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Review

Recent Advances in Molecularly Imprinted Polymers for Glucose Monitoring: From Fundamental Research to Commercial Application

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Abstract: Molecularly imprinted polymers (MIPs) have gained growing interest among researchers worldwide, due to their key features that make these materials interesting candidates for implementation as receptors into sensor applications. In fact, MIP-based glucose sensors could overcome the stability issues associated with the enzymes present in commercial glucose devices. Various reports describe the successful development of glucose MIPs and their coupling to a wide variety of transducers for creating sensors that are able to detect glucose in various matrices. In this review, we have summarized and critically evaluated the different production methods of glucose MIPs and the different transducer technologies used in MIP-based glucose sensors, and analyzed these from a commercial point of view. In this way, this review sets out to highlight the most promising approaches in MIP-based sensing in terms of both manufacturing methods and readout technologies employed. In doing so, we aim at delineating potential future approaches and identifying potential obstacles that the MIP-sensing field may encounter in an attempt to penetrate the commercial, analytical market.

Keywords: glucose sensing; molecularly imprinted polymers; artificial receptors; glucose monitoring; non-enzymatic glucose sensors; clinical analysis; health diagnostics

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1. Introduction

1.1. Glucose Sensing

Glucose plays a key role in numerous biological processes, such as cellular respiration and glycosylation [1,2]. Once its metabolism is disturbed, it may lead to a variety of diseases, such as hyperinsulinism and diabetes [3,4]. The latter is characterized by a high concentration of glucose in the blood and other physiological fluids (hyperglycemia). Classical diabetes diagnostic tests, therefore, aim at directly assessing glucose levels in the blood of patients. More specifically, when the sugar concentration is higher than 7 mmol L^{-1} after no caloric intake for a minimum of 8h or higher than 11.1 mmol L^{-1} two hours after an oral glucose tolerance test (OGTT), the individual is considered to be affected by diabetes [5].

Diabetes is an incurable disease that causes a plethora of symptoms, including increased thirst and hunger, diabetic ketoacidosis, or hyperosmolar coma [6]. However, it does not only cause different discomforts, but is also responsible for severe long-term complications, such as kidney failure, stroke, and coronary heart disease [6,7]. For these reasons, the World Health Organization (WHO) classifies it as one of the top ten causes of death in adults [8]. Unfortunately, this condition has become increasingly more common and predictions estimate that by 2045, the number of sufferers will reach 693 million adults [9]. Due to the potentially life-threatening consequences of hyper- and hypoglycemia, it is

crucial that diabetics monitor their blood glucose levels closely and adjust their diet and insulin therapy accordingly. This has led to the emergence and spread of several low-cost biosensor technologies, such as glucose meters, that enable patients to self-monitor their blood glucose levels. These devices have become indispensable in diabetes management in the current society [10,11].

Before advancements in blood glucose monitoring were introduced, analysis was carried out using urine samples. Most of these tests were based on the technology developed by Benedict in 1908, which relied on the oxidation of glucose in the urine sample by a copper reagent [12]. In 1962, an enzyme membrane electrode system based on glucose oxidase (GOx) was introduced that allowed for the direct electrochemical detection of glucose in whole blood samples [13]. This breakthrough led to the development of the first commercial glucose meter in the 1970s [14], which gradually evolved over the past few decades into the first continuous glucose monitoring (CGM) system that was introduced in 1999 [15]. Over the years, three generations of enzyme-based sensors have been fabricated and commercialized (Figure 1) [16].

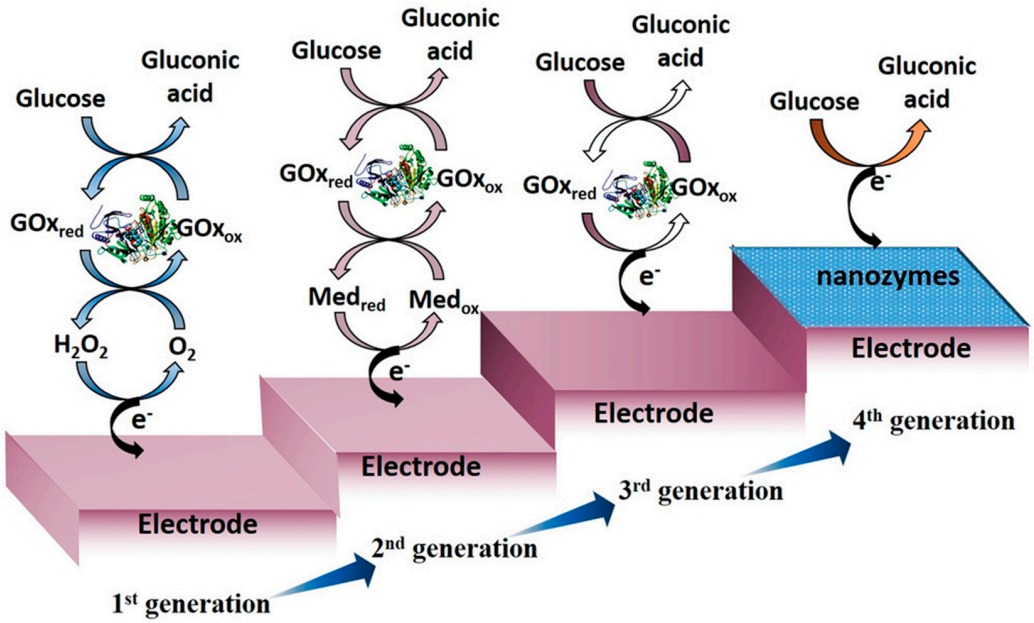

Figure 1. Schematic representation of the working principle of different generations of electrochemical glucose sensors. Figure reproduced with permission from ref. [16].

The first-generation system used oxygen as the electron acceptor. The main drawback of these systems is the influence of dissolved oxygen in the blood samples, which may compromise the accuracy of the measurement [17]. To overcome this issue, a second generation of sensors was created, relying on electron transfer from the enzymes to artificial electron receptors (redox dyes) [18]. To eliminate any intermediate steps, the third generation of sensors utilizes direct electron transfer to the electrode [19]. Currently, the market is in the process of evolving towards a fourth generation of glucose sensors that will not make use of enzymes (Figure 1) [20]. These new technologies can overcome the stability issues associated with enzyme-based sensors, but could also offer advantages in terms of cost-effectiveness and selectivity [21,22].

All medical procedures, including diagnostic tests, can be categorized into the following two major groups: invasive and non-invasive procedures. In glucose monitoring, this often depends on the physiological sample under study [23]. Invasive glucose monitoring implies that the samples in which the glucose levels are measured can only be obtained by puncturing the skin of a patient [24]. For instance, in traditional self-monitoring of blood glucose (SMBG), a drop of blood is drawn from the fingertip of a patient [25]. Many

development studies were performed to optimize this procedure to reduce the pain associated with the measurement, resulting in the use of a blood lancet rather than a traditional needle and syringe [26]. However, this method still causes discomfort and increases the risks of blood-related infections [27]. Therefore, there has been a shift in the research focus towards the development of minimally invasive and non-invasive methods in recent years, although invasive blood glucose monitoring is still the most widely spread commercial approach [28,29]. Non-invasive glucose monitoring typically aims at measuring the glucose concentration in other physiological fluids, such as urine, saliva, sweat, or tears, and relating them to the current blood glucose levels [30]. The increased comfort that these methods offer patients also enables us to increase the number of measurements, opening up the possibility of creating new-generation systems for continuous monitoring [31]. Both the invasive and non-invasive methods can be analyzed with different readout technologies, including electrochemical, mass-sensitive, optical, and thermal methods, with electrochemical transducers being the most used [32]. Since the topic has attracted increasing interest, and due to the benefits of non-invasive monitoring, innovative glucose biosensor technologies have been continuously explored. In fact, numerous studies reported in the last few years have focused on the development of novel wearable sensors that would enable patient-oriented, rapid, and convenient tracking of glucose [33–35]. Such sensors could be incorporated in, for instance, smartwatches [36]. However, the most important challenge associated with the current-generation blood glucose monitoring techniques is the specificity and stability of such sensors in different physiological matrices [37]. A crucial step to overcome these issues lies in the development of new recognition materials that can offer alternatives to the current enzyme-based sensors. Therefore, this review will focus on reviewing the current advances in molecularly imprinted polymers (MIPs) for glucose detection and critically assessing which approaches are the most compatible with the current trend of evolving toward non-invasive glucose monitoring.

