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Molecularly Imprinted Polymer-based Electrochemical Sensors for the Analysis of Antiviral Drugs used in SARS-CoV-2: Innovations and Recent Applications

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ABSTRACT

Viruses that cause infectious diseases pose a vital threat to the health of living beings. Antiviral drugs are widely used to treat these diseases. In recent years, due to the prevalence of infectious diseases and global epidemics, the use of antiviral medications has become increasingly widespread. In recent years, antiviral drugs, particularly SARS-CoV-2, have been used in the treatment of COVID-19, an infectious disease that has caused significant deaths worldwide. These drugs are primarily used to reduce the effects of viruses, prevent their spread, and treat the disease. Therefore, MIP-based electrochemical sensors are widely used to provide rapid, sensitive, reliable, stable, and, most importantly, selective detection of antiviral drugs.

Furthermore, MIPs can be integrated into miniature devices, are reusable, and possess a highly stable structure even under harsh conditions. A review of the literature reveals that these significant advantages of MIP-based electrochemical sensors have made them a substantial asset in the selective and sensitive determination of antiviral drugs. This study investigates the applications, sensor designs, and properties of MIP-based electrochemical sensors, specifically designed for the drugs favipiravir, lopinavir, remdesivir, ribavirin, and umifenovir, which have been widely used in the treatment of SARS-CoV-2 infections in recent years, in both pharmaceutical and biological samples. Furthermore, this review will shed light on the analysis of these drugs and the methods to be developed in the coming years.

Keywords: Molecularly imprinted polymers, electrochemical sensor, drug analysis, real samples

INTRODUCTION

Viruses that cause infectious diseases significantly impact global health due to their rapid spread and serious, life-threatening consequences.[1,2] Antiviral drugs are widely used in the treatment of infectious diseases such as influenza and the human immunodeficiency virus (HIV). Historically, numerous viral outbreaks have occurred worldwide, including COVID-19 and the Asian flu.[3,4] Due to these outbreaks, the development and rapid identification of antiviral drugs are of paramount importance.[5] In recent years, the selective and fast analysis of drugs used in SARS-CoV-2 has been crucial.

Furthermore, these drugs have been widely used in the treatment of infectious diseases in humans and animals, effectively alleviating pain and suffering, extending life expectancy, and significantly improving quality of life.[3] However, over time, the widespread use of these drugs can lead to drug resistance problems. The development of viral resistance can prolong treatment processes, increase the costs associated with chronic diseases, and create clinical needs for new treatments.[1,2]

Antiviral drugs used in the treatment of infectious diseases caused by viruses and bacteria are vital to public health. A detailed review of the literature reveals that many different methods are used for the analysis of antiviral drugs.[5,6]

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These methods include liquid chromatography-tandem mass spectrometry (LC-MS)[7], high-performance liquid chromatography (HPLC)[8], spectrophotometry[9], and electrochemical methods[10]. Due to the preparation of suitable dosage forms and the limited toxicity of antiviral drugs, there is a significant need for sensitive, reliable, and cost-effective methods with short analysis times. Therefore, electrochemical methods, which offer inexpensive, simple, sensitive, and rapid analysis times compared to other analytical methods, are attracting greater interest.[5,11,12] However, the selectivity shortcomings of electrochemical methods are addressed through the design of molecularly imprinted polymer sensors (MIPs).[13]

The fundamental process of MIP formation involves creating cavities that selectively recognize functional groups from the target molecule to be analyzed. The basic components of MIP-based electrochemical sensors consist of the target molecule, functional monomer, crosslinker, and initiator. In the presence of the crosslinker, the most suitable functional monomer for the target molecule is selected, and polymerization is then carried out.[2] Removal of the target molecule after polymerization ensures the formation of specific and selective cavities for the target molecule. Furthermore, MIP-based electrochemical sensors have many advantages, including stability, physical and chemical robustness, cost-effectiveness, and reusability.[11,12] A review of the literature reveals numerous electrochemical studies on MIP sensors for antiviral drugs. Furthermore, MIPs designed to create specific recognition sites for antiviral drugs can be structurally integrated to support various therapeutic applications, such as viral neutralization, immune modulation, and controlled drug release. Therefore, MIP sensors offer versatility and specificity to overcome the challenges associated with traditional antiviral drug analysis.[14]

This study aims to comprehensively examine current applications of molecularly imprinted polymer (MIP)-based electrochemical sensors for the selective and sensitive analysis of antiviral drugs. The impact of infectious diseases on global health, combined with the widespread use of antiviral drugs, necessitates the determination of these compounds using reliable, rapid, and cost-effective methods. Therefore, this study examines the mechanisms, analytical performance, and application areas of MIP-based sensors developed using analytical strategies in biological samples. A literature review was conducted, focusing specifically on systems developed between 2023 and 2025, and aims to guide future research.

