Microchemical Journal 165 (2021) 106151

Contents lists available at ScienceDirect

Microchemical Journal

journal homepage: www.elsevier.com/locate/microc

Review Article

Modified electrodes for electrochemical determination of metronidazole in drug formulations and biological samples: An overview

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ARTICLE INFO

Keywords:
Chemically modified electrodes
Carbon material
Polymer
Real sample analysis
Metronidazole

ABSTRACT

Metronidazole (MTZ) is an antibiotic drug derived from nitroimidazole, widely utilized for the treatment of various diseases caused by anaerobic bacteria and protozoa in human and domestic animal. However, this medicine is banned in several countries due to its high hazardous in nature, results in causing genotoxic, carcinogenic and mutagenic side effects. Several research groups are investigating its toxic adverse effect as well as removal from the environment sources. Thus, numerous analytical techniques have been reported for the detection of MTZ in various sources including drug formulations, environmental sources and biological samples. Herein, a comprehensive literature survey on electrochemical methods for the quantitative determination of MTZ and analogue drugs is shown. In this context, various kinds of chemically modified electrodes (CMEs) based sensors were developed instead of bare electrodes to overcome the obstacles like electrode fouling, less electrocatalytic activity, poor sensitivity and selectivity. Furthermore, CMEs have good anti-interference ability towards several MTZ co-existing substances. This overview presents the merits and demerits of various electrode materials used for the electrochemical detection of MTZ under various experimental conditions towards developing a new protocol or electrochemical strategy to improve the detection limit and standardising the experimental protocol. In addition, new challenges and opportunities of CMEs based electrochemical determination for the MTZ is also discussed.

1. Introduction

Metronidazole (2-methyl-5-nitroimidazole-1-ethanol) is one of the nitroimidazoles derived antiprotozoal drug, developed in 1960 as an effective medicine used to treat several infections caused by anaerobic bacteria and protozoa in human and domestic animal [1,2]. It was reported that metronidazole (MTZ) is an effective antimicrobial agent against anaerobic bacteria (*Bacteroides*, *Campylobacter*, *Clostridium, Fusobacterium, Helicobacter*), anaerobic protozoans (*Trichomonas*, *Treponema*, *Histomonas*), Vincent's organisms, amoebiasis, cytotoxic agent and Crohn's disease [3–7]. MTZ drug is primarily used in domestic animal to treat haemorrhagic enteritis disease and in poultry, histomoniasis and trichomoniasis infections. Despite of its efficient antimicrobial property, MTZ has genotoxic, carcinogenic and mutagenic side effects and so it is highly hazardous to both human and wildlife health [8,9]. Hence, MTZ is banned by several countries including European Union (EU), Ministry of Agriculture of the People's Republic of China and US food and drug administration (FDA). According to the International Agency for Research on Cancer (IARC), it has been reported that MTZ causes cancer in some animals because MTZ used along with animal feed as supplement, however there is no sufficient data to prove the MTZ induced carcinogenicity to human being [10–12]. When it is used for severe infection in long term, it can result in various severe conditions such as peripheral neuropathy, optic neuropathy, neutropenia as well as central nervous toxicities including encephalopathy, seizures and cerebellar ataxia [13,14]. Hence, monitoring the concentration level of MTZ is highly essential for the patients consume MTZ drug in long term [15,16]. Discharging MTZ can accumulate in the open environment due to its high solubility, limited biodegradability, photo and hydrolytic stability. Thus there is an increasing demand to explore scientific methodology for removal as well as degradation of such a drug from various environmental sources.

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https://doi.org/10.1016/j.microc.2021.106151
Received 4 January 2021; Received in revised form 5 March 2021; Accepted 6 March 2021
Available online 17 March 2021

In the past several decades, various analytical techniques such as spectrophotometer, flow-injection analysis, solid phase extraction, colorimetry, gas chromatography (GC), Surface-Enhanced Raman spectroscopy (SERS), liquid chromatography with tandem mass spectroscopy (LC-MS-MS), capillary zone electrophoresis (CZE), thin layer chromatography (TLC), high performance liquid chromatography (HPLC) have been employed to detect MTZ in food products, drugs, environmental and biological samples [17–62], etc. Table 1 and Fig. 1 summarize various methods reported for the determination of MTZ in different types of samples. Most of the methods reported for the detection of MTZ are time-consuming, expensive and eco-unfriendly and need trained technicians. In the recent past, there have been increasing interests on electrochemical methods for the determination of electroactive species due to low cost, more facile, portability, rapid, selective and sensitive, easy handling, accurate detection with lower detection limit, good repeatability and reproducibility [63,64].

MTZ have aromatic nitro group which can undergo facile reduction reaction at various electrode systems such as HMDE, glassy carbon, gold, carbon fiber and carbon paste electrodes. However, those bare electrodes are susceptible towards adsorption of metronidazole and its reducible species during redox reaction, which contaminates the electrode surface and thereby the analytical performances such as sensitivity, selectivity and feasibility and hamper the redox reactions. To overcome such problems, chemically modified electrodes (CMEs) have been frequently employed as working electrode for electrochemical sensing applications [65–69]. Several functionalized materials and nanocomposite like conducting polymers, metal nanoparticles, metal oxides and metal nanoparticles dispersed nanocomposites, redox mediators and clay materials have been utilised to generate CMEs and the consolidated reports of the various detection methods from different samples are given in Figs. 1 and 2. In this context, several research groups have been working to develop electrochemical method with novel sensor materials for the enhanced detection of MTZ in environmental sources and biological samples. As compared to the bare electrodes, CMEs improve the electrochemical response, sensitivity and selectivity with lower detection limit and reduces electrode fouling. The prime objectives of the present work are to consolidate the overall developments and their salient features. It will be useful for the further development of CMEs for a single drug and a combined multidrug formulation as well as other sources. Here we mainly focused to compile the available research data on the electrochemical detection of MTZ using CMEs in various sources like food products, drugs, body fluids, environmental and biological samples.