1.2. General Background on MIPs

Molecularly imprinted polymers (MIPs) have attracted wide interest over the last few decades, as these materials can mimic the natural antibody–antigen and enzyme–substrate systems, but overcome most of the issues that are commonly encountered when using natural receptors in non-physiological conditions [38]. The general principle behind MIP synthesis is the interaction between a target molecule, a functional monomer, and a cross-linking agent. First, the functional monomer(s) and the target molecules form a complex by interactions between their functional groups [39], then the cross-linker stabilizes the complex and is responsible for the rigidity of the polymer. After extraction of the template molecule, nanocavities that are complementary to the extracted molecule are formed (Figure 2) [40]. This complementarity is both morphological and structural, ensuring that the target can selectively rebind to the receptor, which is similar to the key-and-lock mechanism that antibodies and enzymes use to detect their target [41].

Molecularly imprinted polymers can be synthesized using a wide variety of polymerization approaches, including bulk, precipitation, emulsion, photopolymerization, and electropolymerization [42]. Normally, MIPs do not possess signal output ability, which means that they need to be coupled to an appropriate transducer technology to translate the rebinding event into a readable signal [43]. Different works have demonstrated the successful integration of the polymers with several readout technologies, including, but not limited to, the heat-transfer method (HTM), quartz crystal microbalance (QCM), surface plasmon resonance (SPR), surface-enhanced Raman scattering (SERS), chromatographic techniques and various electrochemical transducers [44–47].

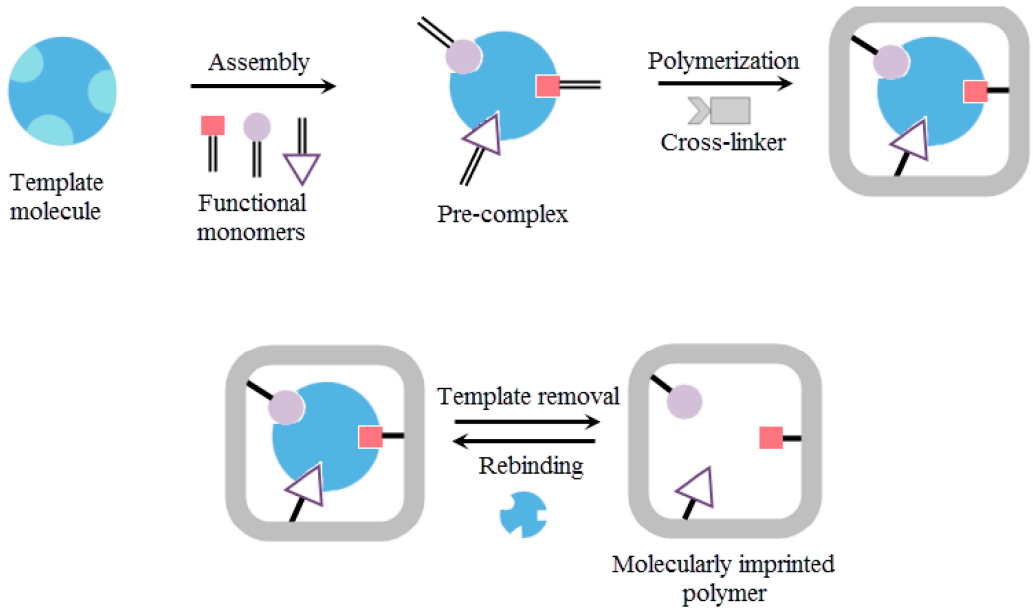

Figure 2. Schematic representation of generic synthesis and rebinding of molecularly imprinted polymers. Figure reproduced with permission from ref. [40].

From a historical perspective, MIPs were reported for the first time in the 1930s [48,49]. However, it was not until the mid-1980s that this technology started to attract wide interest among the scientific community with the works from K. Mosbach and G. Wulff [50–52]. Around ten years later, the first works focused on the use of MIPs in sensing technologies started to appear [52]. Since then, with the emergence of computational technologies and novel methods used to integrate imprinted polymers into readout technologies, MIP-based sensors have become increasingly popular within the scientific community [53,54]. Nowadays, MIP-based sensors are engineered in such a way that they can serve in a versatile array of environments, including physiological fluids [55], foodstuffs [56,57], and wastewater [58].

1.3. Advantages of MIP-Based Sensors in Glucose Sensing

Molecularly imprinted polymers (MIPs) are also known as plastic or synthetic antibodies because they represent a synthetic alternative to biological recognition elements typically found in biosensors [59]. Due to their synthetic nature, they have several key advantages over natural receptors, such as enzymes and antibodies, mainly resulting from their high stability and robustness at different pH and temperatures [60]. The enzyme-based sensors have low stability, which inevitably results in the short shelf-life of the final product [61]. As a result, the scientific community is increasingly moving toward the realization of novel enzyme-free sensors [62,63]. As mentioned above, stability is a key feature of imprinted polymers and consequently of MIP-based sensors; furthermore, their preparation entails a rather short and cost-effective synthesis process [64]. However, despite all the benefits that these materials can provide to the field of biosensors, the commercialization of MIP-sensors has not yet fulfilled its potential [65]. For instance, home test devices for glucose monitoring are still monopolized by glucose oxidase biometers, which measure the concentration of glucose in fingertip's blood [66].

With all the aforementioned assets that MIP-based technologies could provide, they may bring a new perspective to glucose monitoring. As mentioned earlier, we aim to categorize and evaluate the different MIP-based technologies for glucose detection developed in the last few years and assess their advantages and drawbacks in the framework of moving towards stable, disposable enzyme-free sensors for non-invasive blood glucose monitoring. We will critically assess which approaches are the most promising and which

manufacturing and transducer technologies would be ideally suited to bring MIP-based sensors closer to the commercial glucose monitoring market.

2. Production Methods of MIPs for Glucose Detection

In order to synthesize molecularly imprinted polymers, different reagents are required, including a functional monomer(s), template, cross-linker, and a polymerization initiator [67,68]. Their ratio with respect to one another greatly influences the specific interaction between the polymer and the template, and subsequently the binding capacity and imprinting factor of the resulting MIP [69,70]. Depending on the type of polymerization, initiators and solvents also play a vital role in the whole process [71]. Numerous polymerization techniques used to synthesize molecularly imprinted polymers have been explored in the last few decades (Table 1) [72,73], including bulk polymerization, electropolymerization, and photopolymerization [73–76]. More recently, MIPs have been used in combination with other materials such as gold nanoparticles to boost the sensitivity of the resulting sensor or nylon to open up the possibility of creating wearable glucose sensors [77,78]. Inevitably, a slightly different synthetic pathway needs to be employed for such sensors, often leading to additional steps in the fabrication process.

2.1. Reagents for the Production of MIPs

2.1.1. Functional Monomers

The role of the functional monomer is to create a complex with a template molecule before the polymerization [71]. Therefore, the selected monomer needs to be carefully chosen in order to maximize interaction with the template and create receptors with a high rebinding affinity to the target. Monomers that contain free carboxyl groups are of particular interest for creating non-covalent MIPs, as they can act as both hydrogen donors and acceptors and favour hydrogen bonding between the polymer and template [79]. Methacrylic acid (MAA), for example, has been extensively used as a monomer for MIP synthesis, due to its ability to form ionic interactions and hydrogen bonds with a plethora of functional groups on different template molecules [80]. Other functional monomers commonly used for the synthesis of MIPs are as follows: acrylamide (AAM), acrylic acid (AA), 4-vinylphenylboronic acid (VPBA), 4-vinylpyridine (4-VP), and pyrrole (PY) [81]. Additionally, the growing popularity of MIPs has resulted in the synthesis of novel tailor-made functional monomers, opening up the possibility of producing imprinted materials with higher rebinding capabilities.

