Short Review

Molecularly Imprinted Polymer Electrochemical Sensors Based on Synergistic Effect of Composites Synthesized from Graphene and Other Nanosystems

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Graphene (Gr), an extraordinary carbonaceous material has attracted tremendous amount of attention due to its fascinating electrical, thermal and physical properties. Hence, its utilization for the fabrication of electrochemical sensor comprising other nanosystems and Molecular imprinted polymer (MIP) technique has been very effective approach to achieve high selectivity and sensitivity. As a result, this mini review represents a detailed discussion on literature published in recent years comprising all three (MIP, Graphene and Electrochemical sensor) subjects in their research works.

Keywords: Molecular imprinted polymer, electrochemical sensor, graphene, nanosystems

ABBREVIATIONS:
Gr, Graphene; GO, Graphene oxide; RGO, Reduced Graphene oxide; IL, Ionic liquid; CS, Chitosan; SEM, Scanning electron micrograph; TEM, Transmission electron micrograph; EIS, Electrochemical impedance spectroscopy; AFM, Atomic force microscopy; DPV, Differential pulse voltammetry;

1. INTRODUCTION

In last two decades, nanostructured materials have received surge of interest owing to their remarkable properties and have been continuously utilized as efficient electron mediators for the fabrication of highly sensitive chemical and biosensors [1]. Among various nanostructured nanomaterials, the carbonaceous materials such as carbon nanotubes (CNTs) and graphene (Gr) are at the forefront of advanced materials research [2, 3]. Particularly, there is growing interest in graphene chemistry due to its enormous potential in material synthesis at nanoscale. The features that make graphene an ideal material are high surface area, extremely low noise and excellent electrical and thermal conductivity. Moreover, the specific surface area of a single graphene sheet is 2630 m^2 g^{-1},

which is quite higher than that of activated carbons and carbon nanotubes. Therefore, graphene has made its niche in catalysts, sensors, and energy storing and composite materials research areas [4].

Molecular imprinting technique is considered an effective approach where any template molecule is introduced in a mixture of monomer and cross-linker dissolved in a solvent resulting into three-dimensional polymer matrix. After removal of the template from as–prepared polymer, the permanent cavities of the original template is formed which are capable to rebind selectively to the template molecules. The obtained polymer, referred as molecular imprinted polymer (MIP), demonstrates high stability and robustness in harsh synthesis and analysis environment. Since last two decades, extensive research efforts have been devoted for the fabrication and development of the MIPs. Due to their high selectivity and stability, MIPs have been applied for numerous applications such as chromatographic separation [5-7], recognition for peptides and biomolecules [8], capturing of hazardous radioactive waste [9], drug delivery [10] solid phase extraction [11], and recognition element for electrochemical and biosensors [12]. Although, the utilization of MIP as recognition elements in electrochemical sensor has shown promising results, However, MIPs fabricated by the conventional methods pose few drawbacks including slow mass transfer rate and low adsorption capacity. These obstacles have fueled research to utilize materials possessing high surface area such as graphene [13, 14].

Although, MIP based methods are considered highly selective but they again exhibit abovementioned flaws being associated to expensive instruments and arduous sample enrichment processes [15]. Therefore, mentioned drawbacks keep electrochemical sensors at the forefront. Additionally, electrochemical technique usually offers greater sensitivity, in addition to its other outstanding features such as low cost, easy operation, fast response time and excellent potential for miniaturization and construction for portable equipment applications.

Hence, in order to harness the advantages and extraordinary potentials of MIP, graphene and electrochemical sensor technique, many groups have investigated on their application for the fabrication of electrochemical sensors using various compounds.

As a result, this mini review represents a detailed discussion on literature published in recent years comprising all three (MIP, Graphene and Electrochemical sensor) subjects in their research works. The literature survey was performed by putting "Molecularly imprinted polymer electrochemical sensor based on graphene" as key words in SciFinder. We could find several works references appeared in English language journal and few Chinese language contributions which included all the three key words. However, we just selected contributions from works references appeared in English language journal for the convenience.

2. SENSORS BASED ON GRAPHENE AND MIP

In an effort to prepare a sensor for 2,4-dinitrophenol, Liu et al. [16] GO-MIP composite was synthesized. Firstly, the amine functionalized GO was prepared by dispersing GO in 3-aminopropyltriethoxysilane (APTES) followed by imprinting the 2,4-dinitrophenol with o-phenylenediamine (OPDA) by polymerization. The resulting composite was drop coated over GCE

and used as an electrochemical sensor for detecting the target pollutant DNP by cyclic voltammetry (CV), linear sweep voltammetry (LSV), and differential pulse voltammetry (DPV). The as-synthesized material was characterized successfully with Raman, FT-IR, FE-SEM, EDAX and UV-Vis spectrophotometer. Under optimal conditions by the DPV, there was a good linear correlation between the current of the cathodic peak at about -0.35 V (vs. saturated calomel electrode) and the concentration of DNP in the range of 1.0–150.0 µM with the detection limit (S/N = 3) of 0.4 µM. The electrochemical sensor was satisfactorily applied to determine DNP in practical tap water and artificial wastewater samples and provided excellent selectivity over various common interfering species including Na^+, K^+, Fe^{3+}, Al^{3+}, Cl^-, NO_3^-, CO_3^{2-} and SO_4^-, m-dihydroxybenzene (10-fold), p-aminobenzoic acid (10-fold), p-hydroxybenzoic acid (10-fold), phenol (10-fold), 3-NP (1-fold) [16].

The same group used a similar kind of strategy for the fabrication of an electrochemical sensor for the detection of chlortetracycline (CTC) antibiotic based on controlled electrochemical reduction of GO at cathodic potentials. The preparation scheme has been shown in Figure 1.

In order to fabricate the sensor, firstly, GO was synthesized by common Hummers method and casted on GCE. Then, the GO was reduced to RGO (reduced graphene oxide) electrochemically and as-prepared surface was applied to construct MIP sensor by electropolymerization of o-Phenylenediamine (OPDA) with CTC in appropriate experimental conditions. For comparisons, non-imprinted polymer (NIP) was also prepared following the same method except the inclusion of CTC in the polymerization solution.

The successful synthesis and surface morphology of GO and RGO materials were analyzed with XPS, Raman, FT-IR and SEM techniques while the electrochemical studies were done with $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ as the electrochemical probe between the MIP sensor and the target material solution using CV and DPV. The proposed MIP sensor worked satisfactorily in a wide linear concentration range of CTC from 10.0–500.0 µM and offered high selectivity against other interfering compounds with similar chemical structure such as oxytetracycline (OTC) and doxycycline (DC), dinitrophenol (DNP) and phenol. The real application of the proposed MIP sensor was evaluated for the determination of CTC in tap water and laboratory wastewater with excellent recoveries and high stability [17].
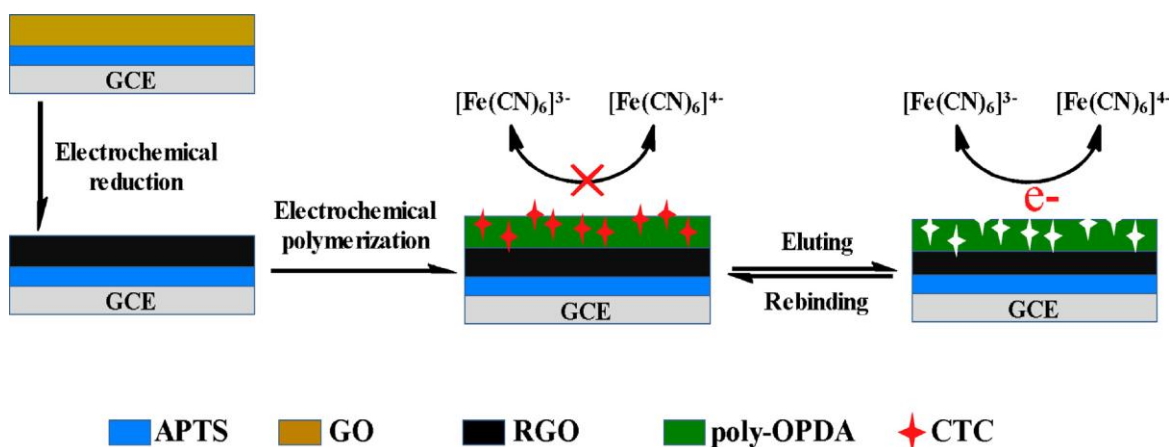

Figure 1. Illustration of fabrication and use of the RGO-MIP sensor (reproduced with permission from reference [17]).