Table 1
Various methods other than electrochemical technique reported for the determination of MTZ.

S. No	Method	Material	LOD	Type of sample	Ref
1.	Fluorescence spectrophotometer	g-C_3N_4 nanosheet	0.008 μg mL^{-1}	Urine and plasma	[17]
2.	SERS	NA	10 μg/mL	Tap, lake, swamp waters and soil	[18]
3.	Fluorescence spectrometer	CDs	0.257 μg mL^{-1}	Honey and MTZ tablets	[19]
4.	Fluorescence spectrophotometer	Turn-off FCNs	279 nM	Commercial tablets and rabbit plasma	[20]
5.	Fluorescence spectrophotometer	GQDs-embedded SMIP	0.15 μM	Plasma matrixes	[21]
6.	Ion Mobility Spectrometry	MIP	10 μg/L	Pharmaceutical and Human Serum	[22]
7.	FIC	ZnO-doped CQDs	1.08×10^{-10} g/mL	Tablet	[23]
8.	CZE	NA	6.0×10^{7} mol/L	Human urine	[24]
9.	HPSAM	NA	0.83 μg mL^{-1}	Human urine	[25]
10.	HPLC	NA	40 ng/mL	Human Plasma	[26]
11.	LC-MS-MS	NA	0.5 μg kg^{-1}	Egg	[27]
12.	Fluorescence spectrophotometer	AuNCs@BSA	0.01 μM	Human saliva	[28]
13.	HPLC-UV	NA	0.002 μg g^{-1}	Tilapia fish muscle	[29]
14.	NS-ESI-MS/MS	NA	0.5 ng mL^{-1}	Human urine samples and drugs	[30]
15.	RP-HPLC	NA	0.33 μg mL^{-1}	Drugs for ovule	[31]
16.	UV–Vis spectrophotometer	nano-Fe_3O_4	NA	Waste water	[32]
17.	LC-MS/MS	NA	0.17 μg kg^{-1}	Bovine muscle	[33]
18.	HPLC	NA	0.25 μg/gm	Brine shrimp	[34]
19.	Colorimetry	MA@GNPs	2 nM	Milk and water	[35]
20.	Magnetic solid phase extraction	TCMP	0.012 ng mL^{-1}	Water	[36]
21.	GC	NA	5.8×10^{-7} mol/L	Chicken muscle	[37]
22.	Fluorescence spectrophotometer	CDs	1.2×10^{-7} mol/L	Tablets	[38]
23.	Luminescence Spectrometer	AEC immobilized dye	9.0×10^{-6} mol/L	NA	[39]
24.	UPLC-MS/MS	MIL-101(Cr)	0.03 μg/L	Water	[41]
25.	PEI	cg-C_3N_4	0.005 μM	Oral medicine	[42]
26.	Sol-gel	MWCNTs/oxide reinforced hollow fibers	0.01 mg L^{-1}	Milk Products	[43]
27.	Luminescent	Eu-TDC	0.58 μg mL^{-1}	Water	[44]
28.	Solid phase extraction	Magnetic nanoparticles	0.05 μmol/L	Milk and honey	[45]
29.	Fluorimetry	PCDs	20 ng mL^{-1}	Milk	[46]
30.	LC–MS/MS	NA	1.0 μg kg^{-1}	Honey	[47]
31.	HPTLC	NA	0.61 μg mL^{-1}	Tablet	[48]
32.	Spectrophotometry	Chloranilic acid	1.88 μg mL^{-1}	Drug	[49]
33.	LC-MS/MS	NA	50 ng mL^{-1}	Human plasma and bile fluid	[50]
34.	Fluorescence quenching	TPPCA	0.004 μg mL^{-1}	Drugs	[51]
35.	LC-MS/MS	NA	3.4 ngL^{-1}, 0.4 ng L^{-1} and 0.3 ng L^{-1}	Water, sediment and fish tissue	[52]
36.	Microbore HPLC method	NA	0.01 μg/mL	Rat blood, brain and bile	[53]
37.	VSM	$ZnFe_2O_4$@MC	28.05 emu/g	Waste water	[54]
38.	Chemiluminescence	CDM	3.91×10^{-7} mol/L	Human plasma	[55]
39.	HILIC	NA	0.008 μg/mL	Serum	[56]
40.	GC–ECNI-MS	NA	0.1 μg kg^{-1}	Offal tissues	[57]
41.	HPTLC densitometry	NA	3.17 ng $band^{-1}$	Acute pancreatic patients	[58]
42.	TLC densitometry	NA	0.32 μg $band^{-1}$	Tablet	[59]
43.	HPLC	NA	2.1 μg/mL	Industrial effluents	[60]
44.	DSC	NA	194.6 J/g	Antimicrobial drugs	[61]
45.	NMR	NA	0.5 mg	Urine	[62]
46.	SERS	G–AuNPs	1.1 mg L^{-1}	NA	[165]

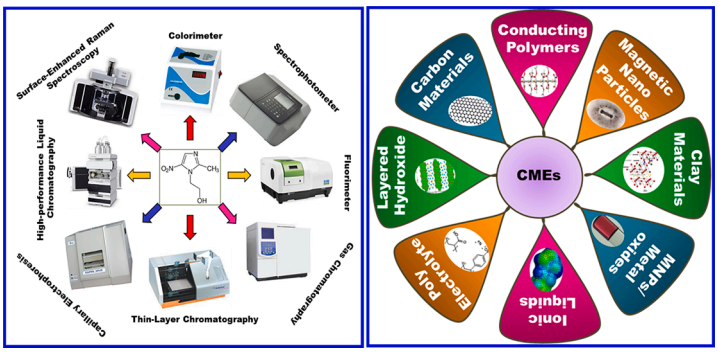

Fig. 1. Different types of methods and materials for the determination of MTZ.