Different functional monomers have also been successfully employed for the synthesis of glucose-imprinted polymers. The monomer choice is strictly linked to the synthetic approach undertaken to create the MIPs. For instance, a rational-design study in which Gaussian 2009 software was used to simulate the interaction between glucose and three commonly used functional monomers in free-radical polymerization (MAA, AAM, and 4-VP) revealed that MAA provides a stronger interaction with glucose, as well as the lowest energy value during the self-assembly phase [82]. However, another study conducted using the same program provided evidence that the reaction with AAM can occur more spontaneously than with MAA [83]. Different studies have subsequently reported the successful use of both MAA [82,84,85] and AAM [86,87], as well as its derivative diacetone acrylamide (DAAM) [88]. Other functional monomers employed in polymer synthesis included AA, which provided interactions with the hydroxyl groups of glucose [89], VPBA, which forms a covalent complex with the template [90,91], vinyl acetate [92], and 3-amino-4-hydroxybenzoic acid [93]. Electropolymerization of pyrrole to create glucose-imprinted MIPs was demonstrated as an alternative approach in an attempt to automatize the synthesis procedure [77,94]. The obtained MIPs were then coupled with nylon fibers [77] or nitrogen-rich carbon conductive-coated TNO structures, which opens up the possibility to integrate electropolymerized glucose MIPs in wearable applications [94].

2.1.2. Template

The vast majority of the synthetic approaches mentioned above employed D-glucose as template molecule [77,88–90,94]. However, as glucose lacks functional groups that enable strong interactions with acidic or basic monomers, more recently, a dummy imprinting approach was introduced by the authors of this paper, using glucuronic acid as a template (Figure 3) [87].

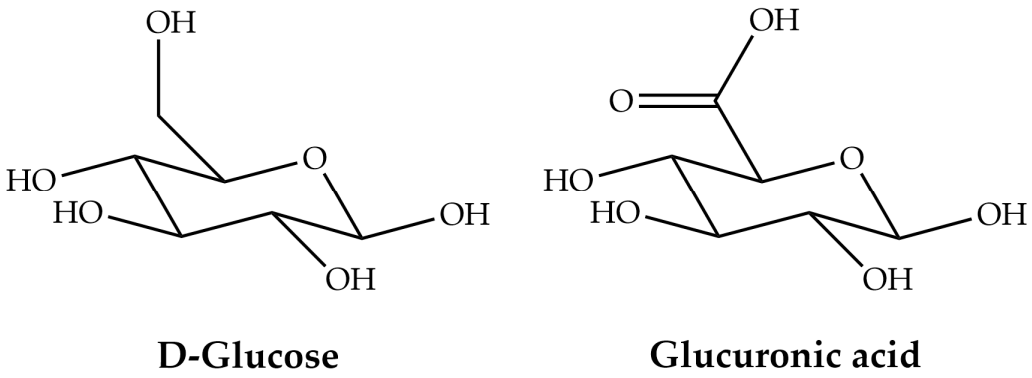

Figure 3. Chemical structures of D-glucose and glucuronic acid.

2.1.3. Cross-Linker

The role of the cross-linker is to enable the formation of a rigid polymer network, so its structure will not be changed by the template removal; hence, the binding sites will not be damaged. At the same time, this would allow the formation of a porous structure into which the targets can diffuse when immersing the MIP into the sample under study [95]. If the amount of cross-linking is too low, the polymer will not be mechanically stable, while if the cross-linking degree is too high, it may reduce the binding capacity of the polymer, as the target cannot penetrate into the polymer matrix and there will be fewer recognition sites available for rebinding [81]. The main drawback related to the cross-linker molecules employed for MIP fabrication is that while the rational design is often aimed at selecting functional monomers with appropriate hydrogen donor/acceptor properties, the cross-linker can also interact with the template and contribute to rebinding, a process that is hard to control and can lead to non-specific interactions. For the development of MIP-based glucose sensors, different cross-linkers were implemented and among these, the most commonly used is ethylene glycol dimethacrylate (EGDMA) [85,87–89]. Another reported cross-linker commonly used for the production of glucose MIPs is N,N′-methylenebisacrylamide [82,86,96].

2.2. Polymerization Methods Employed for Glucose-MIP Fabrication

2.2.1. Thermal Polymerization Approaches

One of the most used methods to produce MIPs is the thermally initiated bulk polymerization approach [97]. This straightforward technique consists of adding a template, functional monomer, cross-linker, and initiator in a solvent and allowing the formation of a pre-polymerization complex through self-assembly. The solution is then polymerized and the resulting product is a monolithic bulk polymer that needs to be ground and extracted with solvents. The interesting features of this approach from a commercial point-of-view are the fact that it is relatively straightforward and allows for the creation of large batches of material cost-effectively. The major drawbacks are related to the tedious grinding and sieving procedure, which is time-consuming, leads to a large loss of product and the generation of a heterogeneous mixture of micro-scaled particles, which increases the batch-to-batch variation and makes it hard to reliably calibrate the resulting sensors [97,98]. The approach has also been employed in the synthesis of MIPs for glucose detection [85,87]. Within this method, different initiators can be employed to trigger the polymerization reaction. As such, molecules such as azobisisobutyronitrile (AIBN) or benzoyl peroxide were used to

initiate the polymerization process. Another approach used to produce bulk MIPs included the oxidation of pyrrole by $FeCl_3 \cdot 6H_2O$, which initiated the formation of polypyrrole [77].

Thermally initiated polymerization can also be used to form thin polymer films; this approach allows the formation of MIP films directly onto the substrate. The approach has been used for the production of glucose MIP films on substrates such as Petri dishes [99] or Ni foam [82,96].

2.2.2. Precipitation and Emulsion Polymerization

To overcome the problems associated with free-radical monolithic bulk polymerization, research on more controllable polymerization methods used to create homogenous particles has intensified over the past decade. Precipitation polymerization is a popular approach in which the reagents are soluble in a solvent that is chosen in such a way that after the polymerization reaction is completed, the resulting polymer is insoluble, and therefore precipitates in the form of small particles [100].

Another popular approach is emulsion polymerization, a technique used to create spherical MIP beads of various dimensions that can be stringently controlled by optimizing the reaction conditions. In this method, surfactant molecules are added to the pre-polymerization mixture, resulting in the formation of spherical beads of surfactant that contain the reagents. The monomers act as oil phases that are shielded from the water phase (the solvent) by the surfactant and undergo cross-linking inside a microreactor, leading to more homogenous spherical particles with a tunable shape [100]. Both techniques have been used for the synthesis of MIP particles that were incorporated into sensing devices for glucose detection [84,92].

Although precipitation and emulsion polymerization have been demonstrated on an industrial scale for various other polymer applications, the creation of MIPs for glucose detection on a large scale is not particularly appealing. Emulsion polymerization would require extra purification steps to remove remnant surfactant and although the particles are more homogenous in size, research has shown that the binding affinity of the MIPs is highly heterogenic, as the formation of an emulsion affects the stability of template–monomer interactions during imprinting. Likewise, the very diluted medium in which precipitation polymerization takes place not only results in a low reaction yield, but also leads to an imprinting effect that is mainly based on several low-affinity interactions, leading to MIPs with limited binding affinity and significant batch-to-batch variance [101].

2.2.3. Electropolymerization

An interesting approach to synthesize molecularly imprinted polymer films that has gained increasing attention from researchers worldwide is electropolymerization. The technique is particularly interesting, as it allows the growth of polymer films in situ onto electrodes by applying electrochemical energy to the system [74]. The advantages over other methods are the high control of the layer thickness and the direct grafting onto the electrode surface [102,103], resulting in a homogeneous and highly reproducible MIP-functionalized substrate that can be used in electroanalysis [74]. This set of features means that they are serious alternatives to commercial enzyme-based electrodes for glucose sensing, as it would also be relatively straightforward to create large batches of MIP-covered chips in an automated manner. Several papers reported this polymerization technique to obtain electropolymerized MIPs for glucose sensing [94,104–106]. In a recent work, Bossard et al. synthesized a glucose MIP on laser-pyrolyzed paper electrodes using 3-amino-4-hydroxybenzoic acid (3,4-AHBA) as a functional monomer [93]. In another published work, Diouf et al. were able to fabricate a MIP-based screen-printed gold electrode by electropolymerizing AAM/N,N′-methylene bis(acrylamide) (NNMBA) in the presence of glucose (Figure 4). Selectivity analyses of the electropolymerized MIP sensor were carried out using two interfering analytes that coexist in physiological saliva samples, lactose and sucrose [86].