In another similar approach, the amine terminated GO was covalently modified onto the electrode surface with diazonium salt reaction to improve the stability and reproducibility of electrochemical sensor for 4-nonylphenol. After synthesizing amine terminated GO ($GO-NH_2$), it was deposited over GCE and electrochemically reduced with CV followed by electrodeposition of 4-nonylphenol imprinted polymer with polypyrrole.

The synthesis of $GO-NH_2$ was confirmed with FT-IR and electrochemical characterization of sensor was carried out with electrochemical impedance spectroscopy and DPV. The DPV exhibited a linear relationship toward the logarithmic value of NP concentrations at a range from 1.0×10^{-11} to 1.0×10^{-8} g mL^{-1} and the LOD was estimated to be 3.5×10^{-12} g mL^{-1}. Furthermore, the proposed sensor was evaluated for selectivity, stability and reproducibility with excellent results [18].

To determine the concentration of dopamine (DA), Mao et al. [19] proposed a novel composite based on graphene sheet/congo red (GSCR) and MIP through free radical polymerization. In order to prepare the electrochemical sensor surface, DA molecules were absorbed over GSCR surface followed by selective copolymerization with methacrylic acid (MAA) and ethylene glycol dimethacrylate (EDMA).
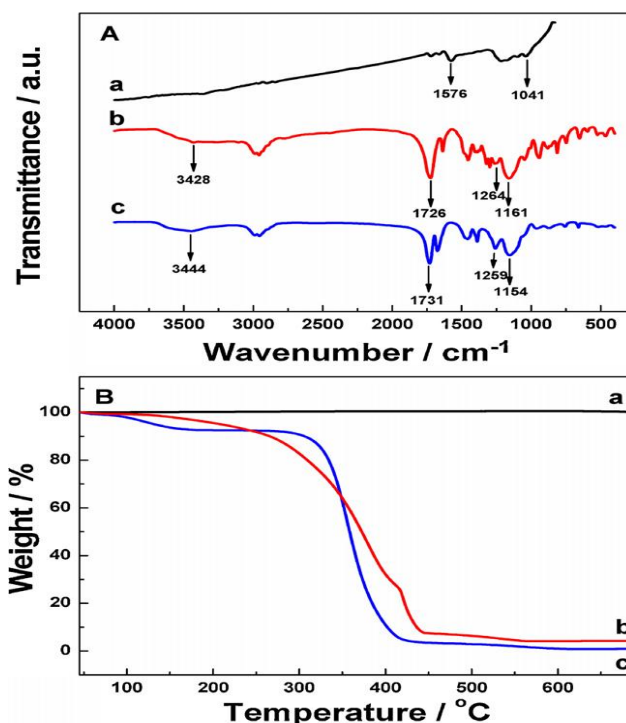

Figure 2. (A) FT-IR spectra of GSCR (a), GSCR-MIPs (b), and MIPs (c); (B) TGA curves at a heating rate of 10°C min^{-1} from room temperature to 700°C under a N_2 atmosphere for crude graphite (a), GSCR-MIPs (b), and MIPs (c) (reproduced with permission from reference [19]).

The characterization of GSCR-MIP surface with SEM, TEM, FT-IR and TGA techniques supported the successful synthesis of the desired material. The FT-IR and TGA patterns of crude graphite, MIP and GSCR-MIP surface are shown in figure 2. The linear sweep voltammograms

(LSVs) of fabricated sensor exhibited selective detection of DA in a linear concentration range of 1.0×10^{-7}–8.3×10^{-4} M which revealed a LOD of 1.0×10^{-7} M. The high selectivity of DA over EP and AA were carried out by during the binding process and characterized by LSV. The as-fabricated DA electrochemical sensor based on GSCR-MIPs composites also offered excellent repeatability with a relative standard deviation (RSD) of about 2.50% for 30 repeated analyses of 20 µM DA.

It was shown that GSCR-MIPs surface possessed large kinetic mechanism, higher selectivity and sensitivity compared to traditional MIPs.

Very recently, Xue et al. [20] developed an interesting method for the determination of methyl parathion (O, O-dimethyl O-(4-nitrophenyl) phosphorothioate, MP), one kind of organophosphorous pesticides which is a widely used insecticide in agricultural production and shows high toxicity to living beings. For the fabrication of target electrochemical sensor, nitrogen doped graphene sheet (N-GS) were prepared and deposited over gold electrode's surface. Finally, the MP-MIP was electropolymerized in presence of phenol as functional monomer in PBS buffer by CV. The successful doping of GS with nitrogen was confirmed by Energy Dispersive X-Ray Spectroscopy (EDX) and Table 1 showed the amount of each element contained in N-GS. It was obvious that the N atom concentration was 8.16 % which increased the electron density of the GS surface. It was observed that doping of GS with N, enhanced the electrical conductivity of the electrode. As a result, the sensitivity of the electrochemical sensor was improved greatly. The N-GS surface possessed wrinkled and flat like structure as characterized with SEM and TEM. The CV was utilized to study the electrochemical performance of the sensor and experimental conditions such as N-GS concentration, ratio of template to monomer, pH and elution time were optimized to obtain highest response from the sensor. Under optimum experimental parameters, the current increased linearly with the increasing MP concentration in the range from 0.1 to 10 µg mL^{-1}, with the low detection limit of 0.01 µg m L^{-1}. The sensitivity, stability and real applicability of the MP sensor were found to be excellent.

Table 1. Atomic concentration of C, N and O of N-GS (reproduced with permission from reference [20]).

Element	C (%)	N (%)	O (%)
Atomic Concentrations	75.79	8.16	16.05

An interesting approach for the fabrication of a disposable and simultaneous electrochemical sensor array based on a molecularly imprinted film at a NH$_2$-graphene (NH$_2$-Gr) modified screen-printed electrode for determination of methcathinone and cathinone (psychotropic drugs) was developed by Zang et al. [21]. Firstly, graphene oxide (GO) was synthesized and split into wrinkled sheets for amine functionalization (NH$_2$-Gr). Finally, the MIP electrochemical sensor array was constructed by electropolymerizing the methcathinones and cathinones with pyrrole as functional monomer in the range from -0.6 to 1.2 V at a scan rate of 50 mV s_1 for 25 cycles in a potassium perchlorate solution on the two working electrodes of SPEs through NH$_2$-Gr coating, respectively. The TEM depicted the successful synthesis of graphene with wrinkled surface while SEM image of