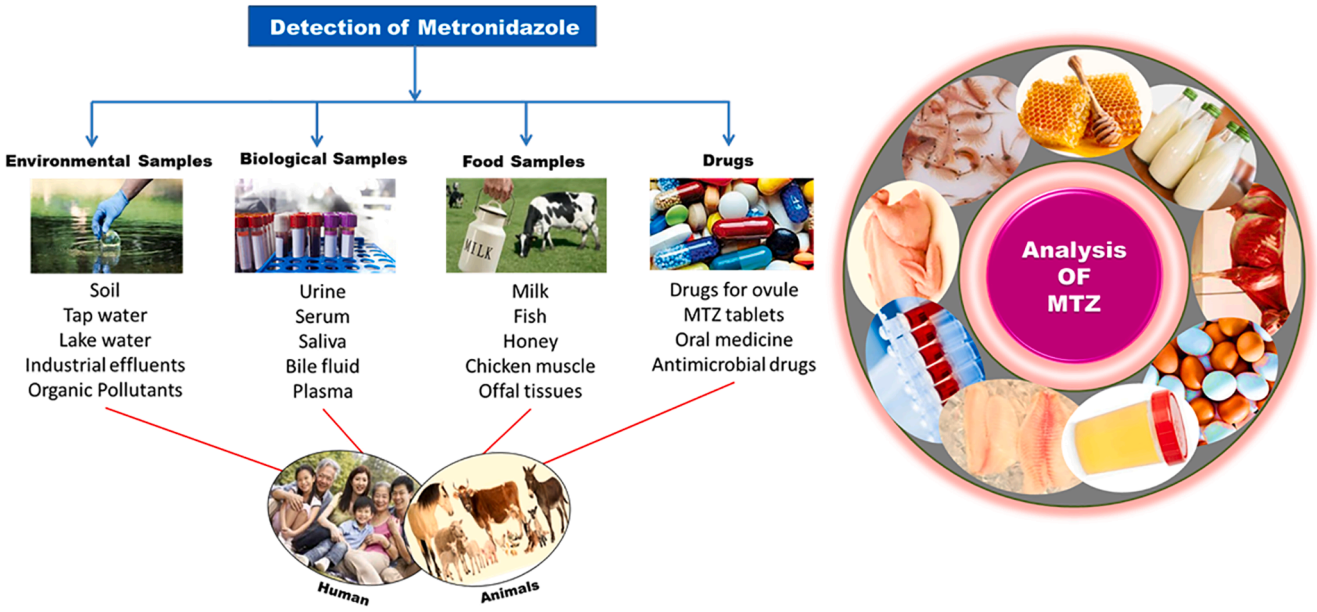

Fig. 2. Various kinds of samples containing MTZ.

2. Electrochemical sensing of MTZ at solid electrodes

In the past several decades, numerous research findings have been reported in the literature for the quantitative detection of MTZ by the electrochemical methods. Initially, Wang *et al.* [70] introduced HMDE based determination of MTZ present in human serum and drug formulations. Later, La-Scalea *et al.* [71] and Gui *et al.* [72] successfully employed HMDE to quantify MTZ in various real samples. In addition, Gui *et al.* studied the electrochemical behaviour of antibiotic residues present in honey and milk samples using HMDE electrode. Chemometric tools such as RBF-ANN, PCR and PLS were also used. Similarly, static mercury drop electrode (SMDE) was explored to study the prototropic properties and natural life time of MTZ (Carbajo *et al.*) [73]. Yao *et al.* reported a new method of the ion implantation process to determine MTZ [74]. In 1998, Senturk and Ozkan investigated electrochemical reduction of MTZ at carbon based electrodes [75] and later, carbon fiber microdisk electrode had been used for the quantification of MTZ present in urine samples [76]. Subsequently, various electrodes (Fig. 3) namely, gold electrode (Au) [77], BFE [78], UTGE [79], BDD electrode [80], CPE [81], and SPCE [82] were exploited for MTZ detection as shown in Table 2. While the usage of solid electrode for electrochemical applications, it is realised that some of the drawbacks such as limited potential range, electrode fouling, lower detection limits, poor sensitivity and reproducibility. In order to overcome those issues, numerous strategies and remedial measures have been investigated to develop

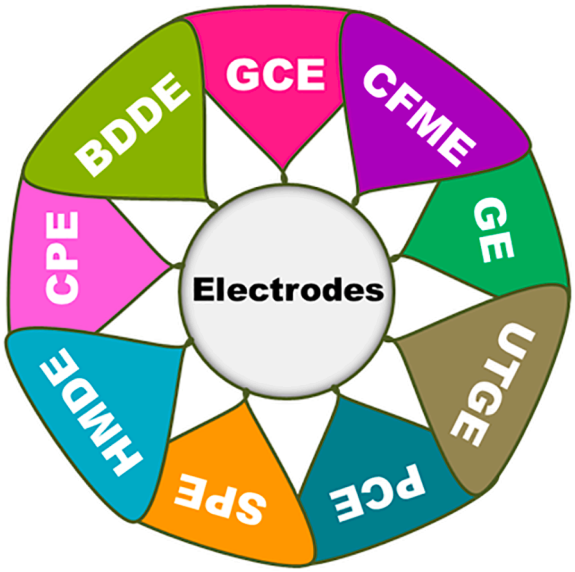

Fig. 3. Different types of bare electrodes explored for the determination of MTZ.