Molecularly Imprinted Polymers

Molecular imprinting technology (MIT) was first introduced in 1970 by Wulff and Klotz based on the guiding principle of molecular imprinting technology (MIPs).[15,16] Molecularly imprinted polymers (MIPs) are synthetic polymeric structures containing specific recognition sites and were developed as an alternative to biological receptors in terms of analyte selectivity. These polymers are synthesized through a polymerization process in the presence of a target molecule (template); the cavities formed by the removal of the template serve as recognition sites specific to the size, shape, and functional groups of the analyte. MIP sensors can therefore be used for the analysis of a wide range of compounds, including both small molecules and macromolecules.[17–19] MIPs are widely used in analytical chemistry, particularly in separation and detection applications, due to their high chemical and thermal stability, low cost, and long lifespan. Thanks to these important features, MIPs have become a significant alternative to natural recognition methods in biological analysis, separation, and detection in recent years. In recent years, the integration of MIPs with electrochemical sensors has enabled the development of highly sensitive and selective sensor systems by combining selective recognition capabilities with electroanalytical techniques.[20,21] In such sensors, the MIP is immobilized on the electrode surface, enabling specific recognition of the target analyte; The electrochemical change resulting from the binding of the analyte is measured using voltammetric, amperometric, or potentiometric methods to determine the analyte concentration. MIP-based electrochemical sensors are particularly prominent as high-performance analytical tools for the determination of trace levels of pharmaceutical compounds in biological samples, monitoring of environmental contaminants, and food safety applications.[22]

Moreover, MIP-based electrochemical sensors can be designed using both direct and indirect analytical strategies for the selective and sensitive detection of antiviral drugs. In the direct detection approach, the binding of the target antiviral molecule to the specific recognition sites on the MIP leads to an electrochemical signal change at the electrode surface. This signal variation is typically monitored using techniques such as differential pulse voltammetry (DPV), cyclic voltammetry (CV), or square wave voltammetry (SWV), depending on the electroactive nature of the analyte. In contrast, indirect detection strategies rely on the modulation of ion permeability, charge transfer kinetics, or accessibility at the electrode surface upon analyte binding to the MIP matrix. These

changes are evaluated through the altered electrochemical response of an external redox probe, such as $[Fe(CN)_6]^{3-/4-}$ or ferrocene derivatives. Both strategies fulfill key analytical performance criteria such as trace-level detection in biological samples, high selectivity, low detection limits, and short analysis times, thereby demonstrating the effectiveness and applicability of MIP-based sensors in pharmaceutical analysis. Furthermore, the portability, reusability, and cost-effective fabrication of these sensors provide substantial benefits for field applications and point-of-care diagnostic platforms. In this context, MIP-based electrochemical sensors offer a promising and reliable platform for therapeutic drug monitoring and pharmacokinetic evaluation of antiviral agents.[23,24]

MIP-based electrochemical sensors utilize various polymerization techniques, including electropolymerization, photopolymerization, and thermal polymerization. The successful design of these sensors depends on polymerization techniques and sensing procedures. Furthermore, although different techniques and strategies are used in the design of MIP-based electrochemical sensors, the preparation procedures are similar. At the very beginning of the polymerization process, the most suitable functional monomer for the target molecule is usually required. Therefore, the polymerization process is carried out in the presence of the target molecule using a suitable monomer and depending on the used technique a crosslinker, basic monomer, porosity agent and an initiator are used. The imprinted regions resulting from polymerization are selective for the target molecule or its structural analogs, so they can often be reattached and released.[20,25]