fabricated polymer showed an elegant "bitter gourd" type of structure. The figure 3 showed the electrochemical behavior of the stepwise fabrication process was studied in 5.0 mM $K_3[Fe(CN)_6]$ solution containing 0.2 molL^{-1} KCl using CV and EIS. The scan cycles of electropolymerization, pH of solution and temperature of $K_3[Fe(CN)_6]$ solution were tuned in order to obtain best current responses.
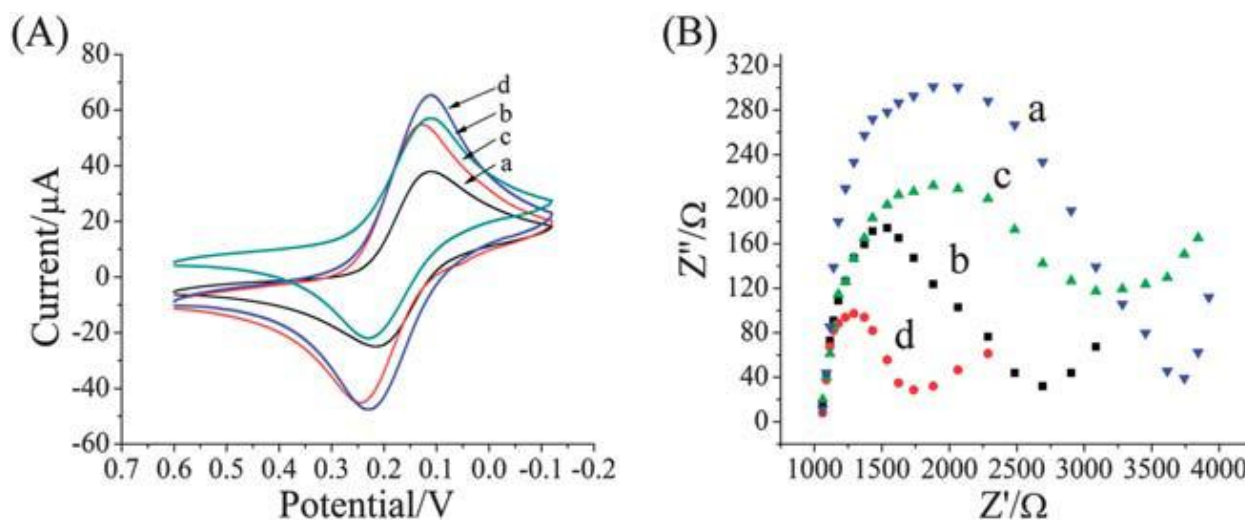

Figure 3. Cyclic voltammograms and corresponding impedance of different modified working electrodes in pH 7.2 PBS containing 0.1 mol L^{-1} KCl and 5.0 mM [Fe(CN)6]$^{3-/4-}$: (a) bare SPE, (b) GR-NH$_2$/SPE, (c) eluted-MIF/NG/SPE and (d) uneluted-MIF/NG/SPE (reproduced with permission from reference [21]).

Under optimized conditions, The current response was linear to methcathinone concentration varying from 4.9×10^{-6} mgmL^{-1} to 9.8×10^{-3} mg mL^{-1} with LOD of 3.3×10^{-6} mgmL^{-1} while it was linear for cathinone from 1.5×10^{-5} mg mL^{-1} to 1.1×10^{-2} mg mL^{-1} with LOD of 8.9×10^{-6} mg mL^{-1}. The fabricated electrochemical sensor excluded crosstalk (the diffusion of an electroactive indicator from one electrode to neighboring electrodes) and the cross-reactivity between methcathinone and cathinone was found to be negligible. Furthermore, it expressed high reproducibility, repeatability and stability with excellent recoveries of methcathinone and cathinone in serum samples in the range of 96.3–104.2%, indicating that the imprinted sensor might be preliminarily applied for the determination of methcathinone and cathinone in the real sample.

Recently, an electrochemical sensor was prepared by utilizing GO and MIP for the determination of Quercetin, a major representative of flavonol and powerful antioxidant. For the preparation of quercetin imprinted polymer incorporated GO modified electrode (MIP/GO/GCE), GO was suspended in DMF and dropped over GCE followed by drying under infrared lamp. Then, electropolymerization was carried in a solution containing appropriate amount of quercetin, pyrrole and H$_2$SO$_4$ using chronocoulometry at 0.7V for 100s and Non-molecularly imprinted polymer electrode (NIP/GO/GC) was prepared as above, but without the template. The experimental steps such as influence of different GO contents, supporting electrolytes, pH and absorption time of templates

over sensor surface were optimized. The electrochemical performance of optimized quercetin sensor was assessed and calibration curve was obtained using DPV.

The fabricated sensor provided the linear oxidation peak current of quercetin in B-R buffer solution in the range from 6.0×10^{-7} to 1.5×10^{-5} $molL^{-1}$ (r2 = 0.997) with a detection limit of 4.8×10^{-8} $molL^{-1}$ (S/N = 3) with good stability and reproducibility. Furthermore, the proposed sensor offered excellent selectivity against some structurally similar compounds (i.e. rutin or morin). The application of the quercetin MIP/GO/GCE sensor was evaluated in complicated matrix of fruit juices with satisfactory recoveries [22].

A highly sensitive uric acid (UA) electrochemical sensor was proposed by lian et al. [23]. This sensor was fabricated by using Gr doped CS as the functional matrix and uric acid as the template molecule. An electrodeposition technique was used to form a controllable GR-CS/MIP composite film on glassy carbon electrode whose uric acid was removed via electrochemical induce elution. Similarly, a chitosan–uric acid (CS/MIP) was also developed for comparison proposes. The SEM of different MIP based sensors and FT-IR for spectra of CS, CS-UA, and CS-Gr-UA composite (GR-CS/MIP) was applied to characterize the properties of the sensors. The electrochemical performance of the proposed sensors was estimated using CV, DPV and EIS techniques. To study the adsorption capacity and rebinding rates of the sensor membrane adsorbed in UA solution, adsorption isotherm and kinetics model were proposed based on the Langmuir equation. The doping quantity of Gr was also optimized for better current response towards UA. The authors also calculated the effective electrode surface with chronocoulomtery indicating that incorporation of Gr could effectively enlarge the adsorption area which in turn increases diffusion coefficient. These results corroborated well with above mentioned proposed adsorption isotherm and kinetics model results. Additionally, the developed sensor exhibited specific recognition to uric acid against the competitors such as AA, DA, caffeine (CF) and xanthine which consisted of structure liked substances and coexisting interference in blood serum. This result proves that graphene will be a good candidate material for enhancing the sensitivity of MIP-based electrochemical sensors to improve their application performance.

A novel composite of RGO and 4-NP imprinted polymer was constructed by Zeng et al. [24]. To construct the desired sensor, firstly, GO was prepared using a from modified Hummer and Offeman method followed by incomplete reduction of GO to RGO. Then, the 4-NP imprinted polymer was synthesized by adding appropriate amount of MAA (functional monomer), EDMA (cross-linker), AIBN (initiator) in solvent and free radical polymerization was proceeded at 60°C for 24 h. The resultant material was eluted with a mixture of solvent in order to extract 4-NP molecules which provided the complementary cavities for rebinding of 4-NP. The non-imprinted polymer was also prepared by following the same procedure but without template for comparison studies. The characterization of RGO-MIP surface was carried out by FT-IR, TGA, SEM and Raman techniques which supported the synthesis of desired material. The fabricated sensor was applied for 4-NP analysis by DPV and the effect of RGO-MIP concentration, absorption time in target solution and pH on the current response of sensor were studied. The 4-NP sensor showed a linear relation between current response and 4-NP concentration in the range of 0.01 to 100.0 µM with LOD of 0.005 µM. The sensor offered high selectivity toward 4-NP compared to NB, DNB, DNT and TNT. Furthermore, high

stability and satisfactory recoveries of target compound during real application in various spiked environmental samples were achieved.