Table 2
Electroanalytical performance on MTZ reduction using bare electrodes.

Electrode	Technique	Linear range	Detection limit	Sample	Ref
HMDE	ASV	–	2.5 nM	Serum	[70]
HMDE	DPV	1.0 – 100 μmol L^{-1}	0.75 μmol L^{-1}	–	[71]
HMDE	DPV	0.04 – 0.30 μg mL^{-1}	6.1 ng mL^{-1}	Milk and Honey	[72]
Co/GCE	LSV	0.4 – 100 μmol L^{-1}	0.2 μmol L^{-1}	Tablet	[74]
AGCE	LSV	2 – 6 μM	1.1 μM	Tablet	[75]
Carbon fiber micro disk electrode	SWV	1 – 22 μmol dm^{-3}	0.5 μmol dm^{-3}	Urine	[76]
Au electrode	CV	0.5 – 800 μM	0.15 μM	Tablet and Urine	[77]
BFE	DPV	0.3 – 30 μM	0.039 μM	Tablet and Urine	[78]
UTGE	DPV	3 – 90 μmol L^{-1}	0.142 μmol L^{-1}	Tablet	[79]
BDD electrode	SWV	0.2 – 4.2 μmol L^{-1}	0.065 μmol L^{-1}	Injection	[80]
CPE	SWV	1.0 – 500 μM	0.297 μM	Tablet	[81]
SPCE	DPV	0.05 – 563 μM	0.01 μM	–	[82]

electrodes with surface modifications using various redox active molecules, perm-selective polymers and electrode activation methods. The remarkable properties of surface modified electrodes are (i) improved electrode activity and sensitivity towards the target material, (ii) fast electron transfer between the analyte and electrode, (iii) enhanced electrocatalytic activity with large surface area, (iv) fast diffusion at electrode surface, (v) free-from interference, (vi) less fouling effect and reduced interfacial distances [83,84]. Moreover, MTZ contains a nitro-group act as a redox centre and it could be monitored very easily by electrochemical method. Mostly, electrochemical reduction of nitro group (−NO_2) [1] undergoes four electron transfers into hydroxylamine (−NHOH) and then [2] followed by a two-electron reduction of −NHOH group transformed into the corresponding amine (−NH_2) [3] depending on the nature of the supporting electrolyte and pH of the medium [85–88]. The electrochemical reduction reaction mechanism of MTZ is shown in Fig. 4.

3. Carbon based electrodes

Carbon electrodes like pyrolytic graphite (PGE), glassy carbon (GCE) and carbon paste (CPE) were commonly used for the various electroanalytical applications. The electrode polishing methods and activation procedures are well documented and important advantages of the carbon electrodes are resistance to acids and bases, chemical inertness and wider potential window. Recently, various carbon based nanomaterials have been exploited for the electrochemical applications including carbon nanotube, carbon dot, carbon onion, ordered mesoporous carbon (OMC), carbon nanohorn and graphene. These electrode materials have received much attraction due to the high surface area to volume ratio and wider potential window. Electrodes decorated with carbon family materials have been utilized for several electrochemical sensor applications due to their attractive properties such as good electrical conductive properties, specific surface area, and fast electron transfer rate [89–93]. Specifically, carbon nanotubes and graphene are broadly used as electrode materials for MTZ reduction due to their superior electrocatalytic activity and high conductivity. Various research findings are available in literature for the determination of MTZ using electrodes modified with carbon-based materials (Table 3). For example, Hu *et al.* [94] proposed a nanostructured film (MWCNT was dispersed into water in presence of DHP to give stable homogeneous MWCNT suspension) modified GCE and achieved the electrochemical detection of MTZ. The developed film modified electrode exhibited good linearity (2.5×10^{-8} to 1×10^{-5} mol/L) with low LOD (6×10^{-9} mol/L), excellent long-term stability (28 days) and reproducibility (RSD = 4.8%, n = 10). The film coated electrode had been fruitfully used to determine MTZ in tablet and injection samples. Moreover, Salimi *et al.* [95] designed SWCNT modified GCE for the simultaneous determination of RT and MTZ. It showed efficient electrocatalytic reduction, higher sensitivity and least LOD towards RT and MTZ.

Similarly, Mao *et al.* [96] investigated electrochemical sensing performance of MWCNT incorporated chitosan-nickel complex for MTZ reduction by self-assembly process. This modified sensor in MTZ