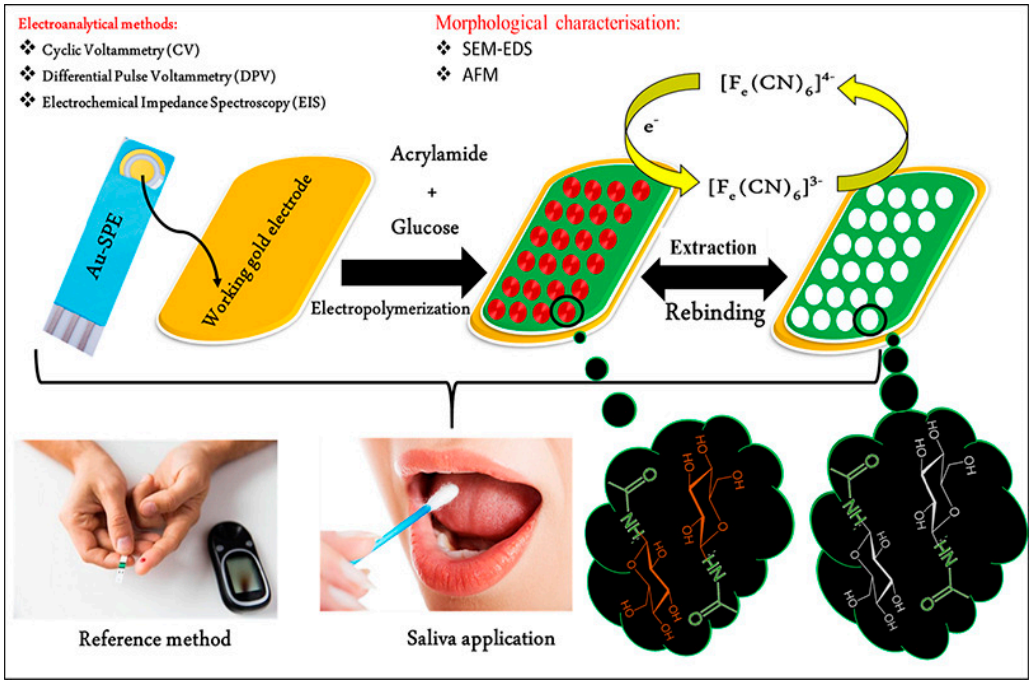

Figure 4. Fabrication of a MIP-based Au SPE by electropolymerizing AAM/NNMBA in the presence of glucose and its application in saliva samples. Figure reproduced with permission from ref. [86]. Copyright 2019, Elsevier.

Electropolymerization can also be used to generate gold nanoparticle-decorated MIPs, and the benefits of such a method were reported to be ultra-high sensitivity, cost-effectiveness, and fast fabrication [78]. Another innovation that stems from this production method is the modification of MIPs with carbon dots and chitosan, with Zheng et al. and Wu et al. proposing this modification and yielding highly sensitive and selective MIP-based electrochemical sensors [83,107]. The main drawbacks associated with electropolymerization are the possible low degree of cross-linking (which hinders the rigidity of the polymeric structure [108]), the limited choice of electro-active monomers (leading to the troublesome rational design of MIPs for certain specific targets) and the difficult up-scaling of the fabrication process (which inevitably results in a diminished commercial potential for such technologies) [65].

2.2.4. Electrospinning

Electrospinning is a method used to create matrices of micro- to nanoscopic fibers [109] that offer a very high surface-to-volume ratio, leading to MIPs with relatively high sensitivity in comparison to other approaches [110]. The technique also offers the possibility of creating wearable textiles into which MIPs can easily be integrated for continuous sensing [111]. In 2021 for instance, Crapnell et al. employed electrospinning to incorporate glucose MIPs into a nylon-based fiber (Figure 5). The findings of this study illustrate a two-step production method (MIP synthesis and electrospinning) for the development of MIP-based wearable glucose sensors that can monitor the amount of glucose in sweat as a marker for blood glucose levels [77]. In this work, Crapnell et al. assessed the sensor's selectivity by exposing the platform to a solution that contained similar molecules (fructose, galactose, and sucrose), in addition to some common constituents of sweat, including urea and L-lactate. The approach is also interesting, as it is possible to mass-produce batches of fibers in a relatively straightforward, fast, and low-cost manner. The MIPs, however, still need to be made via a separate polymerization approach; in this case, via the oxidation of pyrrole and pluronic P123 in bulk.

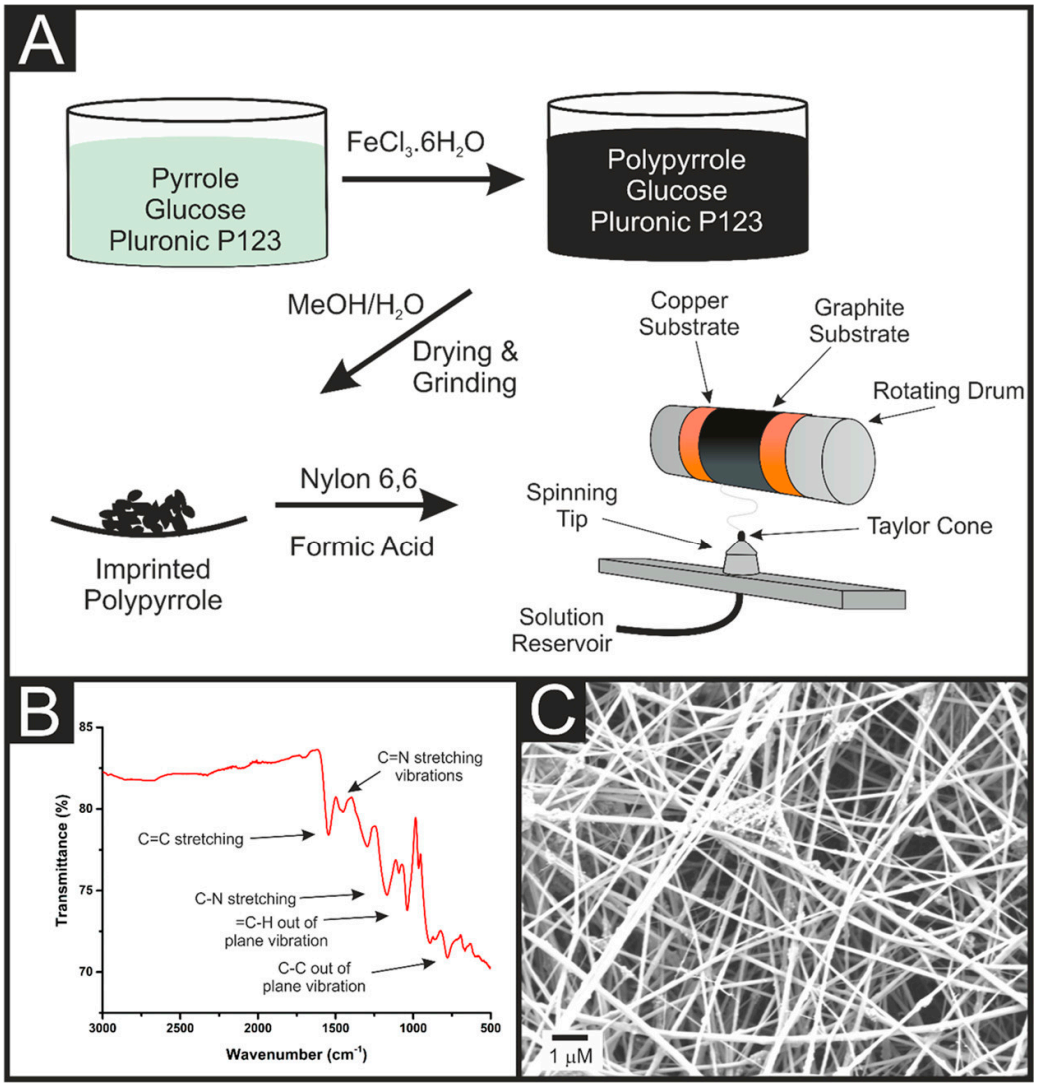

Figure 5. (**A**) Illustration of the production of electrospun MIP sensors. (**B**) FT−IR analysis of the polypyrrole MIP. (**C**) Image of electrospun nylon fibers embedded with PPy MIPs for the detection of glucose. Figure reproduced with permission from ref. [77]. Copyright 2021, American Chemical Society.