3. SENSOR WITH GRAPHENE AND NANOPARTICLES

Due to the increased interest in graphene arising from its exceptional electrical and mechanical properties, the immobilization of metallic and other nanoparticles on graphene sheets has become the focus of many researchers. A typical pristine graphene sheet can be characterized as an ideal substrate for the dispersion of nanoparticles due to its large active surface area per mass unit, in comparison with carbon nanotubes, amorphous carbon, or graphite, which have a lower active surface area because only the external surface is active [25]. Hence, this part will discuss the functionalization of graphene with various types of nanoparticles systems comprehensively and their potential applications for the fabrication of molecular imprinted polymer based electrochemical sensors.

In an approach for the fabrication of sensitive electrochemical sensor for Erythromycin, Lian et al. [26] utilized dual nanoparticles system decorated over gold electrode. Firstly, CS-platinum nanoparticles (CS-PtNPs) composite was synthesized. In second step, for the synthesis of Gr-AuNPs, GO was prepared by simple method followed by the preparation of polyvinyl pyrrolidone-protected graphene (PVP-protected GR). The PVP-protected Gr solution was mixed with HAuCl4 solution and resulting solution was reduced with $NaBH_4$ to obtain Gr–AuNPs. All the steps were verified by UV–Vis spectroscopy. To construct sensor, the gold electrode surface was modified with CS-PtNPs and then with Gr–AuNPs. The resulting modified gold electrode was immersed in a solution of 2-mercaptonicotinic acid (MNA) and erythromycin for 24 h at r.t and then the electrodes were swept fifteen cycles of CV in the potential range of 0.0 to 0.8 V at 50mV/s in the prepared mixture solution to obtain MIP sensor. NIP sensors were also prepared but without inclusion of erythromycin the solution. The electrochemical performance of the sensors was evaluated with CV and experimental parameters were optimized for highest current response. The current response to erythromycin concentration was linear varying from 7.0×10^{-8} mol/L – 9.0×10^{-5} mol/L. The detection limit (LOD) was 2.3×10^{-8} mol/L which was better than that in previous method. The selectivity of erythromycin was excellent in the presence of other analogues such as kanamycin sulfate, neomycin sulfate and spiramycin and the sensor exhibited good stability, reproducibility and repeatability. Moreover, the application of this sensor was checked by spiking real sample of milk and honey with excellent recoveries ranged from 95.8%−103.0%.

Based on the principal of stable complex formation of chemistry of boronic acid and glycoprotein, a biomimetic sensor was fabricated by utilizing the advantages of graphene–Au nanoparticles hybrid as the electrode modifier, and the immobilization of a large amount of 6-ferrocenylhexanethiol, as the electroactive species, onto nanoparticles. The synthesis of GO and Gr-AuNPs composite were carried out by simple but standard procedures. The Gr–AuNPs/GCE was modified by casting of Gr–AuNPs solution and then allowed to dry at room temperature. The MIP modified Gr–AuNPs/GCE, which is marked as MIP/ Gr–AuNPs/GCE, was prepared via electropolymerization of 5×10^{-4} g mL^{-1} BSA (bovine serum albumin as glycoprotein), 5 mM OPD (o-

phenylenediamine) and 10 mM ABA (3-aminophenylboronic acid monohydrate) monomers by CVs (20 cycles) in the potential range of 0.0 – 0.8 V at a scan rate of 100 mVs^{-1}.

Figure 4 showed the representative TEM and SEM images of graphene and Gr-AuNPs. It is appeared from 4 (A) that the GO was basically transparent with several hundred nanometers size and exhibited the wrinkled and flake like structure. Moreover, it could be found that the spherical shaped AuNPs with an average diameter of 7–10 nm were uniformly deposited on the graphene surface and no aggregation was observed as depicted in TEM and SEM images shown in figure 4 (B) and (C).
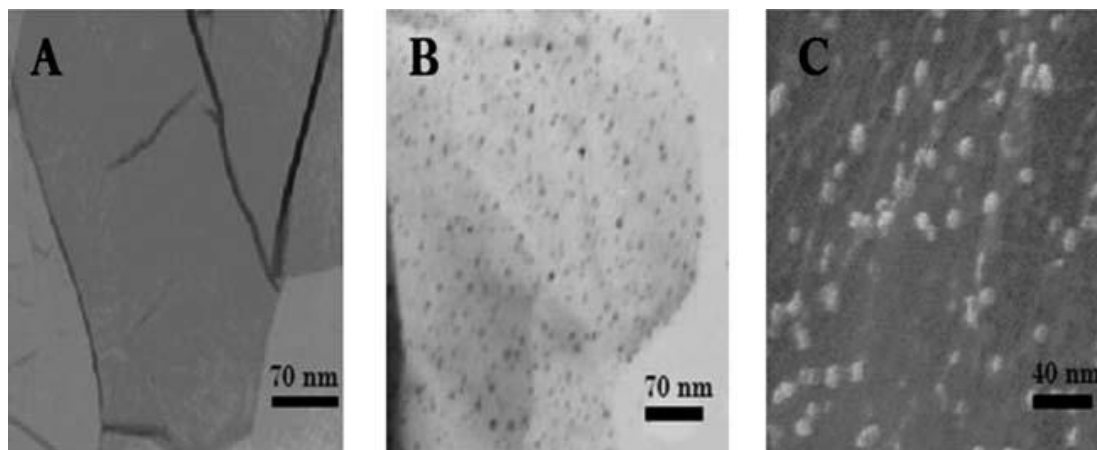

Figure 4. TEM images of GO (A) and Gr-AuNPs (B). SEM image of Gr-AuNPs/GCE (C) (reproduced with permission from reference [27]).

The CV and EIS results were recorded to assess the performance of as-fabricated biomimetic sensor successfully. The results provided the linear calibration graphs of the oxidation peak current of 6-ferrocenylhexanethiol (I) versus logarithm of the BSA concentration range of 1.0×10^{-11} to 1.0×10^{-5} g mL^{-1}. The detection limit was 7.5×10^{-12} g mL-1. The electrochemical sensor shows high selectivity, reproducibility, stability and sensitivity for BSA detection, and it can be potentially applied in practical analysis [27].

A sensitive and selective system for the determination of 17β-estradiol was prepared by a sandwich-type molecular imprinting electrochemical sensor (MIES) by using RGO combined with platinum nanoparticles (PtNPs) by Wen et al. [28].

The Schematic for the preparation of the MIES has been shown in Figure 5. The Functional monomers were chosen with the aid of Gaussian 09 software. The typical SEM images were clicked to evaluate the morphology of the electrodeposited PtNPs, prepared PtNPs, and MIPs films. The CV and EIS studies were carried out for the electrical performances of various modified electrodes including bare GCE, PtNPs/GCE, RGO/PtNPs/GCE, PtNPs/RGO/PtNPs/GCE. Under optimized experimental conditions such as pH of 7 and absorption time of 5 min, two linear ranges of 17β-estradiol concentration from 0.004–0.06 μM and 0.06–50 μM and LOD of 0.002 μM based on S/N = 3 were achieved. The proposed sensor was found to be stable, reproducible and selective. Furthermore, it has

been applied for the determination of 17β-estradiol in real samples of makeups (hand cream and facial cleanser within acceptable recoveries upto ~ 95%.
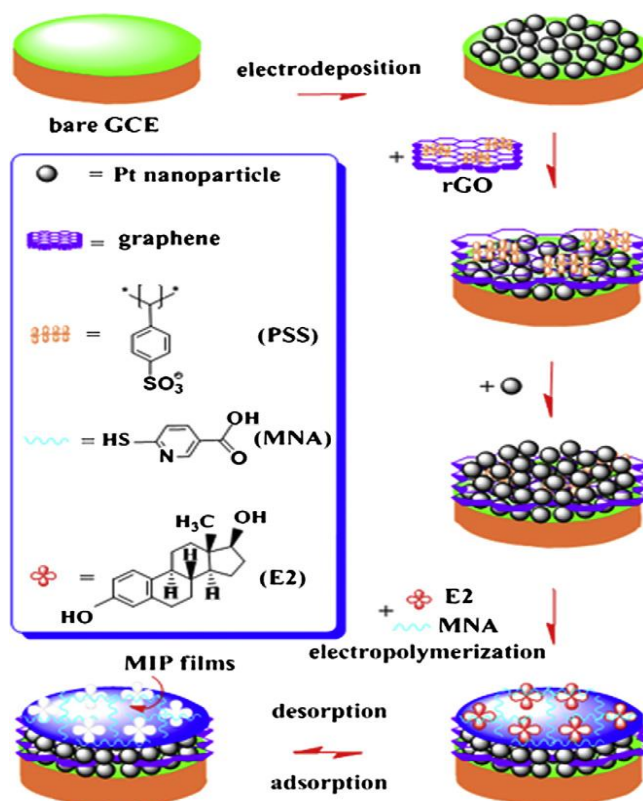

Figure 5. Preparation scheme of MIES sensor (reproduced with permission from reference [28]).