Antiviral Drugs

Favipiravir

Favipiravir (FAV) is a broad-spectrum antiviral agent that inhibits RNA-dependent RNA polymerase (RdRp), thereby preventing viral replication. Initially approved for influenza, it has been repurposed for COVID-19 treatment. Clinical studies indicate that FAV accelerates viral clearance and improves recovery rates in COVID-19 patients. Its antiviral efficacy is dose-dependent, and monitoring plasma levels is important to ensure both effectiveness and safety. FAV has demonstrated superior antiviral activity compared to some other agents. However, potential adverse effects such as teratogenicity and changes in uric acid levels must be considered. [25-27]

Lopinavir

Lopinavir (LOP), a protease inhibitor, is primarily used in combination with ritonavir for HIV treatment. It inhibits coronavirus replication by targeting 3C-like protease (3CLpro), an essential enzyme for viral polyprotein processing. While LOP has shown in vitro activity against SARS-CoV-2, clinical evidence in COVID-19 patients remains mixed. LOP exhibits poor oral bioavailability and high plasma protein binding, which are important factors for pharmacological studies. Its antiviral activity is enhanced when co-administered with ritonavir, which inhibits its metabolism and increases plasma concentration.[28–30]

Remdesivir

Remdesivir (REM) is a monophosphate nucleoside prodrug that is metabolized intracellularly to an active triphosphate form, inhibiting RNA-dependent RNA polymerase and blocking viral RNA replication. It was the first antiviral approved by the FDA for the treatment of COVID-19. REM has shown efficacy against a range of RNA viruses, including SARS-CoV-2, in both in vitro and in vivo studies. Its pharmacokinetic properties and antiviral mechanism make it a key therapeutic option for hospitalized COVID-19 patients; however, careful dosing and monitoring are essential due to potential side effects.[31,32]

Ribavirin

Ribavirin (RBV) is a broad-spectrum antiviral nucleoside analog primarily used in combination with pegylated α-interferon for hepatitis C virus (HCV) infection. It inhibits RNA virus replication and has been investigated against SARS-CoV-2 due to its broad-spectrum antiviral effects; however, in vivo studies have shown limited efficacy despite promising in vitro results. Some studies suggest that RBV can be administered in combination with lopinavir-ritonavir or interferon-α, where early treatment may improve clinical outcomes and reduce hospitalization duration.[33,34]

Umifenovir

Umifenovir (UMI) is a broad-spectrum antiviral agent approved in Russia and China for the treatment and prevention of influenza, SARS, and Lassa virus infections. Due to the high similarity between SARS viruses, the potential efficacy of SARS against COVID-19 has been investigated. In vitro studies have demonstrated antiviral activity, and clinical observations suggest improved symptoms and shorter hospital stays, particularly when co-administered with lopinavir. The mechanism of action involves inhibiting viral fusion and entry, preventing viral attachment, and interfering with viral particle release, thereby affecting multiple stages of the viral life cycle. UMI is generally well tolerated and exhibits low human toxicity, making it a widely used therapeutic option during the COVID-19 pandemic.[35,36]

Daclatasvir

Daclatasvir (DAC) is a highly effective, direct-acting antiviral (DAA) agent, specifically the first clinically validated inhibitor of the Hepatitis C Virus (HCV) non-structural protein 5A (NS5A). It blocks viral replication by preventing genome transfer and inhibiting the formation of the replication complex. DCV is a core list essential medicine due to its high efficacy, favorable safety profile, and stable pharmacokinetics, making it highly versatile for combination therapy. The need for Therapeutic Drug Monitoring (TDM) to optimize patient outcomes and ensure safe dosing is critical, thereby driving the demand for highly selective, fast, and cost-effective analytical methods, such as those employing Molecularly Imprinted Polymers (MIPs), for the determination of therapeutic drugs in biological samples (Table 1).[37]

Applications of Electrochemical Molecularly Imprinted Polymer-Based Sensors

The studies on MIP-based electrochemical sensors for antiviral drugs used in SARS-CoV-2, published in the literature between 2023 and 2025, are summarized below. Additionally, a detailed discussion is provided on the selectivity, sensitivity, recovery, technique, sensor, and linearity ranges of MIP-based electrochemical sensors.