2.2.5. Photopolymerization

Photopolymerization is a technique that uses the energy of a light source to initiate a polymerization reaction. Although the approach is often similar to thermally induced polymerization techniques, it requires the use of different reagents. Depending on the specific approach applied, photoinitiators, photosensitive functional polymers, photo-cross-linkable polymers, and RAFT agents need to be employed in the process [112].

Similar to thermally induced bulk free-radical polymerization, photoinitiated free-radical polymerization is a widely used technique for MIP production. This approach requires a photoinitiator able to initiate the polymerization reaction when exposed to irradiation [113]. The technique has been reported for the synthesis of MIP films/coating for glucose recognition on various substrates, such as QCM electrodes [114], ITO glass plates [90], and stainless-steel wires [91].

Photosensitive functional polymers provide an opportunity to achieve a polymerization reaction without using an initiator reagent by using a photosensitive monomer. This approach has been implemented for the development of a MIP-based glucose electrochemical sensor, by exposing a gold electrode covered with a solution of photosensitive

monomers and target to UV irradiation [108]. In two different works, photo-cross-linkable polymers were used to obtain MIP micelles [115] or nanoparticles [116], which were then electrodeposited onto a bare gold electrode, and finally photo-cross-linked to obtain MIP-functionalized gold electrodes. The specific advantages of each imprinting approach are similar to those in thermally induced methods, allowing the detection of different targets as different polymers can be used, as well as targets that cannot withstand high temperatures. On the other hand, they suffer the same disadvantages that are described above for each polymerization approach and are not compatible with targets that are sensitive to irradiation with high-energy light sources.

Reversible addition–fragmentation chain transfer (RAFT) living polymerization is a photopolymerization approach that allows us to stringently control the polymerization parameters and can be achieved under mild conditions at room temperature in aqueous solutions [117]. RAFT polymerization has been utilized by Zhu et al. for the synthesis of glucose-imprinted polymer particles, with sizes ranging from 200 to 400 nm. The produced MIPs have proven to be effective in detecting glucose in complex matrices, such as human urine samples [88].

2.2.6. Novel Synthetic Approaches for Glucose MIPs

The above-mentioned techniques represent the most used techniques for the production of molecularly imprinted polymers. However, in recent years, novel approaches for MIP synthesis have been developed. Between these, the most promising approach is undoubtedly the so-called solid-phase synthesis of nanoMIPs proposed by the group of Prof. Piletsky [118]. This technique has proven its high industrial potential, as it has been utilized in the successful imprinting of a wide variety of targets by using an automated synthesis protocol [118]. The method has also been employed for the fabrication of electroresponsive nanoMIPs for glucose recognition [119].

Additionally, another approach employed for producing MIP-based glucose sensors involves the production of cross-linked MIP micelles, which were then coupled to glucose oxidase to develop a novel synergistic enzyme MIP detection system [120].

Table 1. Fabrication methods and modifications employed for the production of MIP-based sensing materials for glucose recognition.

Production Method	Approach Modification	Real-Life Sample	LoD	Reference
Thermal polymerization	MIP particles immobilized onto Al-PVC substrate	Urine	PBS: 19.4 µM Urine: 44.4 µM	[87]
Thermal polymerization	MIP-based working electrode	-	43.7 ± 1.6 mV/mmol L^{-1}	[85]
Thermal polymerization and electrospinning	MIP particles electrospun into nylon 6,6 fiber	Artificial sweat	PBS: 0.10 ± 0.01 mM Artif. sweat: 0.12 ± 0.01 mM	[77]
Thermal polymerization	MIP particles drop-casted onto an Au electrode	-	4.4 mg L^{-1}	[89]
Thermal polymerization	-	Artificial tear fluid	10 µg mL^{-1}	[99]
Thermal polymerization	MIP@Ni foam	-	-; 0.45 mM	[82,96]
Precipitation polymerization	GO-MIP sensor	Blood	PBS: 0.02 µm	[84]
Suspension polymerization	MIP-based working electrode	-	53 µM	[92]
Electropolymerization	AuNP-MIP fabricated directly on the gold wire	Blood	PBS and blood: 1.25 nM	[78]
Electropolymerization	MIP-based Au-SPE	Saliva	PBS: 0.59 µg mL^{-1} Saliva: 3.32 µM	[86]

Table 1. *Cont.*

Production Method	Approach Modification	Real-Life Sample	LoD	Reference
Electropolymerization	MIP-based SPCE	Saliva and blood	PBS: 0.19 ± 0.015 µM Saliva and blood: -	[104]
Electropolymerization	MIP/CuCo/SPCE	Artificial and whole blood	PBS: 0.65 ± 0.10 µM Art. blood: 12.02 ± 0.6 mg dL^{-1} Whole blood: -	[105]
Electropolymerization	Electrode modified with chitosan and carbon dots	Blood	PBS: 0.09 µM Blood: 0.11 µM	[107]
Electropolymerization	Laser-pyrolyzed paper substrate	-	1.77 mmol dm^{-3}	[93]
Electropolymerization	Electrode modified with chitosan and carbon dots	Blood and rice wine	PBS: 4.6 nM Blood: 6.41 nM Rice wine: -	[83]
Electropolymerization	CS (MIP)-NiO electrode	-	2.0 µM	[106]
Electropolymerization	TNO substrate	-	1.0 µM	[94]
Photopolymerization	MIP layer onto Au QCM electrode	-	0.07 mM	[114]
Photopolymerization	MIP layer onto ITO glass plate	-	-	[90]
Photopolymerization	MIP coating onto stainless-steel wire	Bovine serum, human urine and plant tissues	PBS: 0.7 µM Real-life samples: -	[91]
Photopolymerization	RAFT polymerized MIPs coating onto GO/GCE substrate	Urine	PBS: 5.88 µM Urine: -	[88]
Photopolymerization	MIP micelles electrodeposited onto the electrode surface	Simulative serum	Buffer: 0.05 mM Sim. serum: -	[115]
Photopolymerization	Photo-cross-linkable polymer	Simulative serum	Buffer: 0.2 µg mL^{-1} Sim. serum: -	[108]
Photopolymerization	Au@MIP NPs electrodeposited onto the electrode surface	Urine	Buffer: 0.003 nM Urine: -	[116]
Solid-phase synthesis	-	-	0.43 mM	[119]
Cross-linked MIP micelles	Fe_3O_4@Au-GOx-MIPs catalytic system	-	5.0 µM	[120]

3. Readout Technologies Employed for MIP-Based Glucose Detection

In order to convert the binding event between the MIP and target into a readable signal, the imprinted polymer needs to be integrated into a sensor platform, by coupling it to an appropriate readout technology [121]. The choice of the transducer employed for signal conversion is crucial for the development of affordable and reliable biosensors; in fact, many examples of very sensitive MIP-based sensors can be found in the literature, but some of them are coupled with highly specialized and costly lab equipment. These sensor technologies are interesting for high-end detection purposes in analytical labs but are less suited for application in point-of-care diagnosis. The great commercial success of glucometers is due to the fact that they are based on simple conductio- or amperometric transduction principles that can be integrated into handheld applications. Furthermore, they are easily calibrated and lead to a very simple concentration reading that enables end-users to measure their blood glucose levels in a fast, relatively low-cost, and user-friendly manner [10,122]. Since the introduction of the first generation of glucose biosensors, remarkable progress in the development of miniaturized and low-cost glucose sensing technologies, both in terms of substrates (e.g., test strips) and transducers (glucometers), has been made [123,124]. Despite different works reporting novel MIP-based sensors for glucose and many other analytes, the field seems to struggle in the last steps toward the commerciality of such technologies [65]. One of the main explanations for this is the greater interest of the scientific community in fabricating more and more sensitive biosensors,

rather than trying to engineer promising technologies to develop more affordable and versatile instruments that offer a commercial benefit to the end-users. In this sense, the most sensitive MIP-based sensors in real-life samples have a limit of detection (LoD) of 1.25 nM in blood [78], 0.12 mM in artificial sweat [77], 3.32 µM in saliva [86], 44.4 µM in urine [87], and 55.5 µM in artificial tear fluids [99]. Although the most sensitive MIP-based glucose sensor found in the literature demonstrates a much lower LoD in buffer solutions [116] (0.003 nM) when compared to the above-mentioned works, the fabrication of an ultrasensitive device for glucose detection represents an academic exercise rather than a useful development in health diagnostics. In fact, the concentrations of the sugar in physiological fluids are in the millimolar or micromolar range.