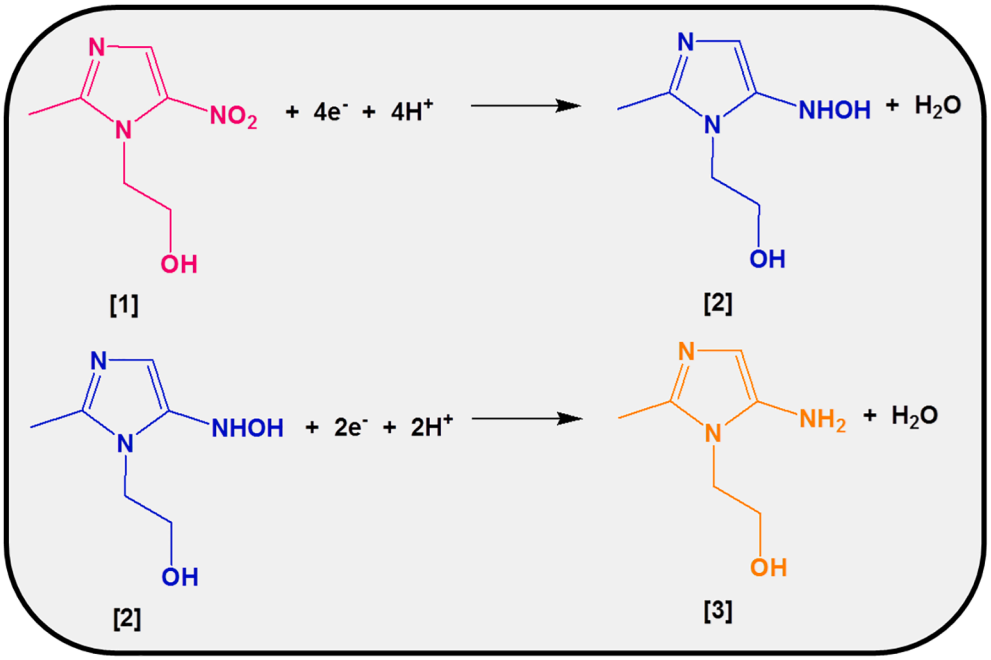

Fig. 4. Electrochemical reduction reaction mechanism of MTZ.

Table 3
Electroanalytical performance on MTZ reduction using carbon materials based electrodes.

Electrode	Mediator	Method	pH	E_{pc} (V)	Conc. Range	LOD	R^2	RSD (%)	Stability	Sample	AR (%)	Ref
GCE	MWNT-DHP film	DPV	BR pH 9.0	−0.71	0.025 – 10 μmol/L	6 nmol/L	0.998	4.8	28 days	Tablet Injection	100.4 99	[94]
GCE	SWCNT	DPV	PBS pH 1.0	−0.15	0.1 – 200 μM	0.06 μmol/L	0.990	4.0	28 days	Tablet	98.5	[95]
GCE	MWCNTs/CTS-Ni	DPV	PBS pH 7.5	−0.65	0.1 to 150 μmol/L	0.025 μmol/L	0.999	2.86	30 days	Tablet Urine Serum	101.2 101 99.8	[96]
GCE	Mo_2C/f-CNF	LSV	PBS pH 7.0	−0.58	0.04 – 467.7 μM	0.002 μM	0.997	1.71	–	Urine	104.5	[97]
GCE	NSP-PC	LSV	PBS pH 7.0	−0.42	0.1 – 350 μM	0.013 μM	0.990	3.8	15 days	Tablet Injection Milk	97.1 97.5 96.7	[98]
GCE	Gr-IL	DPV	PBS pH 7.0	−0.69	0.1 – 25 μmol/L	47 nmol/L	0.999	2.1	7 days	Tablet	100	[99]
GCE	p-GR-Ag	LSV	PBS pH 6.0	−0.55	0.05–4500 μM	0.028 μM	0.996	2.5	10 days	Lake water Urine	99.9 99.6	[100]
GCE	AgNPs/SF-GR	DPASV	CB pH 4.0	−0.37	0.1–20.0 μM	0.05 μM	0.998	2.8	90 days	Shrimp	99.7	[101]
GCE	ZIF-67C @ rGO-0.06	DPV	PBS pH 9.0	−0.57	0.5–1000 μM	0.05 μM	0.999	2.6	15 days	Tablet Tap water	99.5 96.5	[102]
GCE	CNF-Ni Co-LDH	DPV	PBS pH 7.0		0.003 – 0.057 μM	0.13 μM	0.993	2.6	30 days	Human plasma Urine	99.296.6	[103]
GCE	GNF	Amp	PBS pH 7.0	−0.32	0.5–5.5 nM	0.015 nM	0.998	3.0	30 days	Urine	100.6	[104]

detection displayed excellent reproducibility and there was no interference between pharmaceutical and biological samples. In terms of detection limit, the modified electrode delivered best results and also the sensor was tested for human urine and serum samples. Hexagon structure of molybdenum carbide functionalized with carbon nanofiber by sonication method was proposed by Ramki *et al.* [97] to detect MTZ in human urine. This composite modified GCE exhibited admirable electrochemical property and fast electron transfer towards MTZ detection. Yalikun *et al.* [98] developed N, S, P-triple doped porous carbon by pyrolysis and carbonization methods. Doping with heteroatoms (such as N, S, P, K) into carbon material resulted tremendous structural and electrochemical responses. This biomass-derived porous nanostructured carbon improved the electrochemical reduction behaviour of MTZ due to the synergistic effect resulted from low working potential, high sensitivity, selectivity and reproducibility. These electrodes were successfully used for MTZ detection in drug and milk samples. Moreover, an ionic liquid and graphene (Gr-IL) based electrode was reported by Hu *et al* [99]. The Gr-IL was dispersed on GCE surface by simple ultrasonication technique and this modified surface showed higher selectivity due to the combined effect of Gr and IL. Interestingly, this sensor provided the results for wider concentration range with low detection limit and there was no interference. Li *et al.* [100] constructed a p-GR-Ag composite by hydrothermal method and determined MTZ in human urine and lake water. The p-GR contains active sites to anchor AgNPs which effectively increased the electrocatalytic property. Heterogeneous electron transfer kinetics of MTZ was analysed (3.42×10^{-2} cm/s) by rotating disk electrode (RDE). In LSV, the proposed sensor displayed wider linear range and lower detection limit based on S/N = 3 as well as improved anti-interference property during MTZ detection. Similarly, AgNPs/SF-GR modified GCE was fabricated by Zhai *et al* [101] for the simultaneous determination of CAP and MTZ. The surface area of AgNPs/SF-GR/GCE was estimated to be 7.95 mm^2 and it resulted effective electrocatalytic activity because of synergistic effect from AgNPs and SF-GR. Surface concentration, electron transfer coefficient, number of electrons involved in MTZ reduction, diffusion coefficient and LOD were calculated to be 2.295×10^{-10} mol cm^{-1}, 0.365, 3.84 (~4.0), 7.19×10^{-7} cm^2/s, and 0.05 μM, respectively. AgNPs/SF-GR/GCE used to determine MTZ in shrimp samples and resulted high accuracy with good recovery values.