Table 1: Electrochemical sensor applications for Antiviral drug detection

Analyte	Sensor	Linearity range	LOD	Ref.
Favipiravir	PCD-MIP/PGE	5.0×10^{6}-5.0×10^{-5} mol/L	1.67 µM	38
Lopinavir	TP/LOP@MIP/GCE	1×10^{-12} -1.75×10^{-11}	0.180 pg/mL	
	EP/LOP@MIP/GCE	1×10^{-12} -1×10^{-11}	0.183 pg/mL	39
Remdesivir	REM/HEMA/AA/AM	-	-	40
Ribavirin	RPM/FeCu-MOF/MIP	0.1-500 nmol/L	0.086 nmol/L	41
Umifenovir	B3N3/BuMA/MIP/GCE	0.50–7.50 pM 0.25–5.00 pM	48.20 fM 23.40 fM	42
Daclatasvir	POC core/shell MIP	1.0×10^{-6} 1.0×10^{-2}	0.35×10^{-6}	43

Yamani et al.[38] developed, for the first time, a carbidopa-based MIP electrochemical sensor for the determination of favipiravir (FAV). The study aimed to create a low-cost, disposable, and user-friendly sensor capable of rapid, sensitive, and selective measurement of FAV concentrations in human plasma, which is relevant for COVID-19 treatment. Carbidopa was electropolymerized onto a pencil graphite electrode to form the MIP-based sensor, which was characterized using SEM and XPS (Figure 1). Under optimized conditions, the sensor exhibited linear responses over two concentration ranges with a low limit of detection (LOD: 1.67 µM). The PCD-MIP/PGE sensor successfully quantified FAV in pharmaceutical formulations and spiked human plasma samples. The successful application in this complex biological matrix, which often requires extensive sample cleanup in traditional methods, highlights the inherent selectivity of the MIP design. The sensor demonstrated high accuracy and selectivity in plasma, indicating its robust performance for therapeutic drug monitoring (TDM) in COVID-19 treatment. Its disposable, cost-effective, and easy-to-fabricate design makes it suitable for point-of-care (POC) applications.[38]

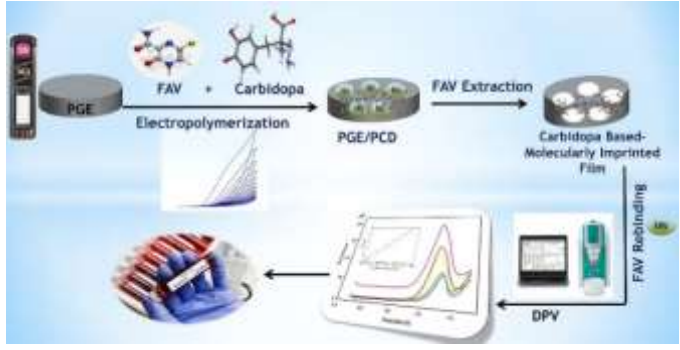

Figure 1. Schematic representation of the developed molecular imprinted polymeric sensor. Reprinted from Yamani et al.[38] with permission from Elsiver

In this study, Faysal et al.[39] developed two different MIP-based electrochemical sensors for the selective and sensitive determination of lopinavir (LOP) in human serum and tablet formulations: thermal polymerization (TP-LOP@MIP/GCE) and electropolymerization (EP-LOP@MIP/GCE) (Figure 2). The polymer matrices were specifically designed to interact with LOP, and characterization confirmed their functional and morphological properties. A key strength of this work lies in the direct comparison of the fabrication techniques: Electrochemical analyses revealed that both the TP and EP sensors exhibited similarly low detection limits in human serum samples (TP: 0.180 pg/mL, EP: 0.183 pg/mL), with wide linear ranges, and high selectivity. Although the difference in LOD is marginal, the EP approach offers superior benefits for sensor fabrication due to its speed and precise control over film thickness directly on the electrode surface. Crucially, the use of the Glassy Carbon Electrode (GCE) acts as a highly conductive and stable support platform, which is fundamental to achieving the reported

ultra-trace sensitivity in complex human serum. This provides a precise, rapid, reliable, and cost-effective approach for LOP quantification with significant potential for clinical applications. [39]