Recently, Wang et al. [29] proposed a simple strategy for the construction of a highly sensitive levofloxacin (LEV) sensor. They synthesized a Gr-AuNPs nanocomposite, drop coated the suspension on polished GCE and dried to obtain Gr-AUNPs/GCE. To construct LEV-MIP sensor, the Gr-AUNPs/GC was immersed in 0.05 M PBS solution of pH 6.8 containing 1 mM pyrrole and 1 mM LEV followed by electropolymerization by CV from −0.2 V to 0.80 V at a scan rate of 50 mV s^{-1} for six cycles. After MIP film formation, the LEV molecules were removed out of the film by overoxidation with three cycles of CV scan from 0.2 to 1.2 V in 0.2 M Na_2HPO_4 solution.

The SEM possessed the standard wrinkled pattern of graphene and spherical forms of AuNPs in respective material of Graphene, Gr-AuNPs composite and MIP/G-AuNPs. The electrochemical response of the LEV-MIP sensor exhibited remarkably enhanced peak, accompanied with negative shift of anodic peak potential, indicating the catalysis of G-AuNPs to the oxidation of LEV compared to Graphene or Gr-AUNPs modified sensors. The electropolymerization conditions and experimental parameters were optimized to get optimum results from the MIP sensor. The proposed sensor showed linearly proportional current response to concentration of LEV in the range of 1.0 –100 µmol L^{-1} and LOD was estimated to be 5.3×10^{-7} mol L^{-1}. According to experimental results shown in literature, the proposed electrochemical sensor exhibited good reproducibility with RSD of 2.62%, good selectivity

in the presence of some analogs, such as chlorotetracycline, oxytetracycline, prulifloxacin, norfloxacin and feasible for the fast determination of LEV in real samples.

4. ELECTROCHEMICAL SENSOR BASED ON CARBON NANOTUBES (CNT) AND GRAPHENE COMPOSITE

Chen et al. [30] proposed an electrochemical MIP sensor for the detection of BSA based on carbon nanotubes (CNT) and graphene composite. Firstly, the GO was prepared and reduced to graphene with hydrazine. The homogenous suspension of graphene in DMF was casted over polished surface of GCE and dried to achieve Gr/GCE electrode. In order to obtain CNT/Gr/GCE electrode, the Gr/GCE was modified with p-nitroaniline in appropriate conditions and electrochemically reduced to amine groups by electrochemical scanning followed by immersion in SWCNTs solution. The BSA imprinted membrane was electrodeposited onto the carbon electrode by performing six cycles of CV from -0.4 and 1.2 V in the presence of aniline, PBS and BSA. Finally, the imprinted electrode was rinsed with a buffer solution containing 5% acetic acid and 10% SDS three times to remove the template BSA. The $Fe(CN)_6^{3-/4-}$ was used as electrochemical probe and electrochemical measurements were carried out using CV, EIS and DPV. The morphology characterization of bare CE, Gr/CE, CNTs/Gr/CE, MIPs/CNTs/Gr/CE was performed SEM technique. The MIPs/CNTs/Gr/CE provided response in the concentration range from 1.0×10^{-4} to 1.0×10^{-10} g mL^{-1} possessing the low detection of 6.2×10^{-11} g mL^{-1} for S/N=3. The DPV exhibited high stability and selectivity in presence of other proteins like human serum albumin (HSA), bovine hemoglobin (BHb). The successful application of the proposed sensor was tested in human serum samples with a good average recovery of 99.5% for six measurements, indicating that the proposed sensor is accurate and reproducible.

For the determination of tryptamine, an imprinted electrochemical sensor based on polypyrrole-sulfonated graphene (PPy-SG)/hyaluronic acid-multiwalled carbon nanotubes (HA-MWCNTs) was fabricated by electropolymerization using tryptamine as the template, and para-aminobenzoic acid (pABA) as the monomer. Under optimum experimental conditions, the current response was linear to tryptamine concentration varying from 9.0×10^{-8} molL^{-1} to 7.0×10^{-5} molL^{-1} and the LOD was 7.4×10^{-8} molL^{-1}. The sensor was high stable, reproducible, selective and applicable in real samples [31].

A complex strategy was applied by Lian et al. [32] for the determination of Neomycin. They fabricated a sensor based on neomycin imprinted polymer by modifying the gold electrode with CS-silver nanoparticles (CS-AgNPs)/Gr-multiwalled carbon nanotubes (Gr-MWCNTs) composites. The MIP membrane was fabricated by electropolymerization of neomycin as the template, pyrrole as the monomer in PBS solution using CV between -0.35 and 0.85V with a scanning rate of 0.05V/s. In order to obtain neomycin imprinted cavities for rebinding, the imprinted molecules of neomycin were extracted. For comparison, NIP sensor was prepared using the same method mentioned above but without the addition of neomycin. The SEM images were taken for morphology and electrochemical performance of fabricated electrode were carried out using CV. Under optimized experimental conditions, figure 6 expressed the linear range of neomycin concentration Vs. current response varying from 9×10^{-9} to 7×10^{-6} molL^{-1} while the LOD was calculated to be 7.63×10^{-9} molL^{-1}. Furthermore, the

sensor was applied for real sample analysis with satisfactory results and found to be highly selective, stable and reproducible.
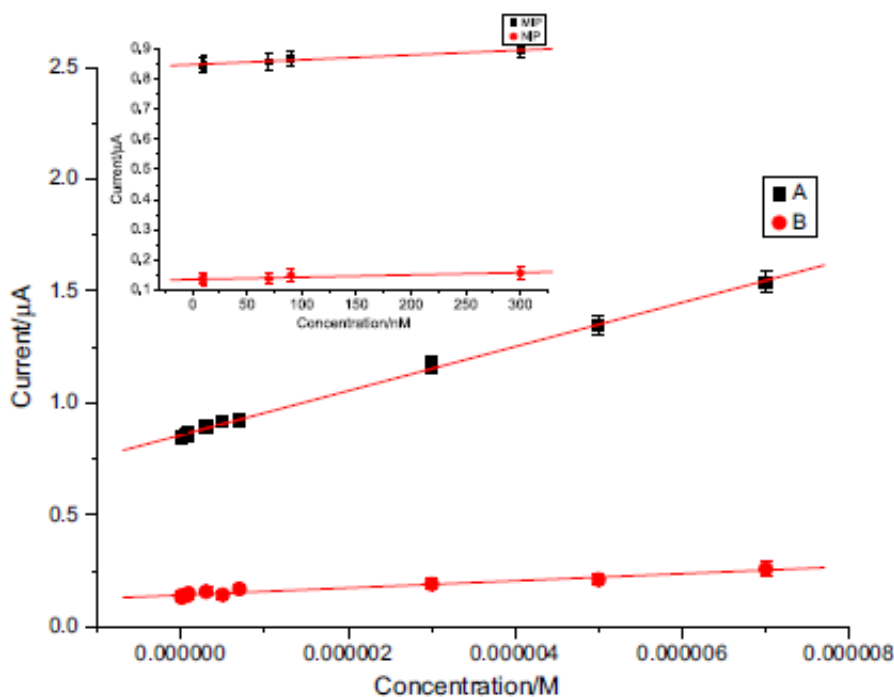

Figure 6. Calibration curves of sensors in different concentrations of neomycin solutions. (a) Neomycin-imprinted sensor, (b) non-imprinted sensor. Applied potential: +0.5 V. Inset figure: calibration curves of sensors in low concentrations of neomycin solutions of Fig. 4 from 9.0×10^{-9} to 3.0×10^{-7} molL^{-1} (reproduced with permission from reference [32]).