The majority of readout technologies employed for glucose detection using MIPs continued on the tradition of using electrochemical transducer principles to create user-friendly readout technology [125]. The specific techniques that were used include amperometry, voltammetry, potentiometry, and electrochemical impedance spectroscopy. Although electrochemical readouts represent the most validated transducer in the glucose sensing field, in the last few years, different alternative technologies have been successfully coupled to MIP-based platforms for the detection of sugars [126]. Therefore, MIP sensors for glucose that use transducers such as QCM [114], HTM [87], SPR [127], GC-MS [91], and fluorescence spectroscopy [99] have started to appear in the last two decades.

3.1. MIP-Based Electrochemical Glucose Sensors

Electroanalytical techniques are a collection of different methods that use electrical stimulation to study surface changes upon rebinding of an analyte or the presence of the analyte in solution. As mentioned, the classic glucometers employ amperometry coupled with an enzyme that is able to selectively oxidize glucose; the techniques have also proven their efficacy when coupled to a MIP-based platform [128,129]. In particular, MIP-based amperometric glucose sensors have been fabricated by preparing molecularly imprinted polymer layers onto different types of electrodes [93,105,106]. Cho et al. have reported the fabrication of a selective MIP glucose sensor based on the direct oxidation of the molecule on a bimetal catalyst with a MIP (Figure 6). In this work, the sensor proved to be highly sensitive and demonstrated excellent performance in artificial and whole blood samples using chronoamperometry analysis. Moreover, the selectivity of the MIP-based platform was thoroughly evaluated by the exposure of the sensor to a wide variety of possible interferences (uric acid, acetaminophen, dopamine, ascorbic acid and L-cysteine), other monosaccharides (galactose, mannose, fructose, and xylose) and disaccharides (sucrose, lactose, and maltose) [105].

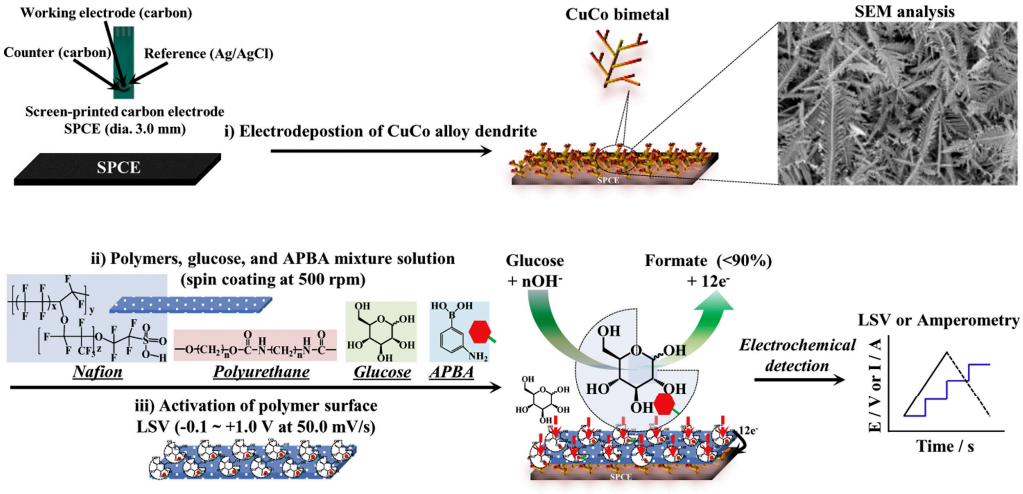

Figure 6. Representation of the glucose-imprinted polymer preparation and the two electrochemical readouts employed for the rebinding studies. Figure reproduced with permission from ref. [105]. Copyright 2018, Elsevier.

In MIP-based potentiometric sensors, generally, the MIP is incorporated into a polymeric membrane and then functions as a conventional ionophore of ion-sensitive electrodes [130]. As such, many works about potentiometric MIP sensors have been reported [130,131]. Between these, some research groups have demonstrated the applicability of potentiometric MIP sensors for glucose detection in buffer solutions [85], as well as in physiological samples, such as saliva and blood [104].

Many MIP-based electrochemical biosensors use voltammetry as an electroanalytical method to detect a specific analyte [132–134]. Voltammetric sensors can recognize a target by analyzing the current change as a function of the potential applied. Voltammetry can then be subdivided into many different types of techniques, depending on the mode of potential control. As such, techniques such as cyclic voltammetry (CV) [84,90,92,107,115,120], linear sweep voltammetry (LSV) [105], square wave voltammetry (SWV) [78,88,108], differential pulse voltammetry (DPV) [83,86,94,107,119] and differential pulse stripping voltammetry (DPSV) [116] have been successfully applied in combination with MIP-based technologies for glucose analysis. In these sensors, the MIP acts as a recognition element that is able to selectively bind to the functionalized surface, resulting in a current change when a potential is applied. An unusual approach using a voltammetric MIP sensor has been employed by Cheng et al. (Figure 7); in this work, a synergistic enzyme–enzyme mimic (represented by the imprinted polymer) system has been developed and the sensor's performance was thoroughly evaluated using CV voltammetry. The fabricated sensor has proven to be highly selective towards D-glucose over three other structural analogues of the sugar (mannose, galactose and D-xylose).

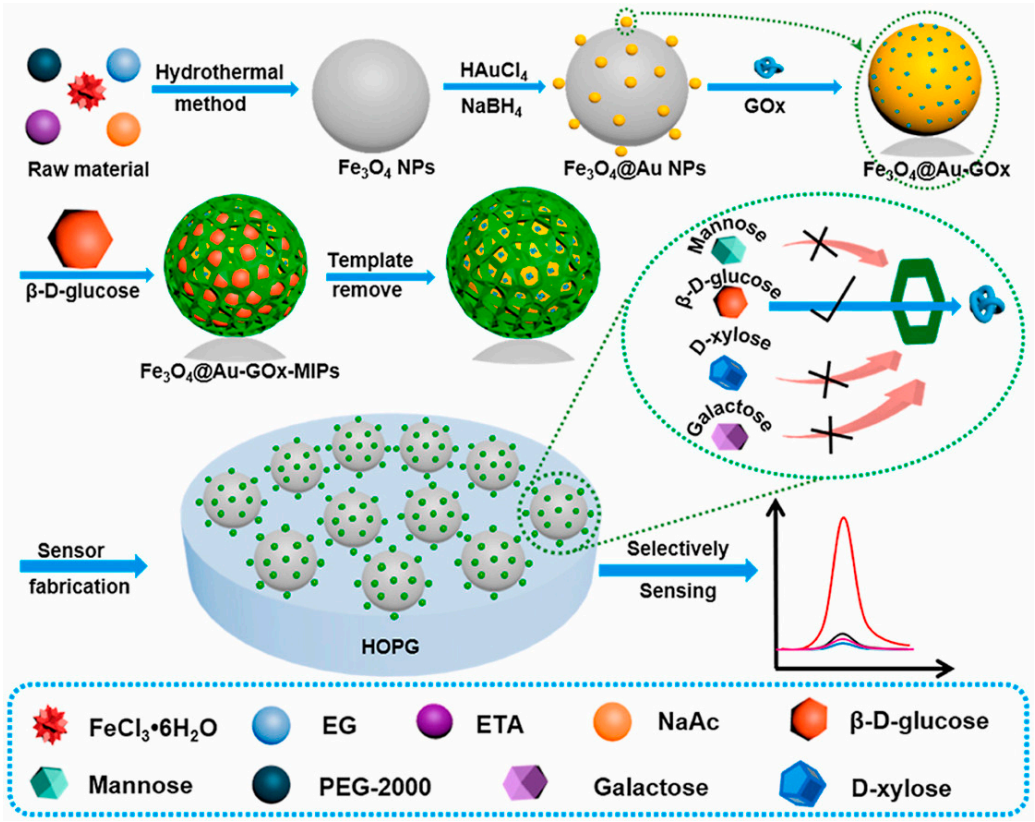

Figure 7. Preparation of the Fe_3O_4@Au-GOx-MIPS sensor and representation of the sensing mechanism achieved with CV analysis. Figure reproduced with permission from ref. [120]. Copyright 2022, Elsevier.