Cobalt and nitrogen co-doped carbon hybrids loaded with GO/zeolitic imidazole framework was reported by Yuan *et al.* [102] (Fig. 5) There was an improved electrochemical performance towards antibiotic due to its hierarchically open pores with abundant electroactive site, improved electrical conductivity, fast electron transfer, wide dynamic range, low LOD and it was explored for sensing MTZ in tap water and tablet samples. Moreover, hierarchical dense Ni-Co layered double hydroxide supported CNF hierarchicaldense (CNF–NiCo-LDH/GCE) developed by Han *et al.* resulted healthier results for the electrochemical determination of MTZ. Biological samples were analysed and it was reported that the modified electrode (hierarchicaldense CNF–NiCo-LDH/GCE) is a more suitable material for the determination of MTZ in pharmaceutical drug and human urine samples with acceptable recovery percentage. [103]. Pandian *et al.* [104] designed defect-free few-layered GNFs by solvent exfoliation process and it showed some edge defects which facilitated fast electron transfer and enhanced electroconducivity with specific surface area. Electrochemical sensing of MTZ using GNFs resulted sharp reduction potential and peak current, fast electron transfer, wider linear range, lower detection limit and strong anti-interference property. MTZ in human urine and drug samples was analysed using GNFs/GCE by amperometry method.

4. Polymer nanocomposite modified electrodes

Polymer-modified electrodes (PMEs) offer several advantages in electroanalytical application. Ionically charged polymers and various functionalised polymers can be used for surface modification of solid electrodes. Polymers like nafion and cellulose acetate have shown some interesting surface properties like hydrophobic and hydrophilic characters and perm selectivity. Such a kind of polymer modified electrodes can be used for the selective detection of charged biologically important molecules as well as await interference with other analytes while analysing multianalytes in simultaneous studies. For example, acceleration of electron transfer reactions, easy immobilizations of specific substrates, favoured accumulation, or choosy membrane permeation can be attained based on the types of polymers and offer higher selectivity, sensitivity and stability in electrochemical devices [105–108]. Moreover, multi-layered polymer coatings can result in a three-dimensional reaction region which can enhance the rate of reaction at surface of the electrode [109]. Polymeric materials can be attached to electrode surface by various ways such as adsorption, physical mixing and