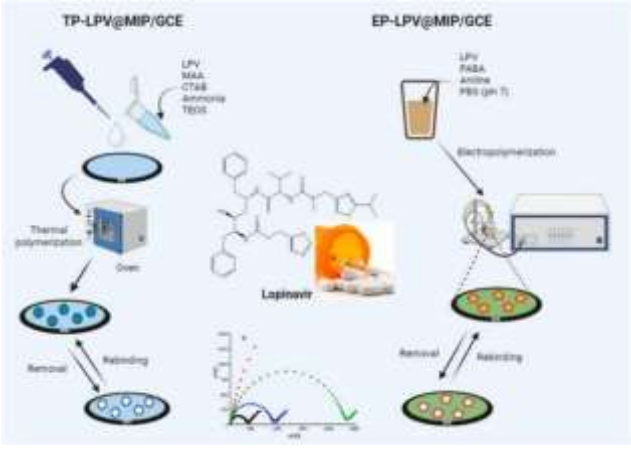

Figure 2. Schematic diagram of the molecular imprinted sensor design for LOP. Reprinted from Faysal et al.[39] with permission from Elsiver

In another study, Wisnuwardhani et al.[40] developed and characterized MIPs for the selective recognition of Remdesivir (REM), an antiviral nucleoside analog with activity against SARS-CoV-2. Computational approaches, including density functional theory (DFT) and GFN2-xTB methods, were used to identify the optimal functional monomer and polymerization solvent, revealing acrylamide (AM) as the most interactive monomer and acetonitrile (ACN) as the optimal solvent. Molecular dynamics simulations further revealed that the 1:1 template-to-monomer ratio exhibited the highest stability, as indicated by the radial distribution function, hydrogen bond occupancy, and Gibbs free energy (ΔG). Laboratory experiments, including the determination of association constants and Job plot analysis, confirmed these computational predictions. The MIPs were synthesized via precipitation polymerization and characterized using SEM, FTIR, and TGA, demonstrating distinct morphologies, thermal stability, and effective template removal (Figure 3). Adsorption studies showed that both MIP formulations exhibited significant selectivity and binding capacity for REM, with imprinting factors of 1.36 and 1.15, respectively, and superior performance in aqueous-acetonitrile solvent. Overall, the study highlights that combining computational and experimental methods provides an effective strategy for designing selective MIPs for REM analysis in pharmaceutical and biological samples.[40]

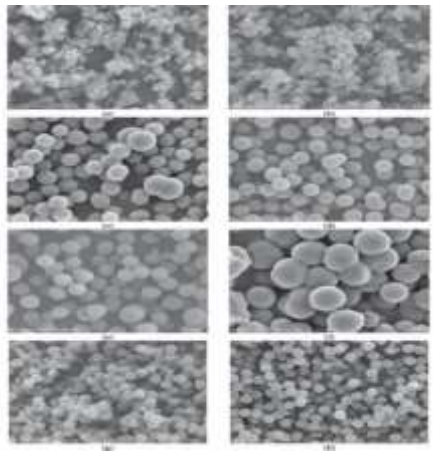

Figure 3. SEM analysis of MIP 1, 2 (a,c) and NIP 1, 2 (e, g) before template extraction; MIP 1,2 (b, d) and NIP 1, 2 (f, h) after template extraction. Reprinted from Wisnuwardhani et al.[40] with permission from Elsiver

In another study, Gao et al.[41] designed a molecularly imprinted electrochemical sensor based on reduced graphene oxide/polydopamine@MXene (RPM), and FeCu-MOF was developed for the sensitive detection of the antiviral drug ribavirin (RBV). The RPM composite enhanced the sensor's active surface area and electron transport. At the same time, FeCu-MOF improved catalytic performance and enabled the electroreduction of H_2O_2 (Figure 4). Optimized molecularly imprinted polymers (MIPs) were developed using density functional theory (DFT) to increase specificity and sensitivity. The sensor achieved detection limits of 0.053 nM (DPV) and 0.086 nM (I-t) and was successfully applied to real food and surface water samples, showing recovery rates from 98.3% to 106.7%. The integration of RPM, FeCu-MOF, and MIP created a dual-signal platform with high conductivity, peroxidase-like activity, and selective recognition cavities, enabling reliable, reproducible, and selective RBV detection in complex matrices.[41]

