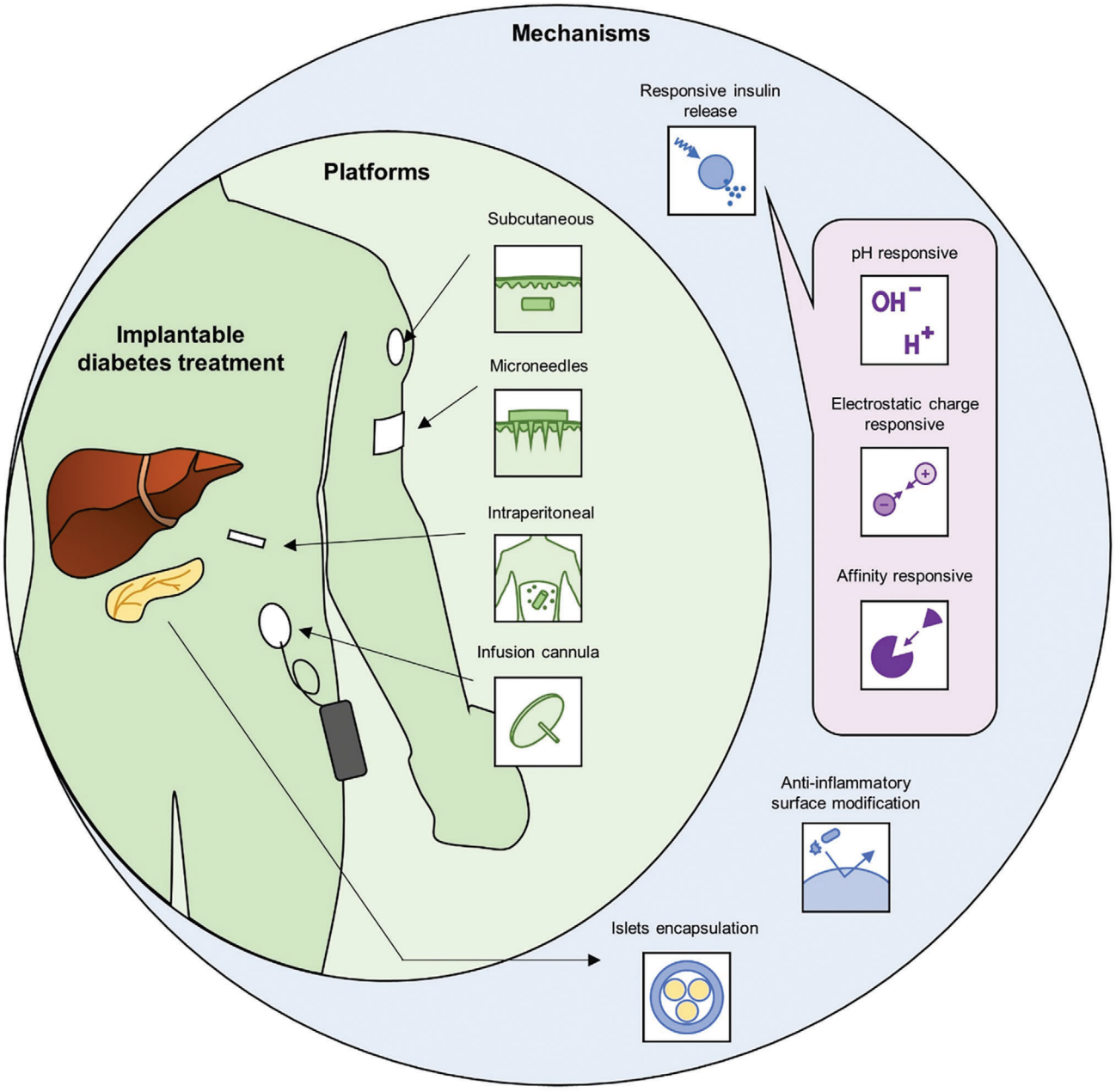

Figure 7. Trends and technologies for implantable drug delivery systems.

patch pump is similar to the traditional insulin pump, but it has a smaller body with an infusion cannula attached (Figure 8b). An insulin patch pump is worn directly on the skin. It can be disposable or refillable, with the fixed or adjustable-rate by using a separate device for wirelessly control.[142]

The implantable insulin pumps are typically placed subcutaneously at the lower abdomen and intraperitoneally infuse insulin via a catheter (Figure 8c). Compared to the subcutaneous approach, intraperitoneal delivery can facilitate the insulin uptake by the liver via the portal system, enabling faster absorption and long-term, more sustained, and stable glucose control.[143,144] Currently, only one model of implantable insulin pump is available on the market—Medtronic MIP 2007D. Once implanted under general anesthesia, its internal battery can last 7–10 years.[145] However, the insulin reservoir (15 mL) requires a transcutaneous refill every 3 months, depending on patient usage. In addition, systematic maintenance, such as pump and catheter rinsing, is recommended every 6–9 months to prevent insulin aggregation and catheter obstruction. Due to its invasiveness, a higher cost (€ 10 ,910 per year compared to €4,810 per year for a traditional insulin pump),[146,147] and shrinking pharmaceutical advantage owing to the rapid development of an improved formula for subcutaneously infused insulin, the implantable insulin pump is losing its commercial appeal.[148] In fact, Medtronic issued a recall