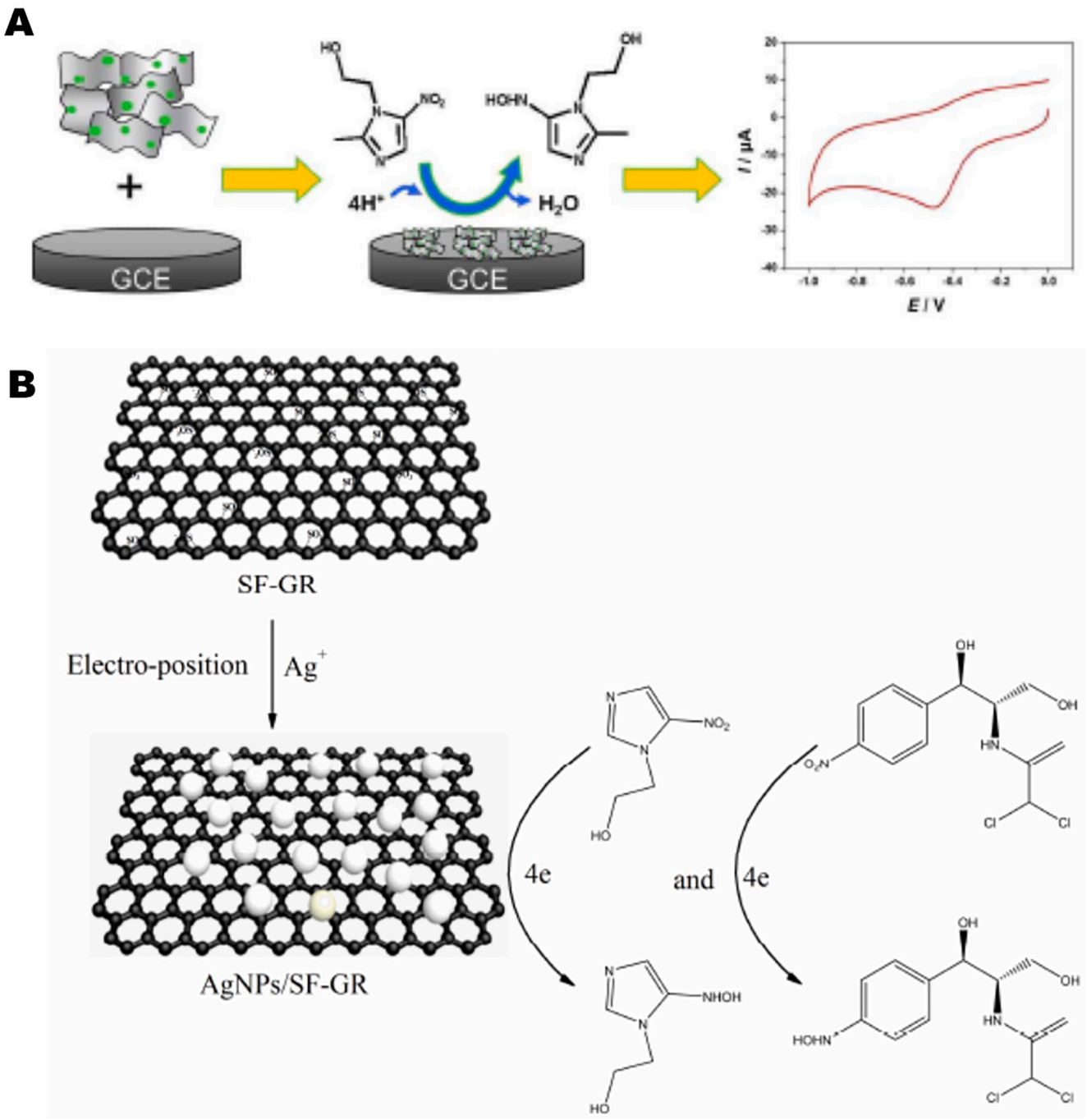

Fig. 5. (A) Schematic diagram represents the electrocatalytic reduction of MTZ using p-GR-Ag/GCE (reprinted from Ref. 101 with permission from Royal Society of Chemistry, copyright 2012). (B) Scheme of the preparation of AgNPs/SF-GR/GCE and the catalytic mechanism for the analysis of MTZ (reprinted from Ref. 102 with permission from Elsevier, copyright 2014).

covalent bonding. Particularly, the electropolymerization technique is used to immobilize a polymer film onto the electrode surface with multiple active sites which offers flexible charge transport, quick synthesis, controllable film thickness, uniform coating, and precise results [110–112].

For example, Zeng *et al.* [113] explored platinum nanospheres/polyfurfural film modified GCE, was prepared by one-step electropolymerization and potential step methods. As a result, superior electrocatalytic activity to the reduction of MTZ, greater sensitivity, wider linear range (2.5 to 500 μmol dm^{-3}) and lower LOD (50 nmol dm^{-3}) (Fig. 6). It was reported that nanopheres enhanced the electron transfer rate due to their remarkable conductivity. Similarly, Wang *et al.* [114] examined polydopamine/MWCNTs–COOH nanocomposites modified GCE for the electrochemical sensing of MTZ in real drug samples using standard addition technique. In this study, the electropolymerization technique was utilised to coat polydopamine on the surface of nanotubes. Therefore, the reduction potential of MTZ showed good linearity and two different types of mechanisms were reported with the electrochemical response based on the effect of pH. It was reported that polydopamine/MWCNTs–COOH/ enhanced the electron transfer process and LOD for reduction of MTZ was 0.25 μmol dm^{-3}. The MTZ concentration in pharmaceutical drugs was effectively determined with the recovery rate of 93.4–118.3%.

The electrochemical reduction of MTZ was investigated by Saglikogl

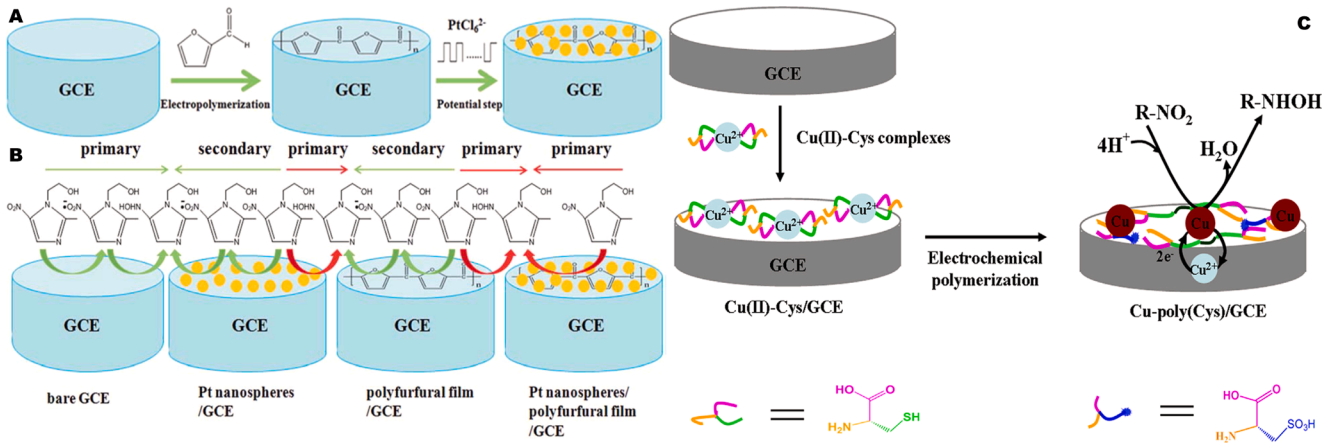

Fig. 6. (A) Scheme of preparation of platinum nanospheres/polyfurfural film/GCE and (B) Electrocatalytic reduction mechanisms of MTZ (reprinted from Ref. 113 with permission from Royal Society of Chemistry, copyright 2017)). (C) Schematic illustrates the fabrication process of biomimetic sensor and electrocatalytic reaction mechanism of MTZ (reprinted from Ref. 116 with permission from Elsevier, copyright 2015).