Another electrochemical method used in MIP biosensors that has gained attention in the last few years is electrochemical impedance spectroscopy (EIS) [135]. Impedimetric MIP biosensors allow the direct detection of a target without using any enzyme labels by

measuring changes in charge conductance and capacitance at the sensor surface when the binding event occurs [135,136]. Thus, different impedimetric sensors for non-enzymatic glucose recognition have been developed in the last five years [82,86,96]. Even though several MIP-based electrochemical sensors for glucose detection have demonstrated to be a promising and reliable alternative to enzymatic devices (Table 2), factors such as their reproducibility in relevant environments and application in different physiological matrices still need to be addressed. In general, electrochemical MIP-based glucose sensors can build on the knowledge obtained in the decades of development in electrochemical enzyme-based glucose sensing. Furthermore, by coupling electrochemical readouts to electrodeposition techniques or electrospinning, there is the potential to use them for continuous monitoring. With this in mind, MIPs function in a different manner than enzymes and no ions are created during binding. Therefore, the effects are usually capacitive and require a reference electrode to distinguish rebinding effects from solvent exchange effects. This makes data interpretation and calibration more difficult. In addition, they require some instrumentation and can only be combined with electrically conducting chip substrates. Therefore, in contrast to enzyme-based glucose monitoring, where electrochemical approaches have shown to be the most suitable tool, in MIP-based glucose sensing, other non-electrochemical approaches might offer certain benefits from a commercial perspective that allow them to become the most predominantly used technology.

Table 2. MIP-based glucose sensors using electrochemical readout technologies.

Readout Technology	Real-Life Sample	LoD	Reference
Chronoamperometry	-	1.77 mmol dm^{-3}; 2.0 µM	[93,106]
Chronoamperometry	Artificial and whole blood	Art. blood: 12.02 ± 0.6 mg dL^{-1} Whole blood: -	[105]
Potentiometry	-	43.7 ± 1.6 mV/mmol L^{-1}	[85]
Potentiometry	Saliva and blood	PBS: 0.19 ± 0.015 µM Saliva and blood: -	[104]
CV	-	0.02 µM;–; 53 µM; 0.09 µM; 5.0 µM	[84,90,92,107,120]
CV	Simulative serum	Buffer: 0.05 mM Sim. serum: -	[115]
SWV	Simulative serum	Buffer: 0.2 µg mL^{-1} Sim. serum: -	[108]
SWV	Human urine	PBS: 5.88 µM Urine: -	[88]
SWV	Blood	1.25 nM	[78]
DPV	-	1.0 µM; 0.43 mM	[94,119]
DPV	Blood	PBS: 0.09 µM Blood: 0.11 µM	[107]
DPV	Blood and rice wine	Blood: 6.41 nM Rice wine: -	[83]
DPV	Saliva	PBS: 0.59 µg mL^{-1} Saliva: 3.32 µM	[86]
DPSV	Human urine	Buffer: 0.003 nM Urine: -	[116]
EIS	-	-; PBS: 0.59 µg mL^{-1} Saliva: 3.32 µM; 0.45 mM	[82,86,96]

3.2. Other MIP-Sensing Readout Technologies for Glucose Detection

Molecularly imprinted polymers are versatile materials that could be integrated into a wide array of non-electrochemical transducers [52,137]. In fact, different works have shown the potential of MIP-based sensors associated with readout technologies that rely on optical, thermal and mass-sensitive methodologies (Table 3) [137].

The first MIP for glucose recognition was developed more than a decade ago by Parmpi et al.; in this work, molecularly imprinted hydrogels were synthesized and their rebinding capabilities were analyzed colorimetrically by using a spectrophotometer [138].

Another colorimetric method (DNS assay) was successfully employed to evaluate the separation of different sugars from urine samples using imprinted polymers [139]. Although these early applications of colorimetric assays gave a deeper understanding of the binding characteristics of the synthesized polymers, they are not suited for diagnostic applications and, in the case of the latter, were mainly used as separation materials rather than sensing elements [140]. Other optical-based technologies have been effectively employed in combination with imprinted polymers, where the MIP film was directly analyzed via different techniques. In two different works, MIP films selective for glucose recognition were prepared onto a gold layer and proof-of-applications in plant tissues or urine were achieved by Raman spectroscopy [141] and surface plasmon resonance (SPR) [127], respectively. Another example of optical readout coupled with MIPs for glucose detection was reported by Manju et al. In this work, a fluorescent MIP film was found to proportionally emit reduced fluorescence with increasing concentrations of glucose in synthetic tear fluids [99]. Optical transducers offer the benefit that they have been used extensively over the past few decades for the highly sensitive detection of numerous compounds in the most advanced analytical applications. For glucose detection, however, they are not suited due to their non-portable and expensive nature. On the other hand, very cheap lateral flow assays, which have also demonstrated great commercial biosensor success, in addition to glucometers (COVID-19 self-tests, pregnancy tests, etc.), have limited application in glucose sensing as they are often qualitative (providing a positive/negative result), while diabetics need to quantify the result. Therefore, the only approach that seems commercially interesting is to work with colorimetric detection principles that allow for quantification by means of a simple handheld spectrophotometer, or even a smartphone camera with an appropriate software package.

Recently, a thermal readout principle that is similar to electrochemical approaches but requires less expensive machinery and offers straightforward data interpretation has been demonstrated for glucose detection (Figure 8). Two studies performed by two different research groups have shown different MIP synthesis approaches and have coupled them to the so-called heat-transfer method (HTM) for the detection of the sugar in artificial [77], as well as physiological, samples [87]. In one of these works, selectivity analyses were performed by analyzing the thermal response of the sensor to three different saccharides (fructose, lactose and sucrose) and demonstrated the sensor's ability to discriminate between these small molecules [87]. The approach is very simple, as glucose MIPs are immobilized onto a cheap chip substrate, and a temperature gradient is applied over the chip using two thermometers and a heat source. Rebinding of glucose leads to a concentration-dependent change in this gradient. The method is extremely low-cost, requiring little to no equipment and data interpretation is very simple, leading to facile calibration. The main problem with HTM as readout technology resides in the difficult miniaturization of the transducer and the need to equilibrate the signal, which, therefore, limits its application in wearable applications for continuous monitoring.

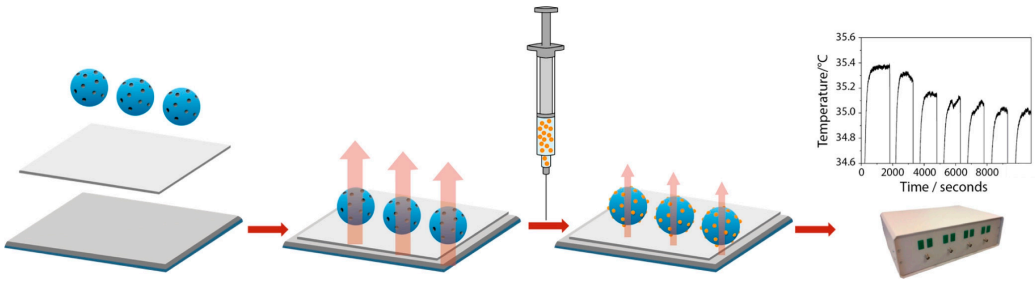

Figure 8. Representation of HTM analysis after glucose rebinding to the MIP-based platform. Figure reproduced with permission from ref. [87].

In a work from 2016, a MIP biocompatible probe was developed and coupled with GC-MS for specific glucose monitoring in bovine serum, human urine and plant tissues

(aloe leaf) [91]. Although the work demonstrates the successful application of the probe in different matrices, the coupling with a technology such as GC-MS highly limits the possibilities of the sensors, due to the costs and the need for trained professionals to operate the instrument. Another non-electrochemical readout technology effectively employed in recent years in the field of MIP-based sensing is quartz crystal microbalance (QCM) [44]. Mass-sensitive devices have been used by two different research groups in combination with MIP-coated QCM chips for glucose detection [89,114]. Although linear dose–response curves were obtained with increasing sugar levels, a real-life sample application is needed to accurately evaluate the sensor's performance in a relevant environment. Moreover, QCMs are hard to miniaturize and mass produce, require gold-coated quartz substrates, which are relatively costly, and it is hard to distinguish specific rebinding from non-specific adsorption and medium change, making this approach a little less attractive from a commercial point of view.