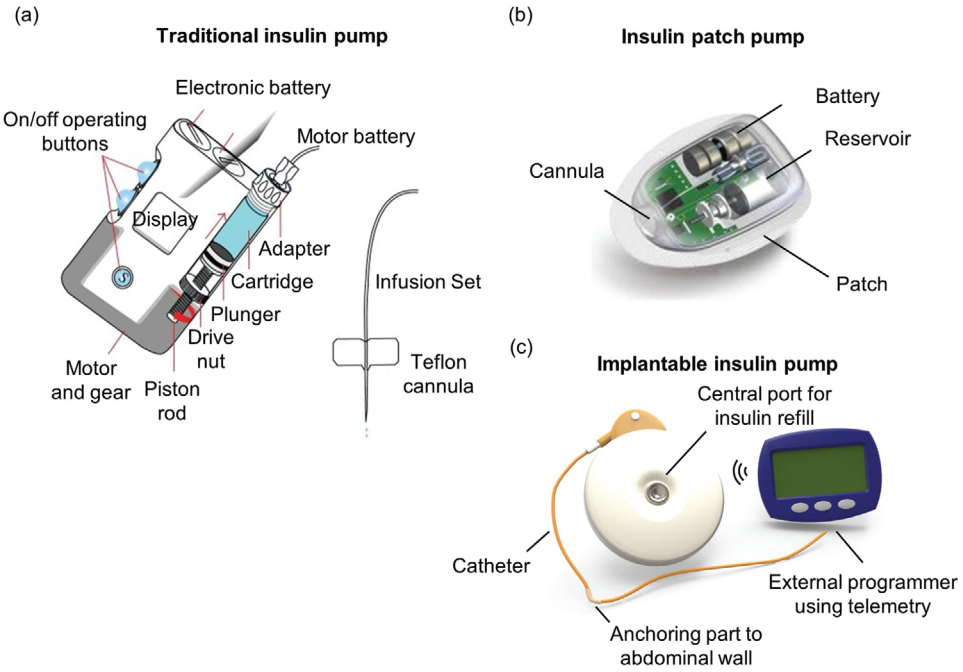

Figure 8. Three types of insulin pumps. Schematic illustrations of the composition of a) traditional insulin pump. Adapted with permission.[218] Copyright 2010, Vasiliki Valla. b) insulin patch pump (OmniPod Insulin Management System, Insulet Corp., Bedford, MA, USA). Reproduced with permission.[219] Copyright 2010, Springer Nature. c) An image of implantable insulin pump.

for any unused pump in April 2020, effectively ending its life cycle.[149] However, there is renewed interest in implantable insulin pumps with reduced size, advanced features, and integrating with implantable glucose sensors for closed-loop systems.[143]

3.2.1. Challenges Associated with Insulin Pumps

One of the inconveniences of the wearable insulin pump is that the subcutaneously implanted cannula needs to be replaced at least once every week.[150] There are also risks of kinking or bending the cannula due to migration and movement of the external components. Most significantly, potential infection and occlusion due to the foreign body response can cause a severe problem for the patient. Various approaches have been developed to extend the lifetime and improve the biocompatibility of the implants. Chug et al. reported that the material for the infusion cannula can be modified to release nitric oxide, which improves biocompatibility by preventing platelet activation and adhesion.[151] Their S-nitroso-N-acetylpenicillamine impregnated coating released NO for more than 14 days, and remained stable for 30 days. In addition to novel materials, surface structures can also be used to prevent surface fouling and foreign body response. In the work by Xu et al., oxygen plasma was used to etch polytetrafluoroethylene (PTFE) surfaces to form nanopillar structures.[152] These nanostructured surfaces have been demonstrated to have bactericidal and anti-inflammatory properties. Several other approaches have been developed to improve the biocompatibility of the implants, including hydrophilic materials, biomimetic, zwitterionic, and other smart polymer materials.[153–155] However, the manufacturability, shelf-life, and cross-compatibility with the insulin still need to be evaluated.

3.2.2. Control Algorithms for Closed-Loop Systems

For patients with diabetes, a fully autonomous system that can monitor and adjust their glucose level day and night is regarded as the "Holy Grail".[156] In such a system, the glucose level can be measured by a wearable glucose sensor and sent to the insulin pump to automatically adjust the infusion rate. However, having a notoriously narrow therapeutic window, insulin infusion needs to be precisely controlled.[157] Advanced insulin delivery algorithms for reduced hypoglycemia events and glycemic variability are the keys to better diabetes management. Using information from glucose sensors, patient activity, and other sensors (i.e., heart rate, temperature), advanced algorithms adjust insulin pumps to an optimized delivery rate. Thus far, algorithms based on proportional integral derivative, model predictive control, and fuzzy logic have been developed and tested.[158,159] Further advanced algorithms are capable of detecting meals, pump malfunction, and possible hypoglycemia events.[160–164]