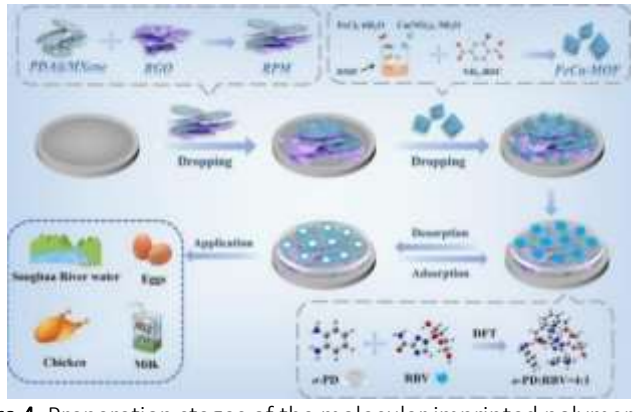

Figure 4. Preparation stages of the molecular imprinted polymeric sensor developed for RBV. Reprinted from Gao et al.[41] with permission from Elsiver

In this study, Cetinkaya et al.[42] developed a borazine-assisted, oriented surface molecularly imprinted electrochemical sensor for the determination of umifenovir (UMI) in serum and urine samples. In this study, pre-polymerization complexes between the target molecule UMI and B_3N_3 were formed and polymerized onto the electrode surface using butyl methacrylate (BuMA) via photopolymerization. The sensor was characterized using cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), contact angle measurements, Fourier-transform infrared spectroscopy (FTIR-ATR), atomic force microscopy (AFM), and scanning electron microscopy (SEM). At the same time, quantum chemical calculations evaluated the molecular changes on the electrode surface. Using differential pulse voltammetry (DPV) and EIS, the sensor demonstrated high sensitivity and selectivity with linear ranges of 0.50-7.50 pM (DPV) and 0.25-5.00 pM (EIS). The sensor exhibited excellent selectivity against structurally similar compounds and potential interferents in biological fluids. Crucially, the sensor was successfully applied to commercial serum and urine samples, demonstrating its versatility across different physiological matrices. The exceptionally low limits of detection (as low as 23.40 fM for EIS) achieved in these real samples, coupled with high repeatability and reproducibility, strongly highlight the potential of this MIP-based electrochemical sensor for highly sensitive and selective UMI determination in clinical and point-of-care (POC) applications, where rapid and accurate analysis of biological fluids is paramount.[42]

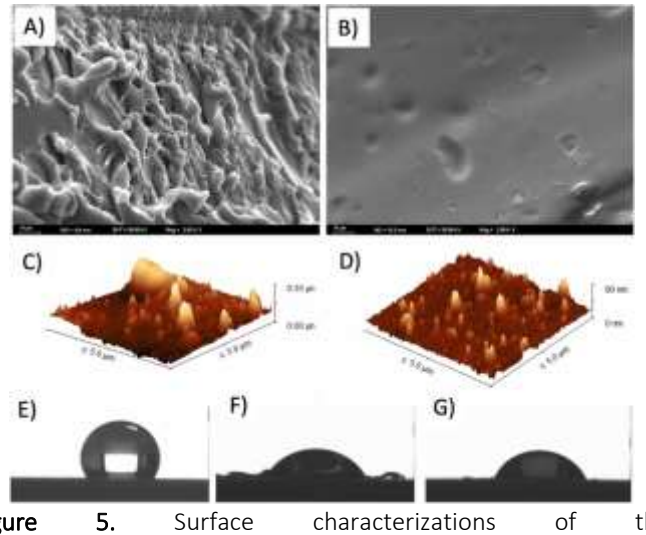

Figure 5. Surface characterizations of the UMI@B3N3/BuMA@MIP/GCE sensor. SEM images of (A) MIP and (B) NIP; AFM images of (C) MIP and (D) NIP; Contact angle images of (E) normal surface, (F) MIP, and (G) NIP. Reprinted from Cetinkaya et al.[42] with permission from Elsiver