5. APPLICATION OF IONIC LIQUID IN MIP BASED ECS

Recently, few research works have shown the utilization of Ionic liquids (ILs) as they possess high ionic conductivity, wide electrochemical windows and good solubility [33]. In addition, they are shown to have excellent shielding effect to the π-π stacking interaction among graphene sheets, thus promoting the dispersion of graphene sheets which in turn improve the performance in fabricating electrochemical sensors [34].

In a recently published work by Zhao et al. [35], a sensitive and selective methyl parathion electrochemical sensor was achieved based on MIP–ionic liquid–graphene composite film coated on glassy carbon electrode (MIP–IL–Gr/GCE). For the fabrication of MIP, certain amount of MP was dissolved in methanol, methacrylic acid, EDMA and AIBN and prepcipitatipn polymerization was proceeded for 24 h at 60°C. The resultant MIP was washed and MP molecules were extracted. Then, commercially available GO was suspended in a solution of ionic liquid 1-(2'-hydroxylethyl)-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]imide([HeMIM][NTf2]) in DMF. Few drops of as prepared solution were casted over pre-cleaned GCE followed by coating of MIP in similar manner and dried to obtain MIP–IL–Gr/GCE. The stepwise morphological and structural modification

characterizations were carried out by SEM and FT-IR. The SEM and FT-IR supported the successful synthesis of desired materials. The CV behavior of as-prepared MIP–IL–Gr/GCE was studies under different optimized parameters including types of IL, amount of GO/MIP, pH of solution and accumulation time of MP. The calibration was plotted between concentrations of MP and their current responses. It presented fine linear relationship in the range from 1.0×10^{-8} M to 7×10^{-6} M. Furthermore, the MP sensor exhibited excellent stability, selectivity, reproducibility and real applicability.

Based on the utilization of IL, a novel molecularly imprinted polymer (MIP) for Cefotaxime (CEF) was synthesized by using gold networks@IL (IL,1-butyl-3-methylimidazolium tetrafluoroborate,[BMIM][BF$_4$]) (GNWs@IL), porous platinum nanoparticles (PPNPs) and carboxyl graphene (COOH-r-GO). The GNWs@IL is prepared by directly reducing HAuCl$_4$ with sodium citrate in [BMIM][BF$_4$] aqueous solution. The PPNPs are well embedded in GNWs@IL due to the adhesion of IL to form GNWs@IL-PPNPs suspension, which is coated on a COOH-r-GO modified GCE to construct a porous three- dimensional networks modified electrode.
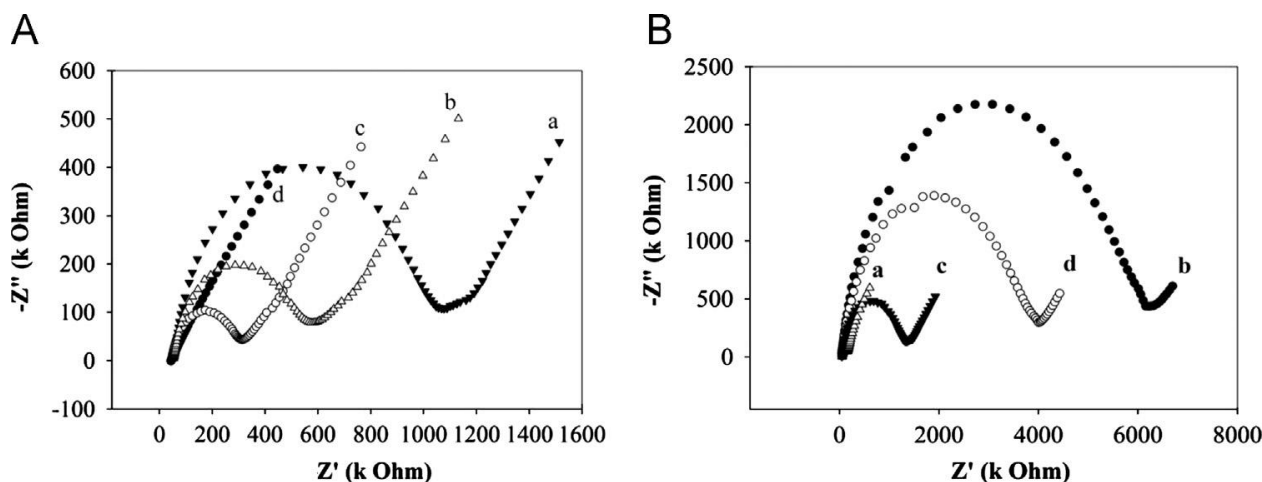

Figure 7. (A) EIS of bare GCE (a), COOH-r-GO (b), PPNPs/COOH-r-GO (c), GNWs@IL-PPNPs/COOH-r-GO (d) in 5.0 mmolL^{-1} K$_3$Fe(CN)$_6$/K$_4$Fe(CN)$_6$ containing 0.1molL^{-1} KCl; (B) EIS of GNWs@IL-PPNPs/COOH-r-GO (a), MIP/GNWs@IL-PPNPs/COOH-r-GO (with template molecules) (b), MIP/GNWs@IL-PPNPs/COOH-r-GO (removing template molecules) (c), and after rebinding of CEF (1.0×10-7 mol L-1) (d) in 5.0 mmolL-1 K$_3$Fe(CN)$_6$/K$_4$Fe(CN)$_6$ containing 0.1molL^{-1} KCl (reproduced with permission from reference [36]).

Then, MIP is prepared by CV at the modified electrode, using CEF as template and o-phenylenediamine as monomer. The SEM and TEM were used to study morphological and structural properties while the EIS was used to characterize the change of electrode surface (shown in Figure 7) after each stepwise modifications carried out over GCE. The various optimized parameters were the effect of the concentration of COOH-r-GO concentration of GNWs@IL, concentration of PPNPs, effect of the mole ratio of template molecule to functional monomer, electrochemical polymerization time, Effect of adsorption time and Effect of pH. Under optimal experimental conditions, the DPVs of

CEF were recorded. As expected, the peak current increased upon the increase of CEF concentration. A linear current response of CEF Vs. its concentrations varying from 3.9×10^{-10} to 8.9×10^{-6} molL^{-1} was obtained. The LOD of the sensor was calculated to be 1.0×10^{-10} molL^{-1}.

Moreover, authors claimed to obtain good selectivity, stability and reproducibility of the sensor. The proposed electrochemical sensor was also applied to real sample successfully [36].