With the rapid development of CGM and insulin pump, a closed-loop system is already a reality. In 2017, Medtronic MiniMed 670G closed-loop insulin pump was first approved by the FDA to treat patients with type I diabetes.[165,166] The glucose level is measured subcutaneously every 5 minutes via the Guardian Sensor 3 and is used to adjust insulin delivery. Multiple clinical trials suggest such a closed-loop system helped patients maintain longer normoglycemia and lower glycated hemoglobin (A1c)

levels.[167–169] Other manufactures (e.g., Dexcom, Tandem, Abbott, SOOIL) have also shown similar promising results in human trials.[170–174] In addition to these conventional approaches, closed-loop systems can be built using a few components (i.e., open-loop glucose monitor and insulin pump, transmitters, receivers, miniature computer) at home, with the help of Open Artificial Pancreas System (OpenAPS).[175] OpenAPS enables users to form a personalized closed-loop system with existing already-approved products to improve their effectiveness. With medical devices and the healthcare industry becoming a more popular target for cyberattacks due to its grassroots and unregulated nature, OpenAPS is especially vulnerable to various attacks.[176] More evaluation of the safety and efficacy of these systems is still needed, and the involvement of regulating agency and manufacturer are encouraged to make the closed-loop systems accessible and successful.

3.3. Responsive Insulin Release

In addition to electromechanical pumps, various material-based approaches have also been developed for the selective and responsive delivery of insulin. Such systems can release insulin in the desired dose and site from pre-implanted depots based on glucose level and physiological conditions. Ultimately, these responsive closed-loop approaches could replace the role of β-cells. Having both glucose-sensing and drug-delivery capacity, novel implantable materials that deliver insulin on demand could relieve diabetes patients from the burden of multiple daily checkups. However, multiple technical and other clinical challenges remain including biocompatibility and in vivo reliability. In this section, the latest progress in novel insulin delivery will be presented.

3.3.1. Passive Insulin Release

Passive insulin release can be triggered by the presence and concentration of glucose. These glucose-responsive approaches are mainly achieved using GOx, phenylboronic acid (PBA), or glucose-binding molecules. GOx enzymatically oxidizes glucose to gluconic acid with hydrogen peroxide as a byproduct (Equation 1). This generates an acidic and hypoxic local environment, leading to degradation or swelling of the implant matrix and subsequent insulin release. In the work by Li et al., GOx was combined with a pH-sensitive peptide hydrogel to achieve glucose-responsive insulin delivery.[177] Such hydrogel remained local pH value at 7.4 when no glucose was present but steadily fell to 4.3 in 12 h when experienced typical hyperglycemic level (400 mg•dL^{-1}). The decreased pH triggered peptide unfolding, disassembly, and subsequently insulin release. When subcutaneously implanted into diabetic mice, their hydrogels maintained normal glucose levels for 4 days.

GOx can also be combined with metal-organic frameworks (MOFs) for glucose-responsive insulin delivery. Zhang et al. encapsulated GOx and insulin into zeolitic imidazole framework-8 (ZIF-8) nanoparticles (**Figure 9a**,b).[178] When glucose diffused into such nanoparticles, catalytic reaction decreased pH value in a microenvironment, leading to the collapse of MOF, triggering insulin release. When injected subcutaneously into diabetic mice, their nanoparticles helped maintain normoglycemia for up to 3 days, without peaks of hypoglycemia or hyperglycemia.

PBA is a synthetic molecule, which can reversibly bind with a glucose molecule and change the equilibrium state of its boronate moiety from the uncharged to the anionically charged state.[179] PBA-based hydrogels can change their hydration level according to the equilibrium state of the boronate moiety with different glucose concentrations.[180,181] In the work by Wang et al., a polymeric complex made of positively charged polymers, pendant amino groups, and PBA groups could load insulin with 49% capacity and remain stable in the absence of glucose.[182] When PBA binds to glucose, positive charge density decreases, weakening electrostatic attraction between insulin and polymeric matrix, enabling responsive insulin release (Figure 9c,d). In their in vivo evaluation, the blood glucose levels of diabetic mice could be maintained within the normal range for more than 8 h, which was much longer than native insulin without responsive release modification.

Glucose-binding molecules such as concanavalin A (Con A) can reversibly interact with glucose. For example, Yin et al. encapsulated insulin using microspheres made of glycidyl methacrylated dextran and Con A, which were further embedded in chitosan hydrogels to form an "artificial pancreas" scaffold (Figure 9e,f).[183,184] When glucose is presented, their microspheres experience reversible crosslinking or dissociation structural change, triggering insulin release. The in vitro test revealed the complete release of insulin at a steady rate in 12 days. No cytotoxicity of their scaffold was seen in the cell viability and proliferation test.