Table 3. MIP-based sensors coupled with non-electrochemical readout technologies.

Readout Technology	Real-Life Sample	LoD	Reference
Raman	Apple	PBS: 1 μg mL^{-1} Apple: -	[141]
SPR	Urine	-	[127]
Fluorescence spectroscopy	Artificial tear fluid	10 μg mL^{-1}	[99]
HTM	Artificial sweat	PBS: 0.10 ± 0.01 mM Artif. sweat: 0.12 ± 0.01 mM	[77]
HTM	Urine	PBS: 19.4 μM Urine: 44.4 μM	[87]
GC-MS	Bovine serum, human urine and plant tissues	PBS: 0.7 μM Real-life samples: -	[91]
QCM	-	4.4 mg L^{-1}; 0.07 mM	[89,114]

4. Promising MIP-Based Technologies for Glucose Sensing

The success of enzyme-based home glucose monitoring can be explained by the fact that there was a large market need, as diabetics previously had no means of routinely assessing their blood glucose levels. This has led to a significant improvement in diabetic treatment and, as a result, the life quality of patients. Since their conception, electrochemical enzymatic glucose sensors have evolved tremendously and have dominated the market. Nonetheless, as the need for continuous monitoring devices and cheaper handheld solutions will continue to increase in the coming years, research towards new and improved ways of measuring glucose will also continue. Therefore, some of the MIP-based glucose sensors developed in the last few years could offer a valid alternative, especially in certain subfields that require specific device characteristics. Although MIPs and MIP sensors are still considered by many as a niche research area, mainly because of the absence of MIP sensors on the market, we conclude that some promising studies on MIP glucose sensors are present in the literature and should be further evaluated to reduce the gap with traditional enzymatic sensors (Table 4).

The different characteristics of the sensor should be taken into account when analyzing the valorization potential of a sensing device. The major bottleneck in terms of commercialization in MIP-based glucose sensing lies in the synthesis approach of the receptors. Mass production is still largely missing with regard to MIPs, although several methods could offer a solution in the future. Bulk polymerization could be an interesting approach if the heterogeneity can be addressed or accounted for through calibration. However, the process of grinding, sieving, and extraction should be optimized and automated. More controlled approaches of photo- and thermal polymerization might overcome the heterogeneity issue in the future, but at this point, the yield of these approaches needs to be approved to make these approaches commercially viable. A potential solution might be to integrate the MIPs directly into a sensing substrate. This can be achieved by directly immobilizing the MIPs

onto an electrically conducting surface through electropolymerization or by impregnating MIPs into fibers by, e.g., electrospinning or electrodepositions. Both methods are currently not scalable and additional research has to be conducted, but one can envision that it should be possible to automate the production process and produce large batches of homogenous MIP-covered chips. For now, the synthesis approach that appears to be the most mature in terms of commercialization is the solid-phase approach that can be automated in a reactor. The reaction yield needs to be improved, but significant progress has been made in this respect in recent years.

Table 4. Overview of promising MIP technologies for glucose sensing.

Readout Technology	MIPs Production Method	Real-Life Sample	LoD	Reference
Chronoamperometry	Electropolymerization	Artificial and whole blood	Art. blood: 12.02 ± 0.6 mg dL^{-1} Whole blood: -	[105]
Potentiometry	Electropolymerization	Saliva and blood	PBS: 0.19 ± 0.015 µM Saliva and blood: -	[104]
CV	Photopol. + electrodeposition	Simulative serum	Buffer: 0.05 mM Sim. serum: -	[115]
SWV	Photopolymerization	Simulative serum	Buffer: 0.2 µg mL^{-1} Sim. serum: -	[108]
SWV	Photopolymerization (RAFT)	Human urine	PBS: 5.88 µM Urine: -	[88]
SWV	Electropolymerization	Blood	1.25 nM	[78]
DPV	Electropolymerization	Blood	PBS: 0.09 µM Blood: 0.11 µM	[107]
DPV	Electropolymerization	Blood and rice wine	Blood: 6.41 nM Rice wine: -	[83]
DPV	Electropolymerization	Saliva	PBS: 0.59 µg mL^{-1} Saliva: 3.32 µM	[86]
DPV	Solid-phase synthesis	-	0.43 mM	[119]
DPSV	Photopol. + electrodeposition	Human urine	Buffer: 0.003 nM Urine: -	[116]
Fluorescence spectroscopy	Thermal polymerization	Artificial tear fluid	10 µg mL^{-1}	[99]
HTM	Thermal polym. + electrospinning	Artificial sweat	PBS: 0.10 ± 0.01 mM Artif. sweat: 0.12 ± 0.01 mM	[77]
HTM	Bulk polymerization	Urine	PBS: 19.4 µM Urine: 44.4 µM	[87]

Although the scalability of the MIP synthesis procedure entails the largest bottleneck concerning their commercialization, transducers undoubtedly play a key role in the development of competitive glucose sensors. Expensive and inaccessible transducers (e.g., GC-MS, Raman spectrometers, SPR systems, etc.) are greatly disadvantaged in the development of PoC sensors, which is the main application for glucose sensors. Therefore, affordable and miniaturized readout technologies represent the election choice and between these, electrochemical readout technologies have made astonishing improvements in terms of affordability, miniaturization, and reliability. They profit from the commercial advances made in enzyme-based sensing and are compatible with some of the most promising MIP synthesis approaches, allowing for continuous monitoring approaches. Optical readout techniques, as mentioned before, are typically either very sensitive and used for lab-based sample analysis or extremely low-cost and user-friendly and used for qualitative diagnosis. However, as illustrated in the study mentioned in the table above, it would also be possible to use a handheld optical detector. In this case, a fluorescent spectroscopy approach was tested, which technically could be used for handheld sensing, but the requirement of an excitation source and fluorescent labels/monomers makes the technology more sensitive and also probably more expensive than electrochemical alternatives. A colorimetric alterna-

tive could offer a solution to this problem in the future. The relatively new HTM approach also has its benefits, mainly laying in the minimum amount of instrumentation required and the straightforward data interpretation, but miniaturization still has to be achieved and researched.

Despite the fact that none of the MIP-based glucose sensors are at the stage of commercialization yet due to the bottlenecks discussed above, the performance of these sensors is rapidly increasing. Some of them reach sensitivities that are superior to those of enzyme-based platforms at a much lower cost, not only achieving detection in blood, but also in other matrices such as urine and sweat. As we move towards the non-invasive monitoring of glucose, these bodily fluids offer several advantages. The concentration in these samples is typically lower, but the MIP-based sensors have proven to have linear ranges in relevant concentration regimes, which offers a commercial advantage over the traditional glucometers.

5. Conclusions and Future Outlook

Recent advances in MIP-based sensor technology published in academic studies demonstrate that these devices are rapidly approaching real-life applications. Their long shelf-life, chemical stability, and low cost make them advantageous over enzymes. In addition, these devices have proven to work in challenging environments such as urine and sweat that contain lower concentrations of glucose. This illustrates their potential application in non-invasive and continuous monitoring tools. However, the main bottleneck that must be addressed remains in the synthesis of large batches of homogenous MIPs. This facet of MIP technology has long been neglected, while enzymatic biosensors, as well as immunosensors, have benefited from decades to even centuries of research on the function, synthesis, and immobilization of these natural receptors.

Slowly, MIP technology is trying to close this gap, with scholars devoting attention to MIP synthesis procedures that not only lead to highly performant MIPs from an academic perspective, but also take the potential scalability and possibility for mass production into account. Technologies such as solid-phase synthesis that takes place in automated reactors or fully automated electrospinning or electropolymerization approaches are rapidly evolving in this direction and multiple research groups are investigating ways to improve the more traditional approaches in this respect. Thus, we believe that MIP-based technologies may be a strong alternative to traditional enzymatic devices in the future and, by addressing the aforementioned obstacles to their commercialization, may finally reach the market. In combination with the continuously growing need for personalized medicine and non-invasive sampling, MIP-based glucose sensors could profit from the momentum and academic know-how in the coming decade or two, to achieve the next step towards commercialization, and therefore real-life application.

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