Same research group presented another electrochemical sensor for the determination of carbaryl based on the application of IL, various types of nanoparticles and graphene. In order to construct the desired sensor, CS-AuPt alloy nanoparticles (CS-AuPtNPs), graphene-ionic liquid-nano Au (Gr-IL-Au) and electrodeposition of carbaryl imprinted poly(p-aminothiophenol) (p-ATP) film over GCE were carried out in sequence. It was proved that CS-AuPtNPs and Gr-IL-Au composites contributed the roles to immobilize monomer p-ATP and to enhance the electrochemical response obtained from carbaryl [Fe(CN)$_6$]$^{3-}$/[Fe(CN)$_6$]$^{4-}$ acted as electrochemical probe. Under the optimal conditions, a linear range from 0.030 μM to 6.0 μM with a sensitivity of 4.0 μA/μM mm^2 was obtained. The sensor exhibited LOD of 8.0 nM. The resulting sensor displayed good selectivity and stability towards carbaryl and successfully applied to the determination of carbaryl in practical samples and the recovery was 96 - 105% as reported by authors [37].

6. MIXED APPROACHES FOR THE MIP ELECTROCHEMICAL SENSORS

This section will present the fabrication of electrochemical sensors based on mixed approaches.

Zeng et al. [38] reported a different procedure on the preparation of dopamine imprinted polymer modified over SiO$_2$-coated GO surface through γ-methacryloxypropyltrimethoxysilane (γ - MAPS) chemistry. The SiO$_2$-coated GO sheets were synthesized in a water–alcohol mixture with sol–gel technique. The fabrication scheme of GO/SiO$_2$–MIP has been depicted in Figure 8. The stepwise modifications of surface were characterized SEM, AFM, FT-IR, TGA and Raman spectroscopy. The parameters including special binding, adsorption dynamics and selective recognition ability using DPV were evaluated. The dopamine sensor provided a linear current response vs. various dopamine concentrations from 5.0×10^{-8} to 1.6×10^{-4} M with a LOD of 3.0×10^{-8} M. The sensor showed negligible interference in the presence of other structurally similar molecules such as norepinephrine and epinephrine. In addition, the sensor was successfully applied to the determination of DA in injections and human urine samples.

A simple strategy to prepare dopamine imprinted electrochemical sensor based on Gr-CS composite has been proposed. Firstly, DA–Gr–CS deposition solution was prepared by ultrasonically dispersed 0.05 g Gr into the 10 mL 5 gL^{-1} CS solution (pH = 5.0) firstly and then added into 1.0×10^{-3} M DA drop by drop. Finally electrodeposition was performed by immersing GCE into as-prepared solution at -1.1 V for 3 min and dried. Later, the imprinted DA molecules were eluted in KCl and ethanol mixture at a potential of 0.3V for 20 min to achieve imprinted cavities for DA inside polymer network. The XRD, attenuated total reflection infrared spectroscopy (ATR-IR), EIS, CV and DPV characterization supported the synthesis of desired material. The calibration curve was plotted in the concentration range of DA from 1.0×10^{-9} to 8.0×10^{-8} M and 1.0×10^{-7} to 1.0×10^{-4} M with LOD of

1.0×10^{-11}M. The developed sensor exhibited good selectivity toward and applicability in blood serum samples with a recovery of 96.7–105.0% [39].
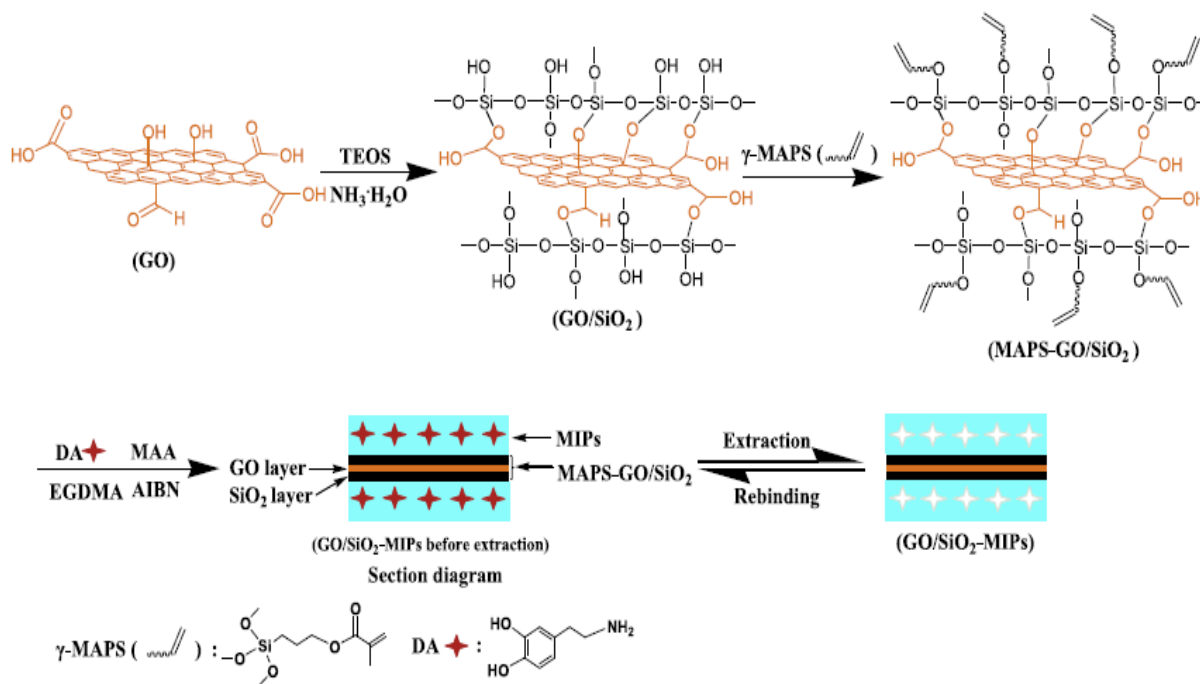

Figure 8. Fabrication scheme of GO/SiO$_2$–MIP (reproduced with permission from reference [38]).

In a study performed by Cui et al. [40], an electrochemical sensor for the detection of butylated hydroxyanisole (BHA) in foodstuffs based on composite consisting of graphene–Prussian blue (GR–PB). Prussian blue (PB), a metal hexacyanogerrate and inorganic conductive film, has been used to prepare chemical sensors and biosensors owing to extraordinary electrochemical and electrocatalytic property. Hence, a composite of PB was synthesized by utilizing RGO and coated over GCE followed by electropolymerization of BHA with pyrrole under appropriate experimental conditions to acquire BHA-MIP/Gr-PB/GCE sensor. The morphological characterization was studied by SEM while the electrochemical performance of the sensors was studied by CV and EIS. After careful optimization of experimental parameters, a wide linear concentration range varying from $9 \times 10-8$ mol L^{-1} to 7×10^{-5} mol L^{-1} with LOD of 7.63×10^{-8} mol L^{-1} was obtained. To evaluate the selectivity of as-fabricated sensor toward BHA, some analogues such as butylated hydroxyl toluene (BHT), ascorbic acid and citric acid were used. However, the interference was found to be weaker. The sensor also depicted high reproducibility, repeatability and stability with RSD of 4.1%. Finally, the proposed sensor was employed in testing of BHA in potato chip samples by standard addition method and the recoveries were from 96.7% to 103.0%, with an RSD of less than 5.2%.

Hence, it was concluded that the combination of Gr and PB has a synergistic effect which exhibited high electrocatalytic activity and electrocatalytic sensitivity.

A simple and exciting strategy was developed for indirect determination of tetrabromobisphenol A (TBBPA), a brominated flame retardants (BFRs) used in the manufacturing

sector around the world. For TBBPA sensor, laboratory synthesized 4-nitrobenzenediazonium benzenediazonium tetrafuoroborate was electrodeposited over GCE using CV from -0.5 to -1.8 V for five cycles at a scan rate of 50 mV s^{-1}. Then, the nitro groups were electrochemically reduced to amine groups by scanning the potential from -0.4 V to -1.6 V at 50 mV s^{-1} in a 10% ethanolic solution for three cycles to acquired amine terminated benzenediazonium modified electrode (NBD/GCE). Then, it was immersed in GO solution and electrochemical reduction of GO was conducted by CV scan from 0 to -1.3 V at a scan rate of 50 mV s^{-1}for four cycles in 0.5 M NaCl solution. Finally, MIP film was fabricated by introducing TBBPA in pyrrole solution by CV scanning between 0 and 0.85 V with a scanning rate of 50 mV s^{-1} followed by drying and template extraction.