3.3.2. Active Insulin Release

Diabetes patients can also use external stimuli, such as magnetic field, ultrasound, mechanical stress, and light, to actively trigger insulin or drug release on demand.[185–191] In the work by Di et al., insulin was loaded into poly(lactic-co-glycolic acid) nanocapsules (with 12% loading efficiency), which were further encapsulated within chitosan microgels.[188] Without the external stimulation, insulin passively diffused out of microgels and enabled background basal dosage. Insulin release rate tripled when focused ultrasound was applied externally, enabling on-demand bolus dosage. The consistent release rate was observed for more than 10 days when 10 mg of insulin-containing microgels and once per day activation regimen was used. In their in vivo test, insulin-loaded microgels were subcutaneously implanted into diabetic mice via injection. Normoglycemia or significantly reduced blood glucose level was achieved for 10 days. In another example, Lee et al. developed a battery-less implantable insulin pump actuated by a magnet.[186] A pen-typed device with a magnet was used to trigger the insulin dosage of 0.81 ± 0.04 U ($\approx$160 doses) with high repeatability. In a 60-day in vivo test, diabetic rats had decreased blood glucose concentration and maintained normoglycemia for 11 days with a once-daily dose and the remaining days with twice-daily doses. One of the main drawbacks of such magnetic implantable devices is the interference with ambient magnetic fields and magnetic resonance imaging (MRI). Although users of implantable electronic devices such as pacemakers or implantable cardioverter-defibrillators can undergo MRI with special protocol

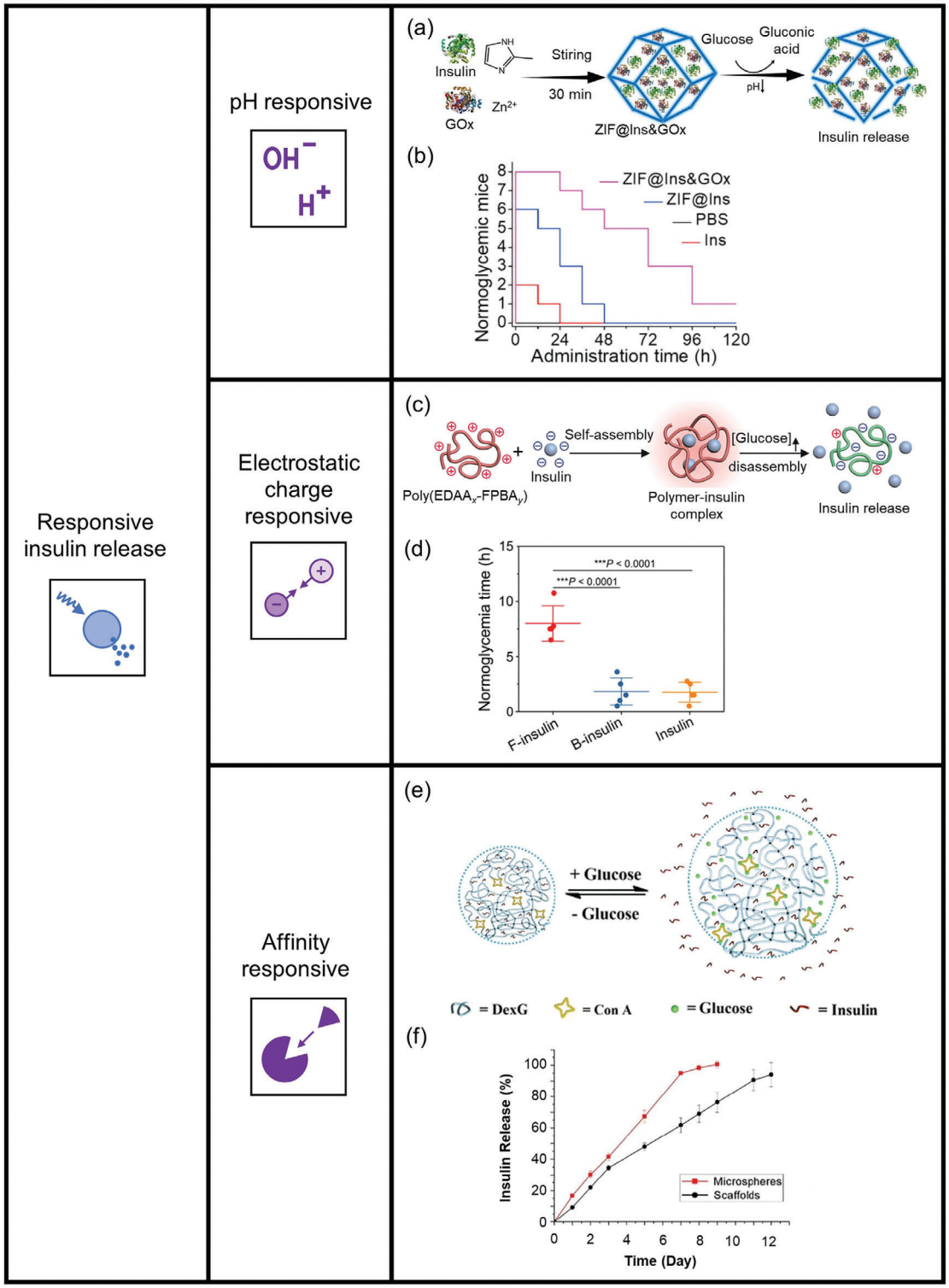

Figure 9. Implantable materials for the stimuli-responsive insulin release for the treatment of diabetes. a) Schematic illustration of insulin releasing mechanism of a GOx combined MOF. Reproduced with permission.[178] Copyright 2020, Elsevier. b) The number of normoglycemic mice over time for different groups. Reproduced with permission.[178] Copyright 2020, Elsevier. c) Schematic illustration of glucose-sensitive charge reversal-based insulin release mechanism. Reproduced with permission.[182] Copyright 2019, AAAS. d) Normoglycemia time of the mice subcutaneously injected with poly(EDAA0.4-FPBA0.6)-complexed insulin (F-insulin), poly(EDAA0.4-PBA0.6)-complexed insulin (B-insulin) and native insulin. Reproduced with permission.[182] Copyright 2019, AAAS. e) Schematic illustration of glucose-responsive insulin releasing mechanism of Con A based microspheres. Reproduced with permission.[183] Copyright 2019, Elsevier. f) Insulin release profile of scaffolds and microspheres for 12 days. Reproduced with permission.[183] Copyright 2019, Elsevier.