This study reports the development of a disposable, portable screen-printed potentiometric sensor based on core/shell surface molecularly imprinted polymer (MIP) technology for the highly selective and rapid analysis of the antiviral drug Daclatasvir dihydrochloride (DAC). The core/shell MIP, serving as the recognition component, was fabricated on the surface of vinylated silica nanoparticles (Si-NPs), which were synthesized via the Stöber method. A copolymerization reaction was performed using methacrylic acid (MAA) as the functional monomer, ethylene glycol dimethacrylate (EGDMA) as the cross-linker, and a free radical initiator, with DAC acting as the template molecule. The chemical composition and morphology of the resulting core/shell nanoparticles were successfully characterized using Fourier transform infrared (FTIR) spectroscopy, X-ray photoelectron spectroscopy (XPS), and scanning electron microscopy (SEM) analyses. The sensor exhibited a linear calibration response ranging from 1.00×10^{-6} to 1.00×10^{-2} mol/L, with a calculated slope of 36.44 mV/decade. The limit of detection (LOD) and limit of quantification (LOQ) were determined to be 0.35×10^{-6} mol/L and 1.00×10^{-6} mol/L, respectively. Examination of spiked biological samples confirmed the sensor's applicability for DAC detection in real matrices, yielding recoveries between 99.51% and 114.54%. This new generation sensor demonstrates significant potential for reliable use in point-of-care testing (POCT) applications and biomedical research involving DAC analysis.[43]

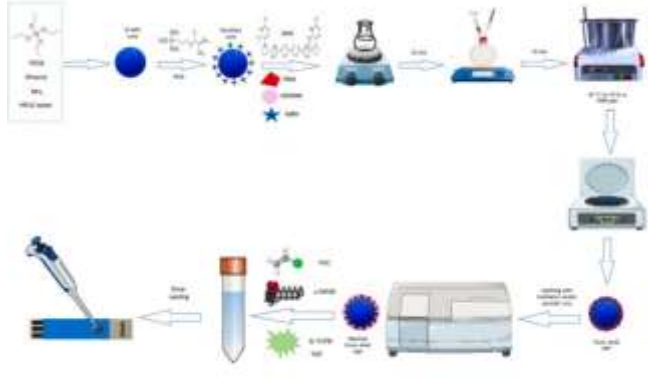

Figure 6. A schematic diagram for the synthesis of the core-shell MIP and the sensor assembly. Reprinted from El Azab et al.[43] with permission from Elsevier

DISCUSSION

Viruses that cause infectious diseases continue to pose a significant threat to global public health due to their rapid transmission and potentially fatal outcomes. Antiviral drugs play a crucial role in the treatment of viral infections such as influenza and HIV, and recent global pandemics, including COVID-19 and Asian flu, have further highlighted their importance. These epidemiological developments have accelerated the need to develop and rapidly identify effective antiviral agents. In particular, selective and timely

analysis of drugs used in the treatment of SARS-CoV-2 has become critical in recent years.

A comprehensive review of the literature reveals that a variety of analytical techniques, including LC-MS/MS, HPLC, spectrophotometry, and electrochemical methods, are used for the quantification and characterization of antiviral drugs. Among these, electrochemical techniques are gaining increasing attention due to their simplicity, cost-effectiveness, rapid response times, and high sensitivity. However, traditional electrochemical methods often suffer from limited selectivity, especially in complex biological matrices. To overcome these limitations, molecularly imprinted polymer (MIP)-based electrochemical sensors have emerged as a promising alternative. These sensors use synthetic recognition elements that mimic biological selectivity by creating specific cavities complementary to the target antiviral molecule. The fabrication process involves polymerization of functional monomers in the presence of the target analyte and a crosslinking agent, followed by template removal to create selective binding sites. MIP-based sensors offer several advantages, including chemical and thermal stability, reusability, and adaptability to various sample types. Recent studies have demonstrated the applicability of MIP sensors for detecting a wide range of antiviral drugs, with potential applications in therapeutic areas such as immune modulation, viral neutralization, and controlled drug delivery. Their integration into point-of-care platforms and field-deployable systems further enhances their use in clinical and epidemiological settings. This review summarizes the current developments in MIP-based electrochemical sensor technologies for antiviral drug detection over the past few years, highlighting their analytical performance, operational mechanisms, and scope of application. These findings are expected to inform future research directions and support the development of next-generation diagnostic tools for the management of infectious diseases.

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