The electrochemical characteristics and morphologies of the imprinted sensor were investigated using CV and SEM, respectively. The direct determination of TBBPA is very difficult task as it provides poor peak current due to contaminants. Hence, indirect detection for TBBPA was successfully implemented by monitoring the peak current of Fe(CN)$_6^{3-/4-}$-TBBPA complex. The authors reported to achieve a linear current response from 0.5 to 4.5 nM with a LOD of 0.23 nM. The fabricated sensor showed good selectivity against other coexisting interfering species, reproducibility of about 15 days with just 4.5% decrease in response and satisfactory application in rain and lake water samples [41].

Yang et al. [42] presented a sensitive molecularly imprinted electrochemical sensor based on one-step controllable electrochemical modification of poly(pyrrole)-GO-binuclear phthalocyanine cobalt (II) sulphonate (PPY-GO-BiCoPc) for the determination of quinoxaline-2-carboxylic acid (QCA). All the reagents were commercially available and the sensor was fabricated as follows; the GO was dispersed in pyrrole and BiCoPc . Then, pre-cleaned GCE was immersed in the mixture and CV was performed from −0.2 to +0.8 V (vs. SCE) with a scan rate of 20 mV s−1for 3 cycles to achieve PPY-GO-BiCoPc/GCE. Finally, MIP/PPY-GO-BiCoPc/GCE was prepared by electropolymerization of QCA and monomer o-phenylenediamine (oPD) from 0 to +0.8 V for 5 cycles at a scan rate of 50 mV s−1. The stepwise modification of GCE surface was studies by SEM and electrochemical performance was evaluated with CV. Under the optimized experimental parameters, the proposed MIP sensor possessed good linear relationship of anodic current response of square wave voltammetry (SWV) to the concentration of QCA in the range of $1.0 \times 10^{-8} - 1.0 \times 10^{-4}$ and $1.0 \times 10^{-4} - 5.0 \times 10^{-4}$ mol L^{-1} with LOD of 2.1 nmol L^{-1}. The proposed sensor exhibited good selectivity and applied successfully to determine QCA in commercially available meat samples with acceptable recoveries between 91.6–98.2%.

Recently, a highly sensitive imprinted electrochemical determination of chrysoidine was carried out based on magnetic GO/β-cyclodextrin/gold nanoparticles composites (MGO/β-CD@AuNPs). Firstly, MGO were synthesized by coprecipitation method in the surface of GO using appropriate amount of ferrous and ferric chloride dissolved in aqueous ammonia. Because of the excellent properties of resulting MGO, β-CD was adsorbed easily on MGO by hydrogen bond. Then AuNPs were assembled on the surface of MGO/β-CD by Au–S bond. Subsequently, GCE was kept in the solution of chrysoidine, pyrrole and KCl and imprinted polymer membrane was formed by CV electropolymerization between -0.1 V and 0.1 V at 100 mV s^{-1} for fifteen cycles, dried and templates were extracted. The NIP sensor was also prepared using the same procedure except chrysoidine.

The surface of GO, AuNPs and MGO/β-CD@AuNPs were characterized by SEM, FT-IR and XRD. The electrochemical behaviors of various modified electrodes were studied by CV and EIS with $K_3Fe(CN)_6$ as the redox probe. After careful optimization of different experimental conditions, the current response and concentrations of chrysoidine showed a good linearity between from 5.0×10^{-8} to 5.0×10^{-6} molL^{-1} was obtained. The LOD was 1.7×10^{-8} molL^{-1}. The established sensor possessed excellent selectivity in the presence of some common ions such as NH^{4+}, Na^+, K^+, Fe^{2+}, SO_4^{2-}, CO_3^{2-} and colorants methyl red, helianthin. It also showed good reproducibility and stability. Furthermore, it was applied for the determination of chrysoidine in spiked water samples with satisfactory recoveries [43].

In another approach reported by Deng et al. [44], a MIP electrochemical sensor for the determination of bisphenol A (BPA) was fabricated using acetylene black paste electrode (ABPE). Firstly, unexfoliated GO was synthesized followed by preparation of a solution consisting of BPA, CS and GO. The as prepared solution was drop coated over well-polished ABPE body. The electrode was tagged as BPA-CHIT-GO/ABPE. The imprinted molecules of BPA were removed by CV potential sweeping the modified electrode in 0.1 M HCl between 0.2 and 1.2 V repeatedly. Finally, as-modified electrode was kept in PBS buffer at -1.2 V for 120 s to achieve MIP–Gr/ABPE. The non-imprinted electrode (NIP–Gr/ABPE) was prepared under the same experimental conditions but without BPA molecules. FT-IR was used to characterize the different modified electrodes (stepwise modifications) and electrochemical measurements were carried out using LSV and CV as required. After optimizing the experimental conditions including type of supporting electrolytes, pH of the solution and accumulation time of molecules over MIP surface, authors obtained two linear relationships from 8.0 nM to 1.0 μM and 1.0 to 20 μM between the anodic peak current and BPA concentrations. The LOD was calculated to be 6.0 nM. The proposed sensor showed excellent selectivity, reproducibility and stability. Finally, it was employed to detect BPA in plastic bottled drinking water and canned beverages and recoveries of BPA achieved were in the range of 92–106%. These results were in good agreement with the results obtained from HPLC technique.

7. FUTURE PERSPECTIVES AND CHALLENGES

From the literature review during the preparation of the present review, it was realized that future of the electrochemical sensors based on MIP and Graphene (or GO) is bright. The goal of an electrochemical sensor is high sensitivity and fast analysis time. The approaches where utilization of Gr/GO together with other nanomaterials such as AuNPs, AgNPs, PtNPs and other inorganic or organic conductive films exhibit an extraordinary synergistic effect required for fast electron transfer and electro-catalytic activities. Furthermore, the MIP technique offer specificity which is another important aspect needed during real sample applications of the established sensor. Hence, it could be envisaged that MIP together with graphene system could provide an excellent platform for electrochemical sensor. In near future, the readers can expect huge research articles based on these principles and system.

However, the road ahead brings many challenges for scientists. Firstly, the problem may lie in the fabrication of good quality of Gr/GO and their reproducibility which is main concern during graphene synthesis. Furthermore, challenges remain in understanding and developing the chemistry of various types of graphene (with different morphologies) and their structural properties [45].

Second, MIP technique shows unique features of selectivity, however, non-specific selectivity, the formation of non-uniform imprinted cavities, selectivity of analogues over imprinted templates, deep burial of cavities inside polymer network and synthesized nanocomposite are the main challenges.

Hence, careful considerations of all the experimental conditions may alleviate the approach.

8. CONCLUDING REMARKS

In summary, this review briefly summarizes various combined approaches of MIP technique, graphene and other nanosystems for the fabrication of various electrochemical sensors. It was observed that since last 2-3 years, many articles have been reported on these approaches. These sensors exhibit excellent sensitivities, reproducibilities and stabilities. Due to the incorporation of MIP, they are found to be highly selective and can easily be applicable for real sample applications. The superior electrochemical sensing performances of MIP and graphene/other nanocomposite systems -based electrodes towards the detection of various biomolecules and chemicals have been demonstrated in this review, especially the recent progress of applications of graphene in electrochemical sensors has been addressed. It is expected that more electrochemical studies on these combined strategies should show up in the near future

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