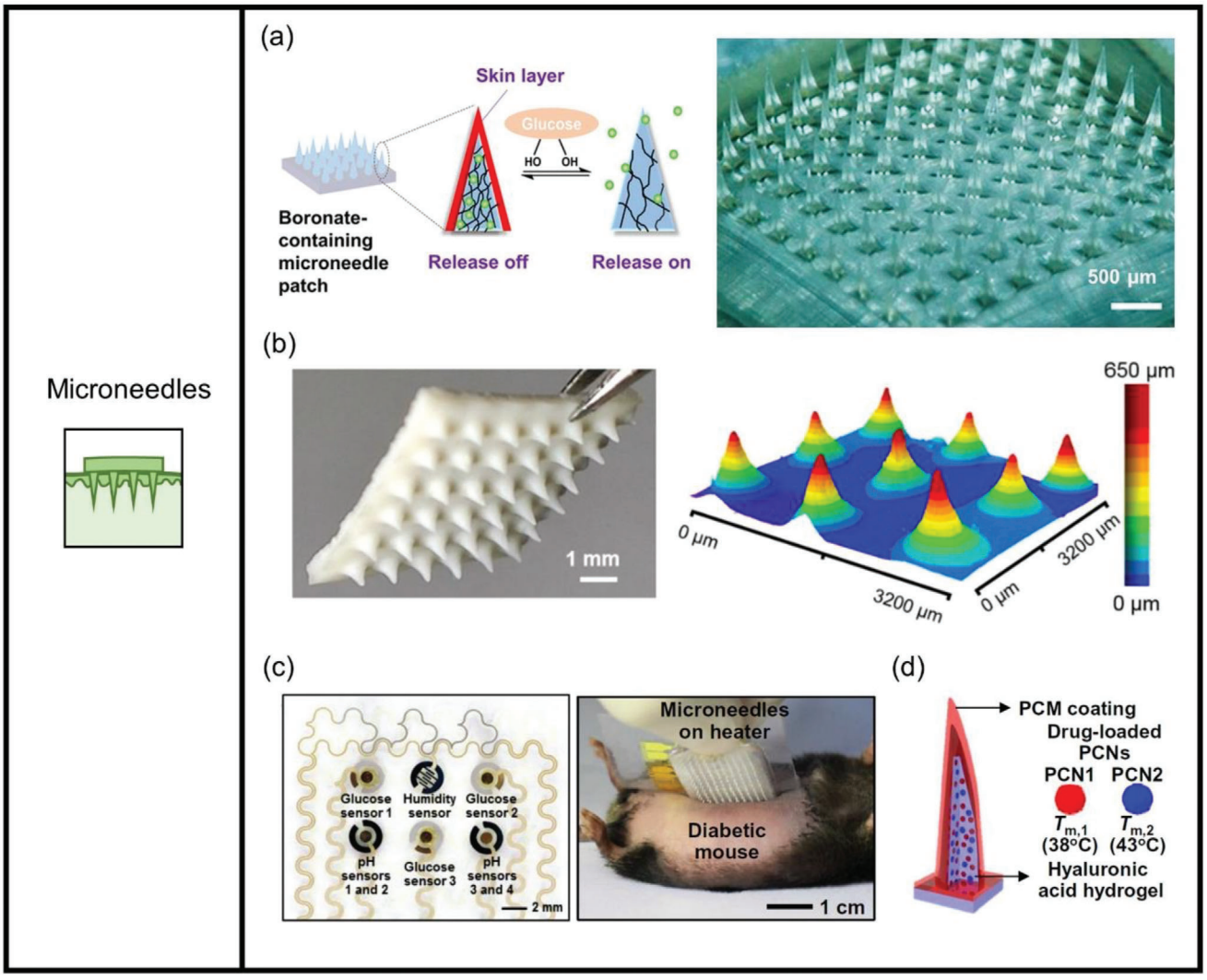

Figure 10. Microneedles for the transdermal drug delivery for the treatment of diabetes. a) Boronate-containing, PBA-based hydrogel microneedle patch. Reproduced with permission.[180] Copyright 2020, American Chemical Society. b) 3D printed, insulin loaded bioink-based microneedle patch. Reproduced with permission.[195] Copyright 2020, Elsevier. c) A wearable patch with multimode sweat sensor array (left), and the microneedles integrated with heater (right). Reproduced with permission.[30] Copyright 2017, AAAS. d) Schematic illustration of a drug-loaded hyaluronic acid hydrogel-based microneedle. Reproduced with permission.[30] Copyright 2017, AAAS.

and device design, the safety of implantable drug delivery devices needs to be carefully evaluated.[192]

3.3.3. Microneedles

Recently, transdermal administration of insulin via microneedles has become a popular research topic due to its self-administrative, minimally invasive, and painless nature. These advantages could improve patient compliance, which is still one of the primary obstacles to satisfactory diabetes management.[193] Groups have shown the potential of integrating various stimuli-responsiveness into the material of the microneedles for the effective release of insulin. In the work by Chen et al., microneedles made of boronate-containing, PBA-based hydrogel responded to glucose at normoglycemia and the normal body physiological condition (**Figure 10a**).[180] Their formula also had a consistent release profile independent of temperature (28–39 °C), eliminating the concern for variable skin temperature in patients.

Besides the traditional fabrication processes such as micromolding, laser cutting, lithography, and etching, a 3D printing technique was also applied for the fabrication of microneedle.[194] In the work by Wu et al., microneedles were made by 3D printing of insulin-loaded bioink, followed by post-stretching and cross-linking to form needle-like tips (Figure 10b).[195] Their bioink consists of alginate, hydroxyapatite, PBA, and insulin. Microneedles swell in solution, forming a porous structure, and allowing glucose to diffuse in and react with PBA for responsive release. In their in vivo evaluation, microneedles maintained normoglycemia for diabetic mice for up to 40 h. Compare to microneedles control without PBA, burst release of insulin induced hypoglycemia after 3 h. In a 4-day observation, mice treated with

their microneedles consumed less water, produced less urination, lost less body weight, and showed decreased glycated albumin levels, all indicating successful management of diabetes.

Microneedles can also be combined with a glucose monitor system to form a computational closed-loop diabetic management system. In the work by Lee et al., a wearable patch combined with a multimode sweat sensor (glucose, pH, humidity, and temperature) and temperature-triggered delivery of a non-insulin hypoglycemic drug (metformin) was presented (Figure 10c,d).[30] Microneedles made of biocompatible hyaluronic acid hydrogel were coated with drug-loaded phase change nanoparticles (PCNs). Two PCNs made with either palm oil (melting temperature $T_m = 38$ °C) or tridecanoic acid ($T_m = 43$ °C) remained stable and intact even after microneedles have penetrated the skin. When hyperglycemia was detected (GOx based electrochemical sensing with pH, humidity, and temperature compensation), integrated heaters triggered the release of the drugs. Six different drug release profiles were achieved by using three heating elements and two temperature points (40 and 45 °C). In their in vivo tests, the blood glucose level of diabetic mice was lowered in a controllable fashion (from > 22 mM to 7.6 mM, with < 11 being normoglycemic state) within 6 h.

3.4. Islet Encapsulation

Islet implantation is a compelling method to restore pancreatic functionality using a bioengineered bio-similar solution. In the host body, β-cells islets react to different glucose levels and secret insulin, forming a natural biological closed-loop system. However, when using islet implantation to treat diabetes, the encapsulation of islets is essential for the survival and proper function of the β-cells. Besides requirements for robust physical and mechanical designs to facilitate facile implantation, monitor, and possibly retrieve, the encapsulation needs to have excellent biocompatibility for long-term safety profiles and selective permeation.[140,196,197] The encapsulation needs to create and maintain a local environment that allows the exchange of nutrients, metabolic molecules, and waste while rejecting the immune mediating cells (i.e., complement, immunoglobulins, cytokines).[198] Such immuno-isolation or immune-stealth properties can relieve patients of islets implant from burdens of lifelong immunosuppression regimen or concerns of possible rejection or failure.[199]

In the microencapsulation, an individual or a small cluster of β-cells or islets is enclosed in a microscale capsule. These approaches maximize the surface area-to-volume ratio to promote the exchange of molecules, which could mitigate acute islet loss due to poor oxygenation and vascularization shortly after implantation. However, due to the large number of islets needed per implantation (10 000 per kilogram of body weight), the uniformity of capsules is hard to control.[200] In the macro-encapsulation, many islets are housed in one capsule with a larger dimension, making it easier to fine-tune and monitor each capsule. However, this approach suffers from poor diffusion of nutrients.

In the work by An et al., the Thread Reinforced Alginate Fiber For Islets enCapsulation (TRAFFIC) device was made by combining alginate hydrogel and nylon thread (**Figure 11a**).[201] Twisted-then-folded nylon sutures were first coated with poly(methyl methacrylate)/N, N-dimethylformamide/calcium chloride (PMMA/DMF/$CaCl_2$), then alginate hydrogel via in situ cross-linking. The TRAFFIC devices showed excellent biocompatibility, demonstrated by the lack of fibrosis after 7 months of intraperitoneal implantation in mice (Figure 11b). During the in vivo testing, human or mice islets were encapsulated and implanted into diabetic rats which showed long-term (1–4 months) normoglycemia. In comparison, unencapsulated islets did reduce glucose levels briefly but experienced rejection after 2 weeks.

In the work by Bose et al., an implant that can encapsulate various therapeutic xenogeneic cells was presented (Figure 11c).[202] It consisted of silicone elastomer with microchannels for cell reservoir, and polycarbonate track-etched membrane with distinct pore sizes (< 0.8 μm) to preventing immune cell infiltration and implant rejection response. They also tested different antibiofouling coatings using mice intraperitoneal implants model and revealed tetrahydropyran phenyl triazole had better antifibrosis property than well-known zwitterionic materials. The coated implants demonstrated long-term (> 120 days) delivery of erythropoietin hormone. When encapsulated with rat pancreatic islets, such device retained normoglycemia on diabetic mice for over 75 days.

In the work by Liu et al., a macro-porous structure with a secondary core-shell structure was printed using a 3D coaxial printing approach (Figure 11d).[203] Alginate/gelatin methacryloyl bioink had good stability, printability, and biocompatibility for islet's survival. The 3D macroporous structure ensured minimum distance between each islet and surrounding tissues for ample nutrients and oxygen diffusion. Encapsulated islets in the core were further provided with supporting cells in the shell. The in vivo tests showed good implant integrity after 21 days in mice, and visible vascularization after 14 days. However, in vitro tests of insulin secretion suggested that encapsulated islets were compromised after 3 days in the culture medium, which was possible due to interfered glucose diffusion or hypoxia condition.

4. Conclusion and Prospects

In this review, we summarized the recent development of novel sensing and treatment methods for diabetes care. In particular, we highlighted the emerging trends of wearable glucose sensors and their sensing modalities. In the section on implantable drug delivery, we summarized currently available treatment plans for diabetes patients as well as one that can form closed-loop systems. Significant progress has been made in glucose monitoring and drug delivery methods toward an accurate, painless, and continuous evaluation of glucose level, and more efficient and timely medication, respectively. The wearable platforms of glucose sensors were tailored for specific target body fluids (e.g., tear, sweat, ISF, and saliva) and the locations on the human body. In parallel, methods for diabetes management and treatment have progressed rapidly. Insulin pump with better biocompatibility design, accurate delivery rate, and precise control algorithms made the proliferation of closed-loop system closer to reality than ever. Novel materials enable alternative biological closed-loop systems routers such as glucose-triggered insulin release, painless microneedle insulin delivery, and islet transplantation as a potential cure.[26,204] The integration of wearable glucose sensors

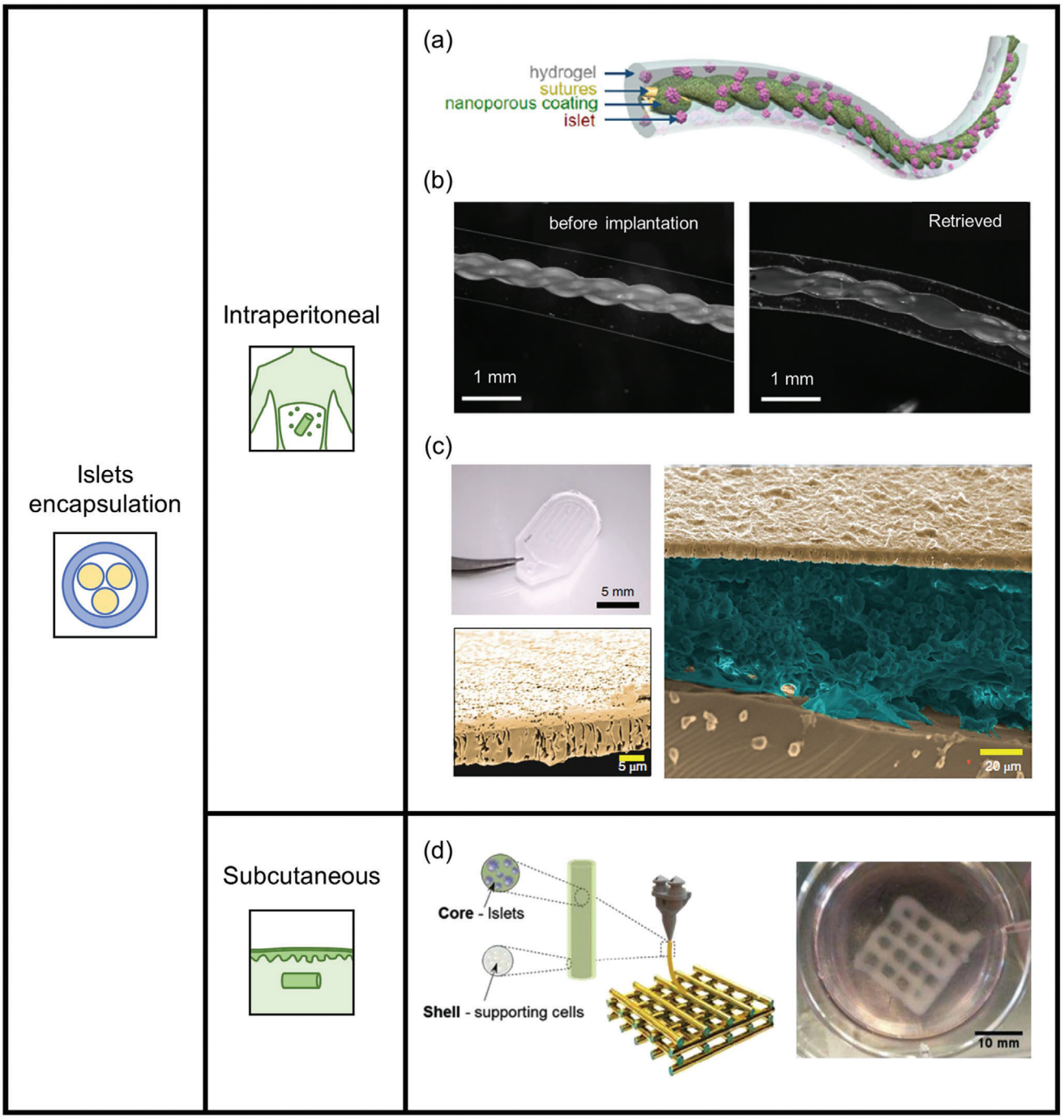

Figure 11. Islet encapsulation for the implantation of the β-cells. a) Schematic illustration of the TRAFFIC device. Reproduced with permission.[201] Copyright 2015, National Academy of Sciences. b) Microscopic images of the device before (left) and after (right) the 7 months of implantation in mice. Reproduced with permission.[201] Copyright 2015, National Academy of Sciences. c) A retrievable macroscopic encapsulation device for the long-term implantation. Reproduced with permission.[202] Copyright 2017, Springer Nature. d) Coaxially 3D-printed islets microencapsulation implant. Reproduced with permission.[203] Copyright 2019, John Wiley and Sons.

with these novel drug delivery methods has become a topic of intense research toward a complete closed-loop program for diabetes management.

Challenges remain in both wearable glucose sensors and implantable drug delivery systems. For wearable glucose sensors, the major challenges are to ensure the measurement accuracy, longevity, reproducibility, and wireless power supply. The measurement accuracy is influenced by multiple factors, such as the contamination of body fluids, environmental interferences (e.g., pH, temperature, and humidity). Frequent calibration steps with

finger pricking measurements as a reference are also required. Given that the glucose concentrations in biofluids are lower than blood glucose concentration, the measurements largely rely on the minimum resolution and sensitivity of the sensors. The delay in the fluctuation of glucose concentrations in body fluids also causes inaccuracy, which is problematic especially for hyperglycemia diabetics. The challenges associated with the reproducibility of these sensors not only depend on the repeatability of sensing performances but also the consistency in extracting body fluids. In addition, a better understanding of the correlation between the glucose concentration in body fluids and the blood glucose concentration is also required for improving reproducibility. Recent approaches for self-powering of these glucose sensors through the use of biofuel cells can potentially eliminate the challenges associated with wireless power supply.[205–208] Biofuel cell relies on the metabolites such as glucose and lactate contained in body fluids to generate electrical energy. For instance, the redox reactions of glucose on the electrodes generate electrons that flow into the circuits to generate the electrical current. The magnitude of the current is determined by the concentration of glucose. The sustainable bioenergy harvesting from perspiration enables the compact design of wearable glucose sensors by eliminating the external power supply. It would be promising to develop a stretchable form of biofuel cells that can be monolithically integrated with the various wearable glucose sensors discussed in this review. Progress has been made with nanostructured materials of carbon nanotubes, fiber with multiwalled carbon nanotube sheets, and metallic cotton fibers.[19,208,209]

For implantable drug delivery systems, the major challenges are to ensure biosafety and biocompatibility. Biocompatible polymers are used to encapsulate the devices to minimize foreign body responses, thereby increasing their lifetime. For responsive insulin release, accidental burst release may be life-threatening but can be reversed by the simultaneous or backup release of glucagon or other metabolic hormones.[210] The location of the insulin release reservoir is also worth studying. Transdermal microneedles provide minimized invasiveness but suffer from the limited payload. A subcutaneous router is a popular area of research one but it does not provide direct access to the portal system, which can delay the insulin uptake.[143,144] For islet encapsulation, membrane materials that can fully reject immune cells while allowing access to other molecules and nutrients still require optimization. The long-term monitoring of encapsulation materials has not yet been addressed. Although various trials on large animals have been conducted, in-human trials to confirm the safety and efficacy of the fully encapsulated islets are still needed. Additional studies are also needed to understand the impact of different physiological conditions between people in order to tailor the functions of these implantable devices for personalized diabetic treatment.

In summary, the recent advances in wearable glucose sensors and implantable drug delivery systems have paved various approaches for expanding the treatment options for diabetes patients. A fully closed-loop system by coupling the wearable and implantable devices could enable a more reliable management plan for diabetics continuously and autonomously regardless of their daily routes. Given the urgent needs in diabetes care, future research in both wearable glucose sensors and implantable drug delivery systems remains critical.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

diabetes management, wearable sensors, implantable drug delivery devices, body fluids, glucose

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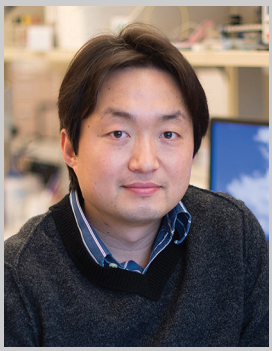

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