et al. [115] using *p*-ABSA modified GCE by electropolymerization method. It was reported that enhancement in the sensitivity, stability and electroactivity for the reduction of MTZ was resulted from the electrostatic interaction between *p*-ABSA/GCE and MTZ and the LOD was 3.73×10^{-7} mol/L. The authors suggested *p*-ABSA/GCE for quantitative detection of MTZ in real drug samples. Likewise, Zhang *et al.* [116] successfully developed the electrochemical sensing platform for determination of MTZ using β-CD-GNPs/poly(L-cys) modified GCE. Excellent performance was obtained due to β-CD, cyclic oligosaccharide which can form different inclusion complexes with a variety of molecules due to their hydrophobic internal cavities and hydrophilic external surface. An improved accumulation time (120 s) of MTZ on electrode surface was observed and the stable noble GNPs were used to enhance the electrical conductivity and biocompatibility. Meanwhile, poly (L-cys) provides a stable matrix for the adsorption of β-CD-GNPs, decreases over-potential of MTZ and enhanced the effective surface area. The recovery ranged from 99.19 to 101.03%, implies that there is a good accuracy in the determination of MTZ using β-CD-GNPs/poly(L-cys)/GCE.

Cu-poly(Cys) film modified electrode was prepared by simple electropolymerizion method and exploited as a nitroreductase mimetic for the detection of MTZ. Usually, Cu^{2+} react with cysteine to form Cu(II)-Cys complex and the authors hypothesized that electropolymerization mechanism of coordinated and non-coordinated cysteine molecule is similar. The following mechanisms were predicted by Yang *et al.* [117] for the formation of Cu-poly (Cys) film by electropolymerization.

$$Cu \rightarrow Cu^{2+} + 2e^-$$

$$Cu^{2+} + 2e^- \rightarrow Cu$$

$$RSH_{ads} \rightarrow RS^{\bullet}_{ads} + H^+ + e^-$$

$$2RS^{\bullet}_{ads} \rightarrow RSSR_{ads}$$

$$RS^{\bullet}_{ad} + 3H_2O \rightarrow RSO_3H_{ads} + 5H^+ + 5e^-$$

The authors reported a microenvironment for the enzymatic reaction offered by cysteine film. On the Cu-poly(Cys) film, NO_2 group was reduced into NHOH successfully through the transition from Cu(0) into Cu(II) and the suggested mechanism is given below;

$$R\text{–}NO_2 + 4H^+ + 2Cu \rightarrow R\text{–}NHOH + 2Cu^{2+} + H_2O$$

$$Cu^{2+} + 2e^- \leftrightarrow Cu$$

From this, number of electrons involved in the rate determining step for the irreversible electrode reaction was found to be 1. A plot of the scan rate-normalized current against scan rate indicates that the electrode process is electrochemical followed by chemical reaction (electrochemical-chemical catalytic) which also provides evidence for the above mechanism. Kinetic information of Cu-poly(Cys) film electrode was investigated by RDE technique. Diffusion coefficient and total number of electrons involved in the reduction of MTZ were found to be 3.966×10^{-6} cm^2/s and 4 respectively at Cu-poly(Cys) film using Levich equation. Furthermore, enzyme-like catalytic process to the reduction of antibiotic was indicated by the Michaelis-Menton profile.

Similarly, detection of MTZ in human urine and water samples has been reported based on the composite film of cysteic acid and PDDA functionalized graphene [118]. Here, cysteic acid was electrochemically grafted on PDDA-GN by voltammetry oxidation of cysteine, which results in the oxidation of disulphide to sulfonate and indicates the formation of cysteic acid. It can promote the reduction of MTZ with the surface area due to the synergistic effect between cysteic acid and PPDA-GN. Zhang *et al.* [119] reported a PDDA-GN and DNA assemblies (containing double helix and hairpin structures) modified GCE to detect MTZ in water samples. Positively charged PDDA-GN had been anchored with negatively charged DNA through electrostatic interaction which result a better electrocatalytic activity with large surface area. Therefore, this bio-sensing platform has good accuracy and high stability with better sensitivity for determination of MTZ in water samples.

Xiaobo *et al.* [120] described simultaneous electrochemical determination of RT and MTZ with a poly (chromotrope 2B) modified activated GCE. Surprisingly, the PCHAGCE resulted tremendous electrocatalytic property towards the reduction of RT and MTZ in PBS (pH 6.0) with the detection limit of 5.4×10^{-7} and 3.3×10^{-7} mol/L, respectively. Likewise, 3D-HPG/PTH film modified GCE prepared by a simple electropolymerization technique which was explored for the determination of MTZ by voltammetric method [121]. An enhanced electron transfer with high sensitivity and low LOD was reported. The overall electroanalytical performance of various polymer modified electrodes on MTZ reduction are listed in Table 4.

5. Molecularly imprinted polymer (MIP) electrodes

MIPs are the highly selective polymeric materials based on functional monomer and cross-linked agent. They have specific binding sites and recognition ability for target molecules. MIPs have been employed for numerous applications in the field of proteomic analysis, biomimetic catalysis, chromatographic separation, drug delivery, fabrication of biosensors, plastic antibody synthesis [122–125]. Furthermore, various materials (metal oxides, nanoparticles, carbon materials, polymers) are used as supporters for the surface of the MIPs and they result more effective recognition sites, high surface-to-volume ratio, quick mass

Table 4
Electroanalytical performance on MTZ reduction using various polymer modified electrodes based electrodes.

Electrode	Method	pH	E_{pc} (V)	α	D (cm^2/s)	Linear range	LOD	Sample	Ref
PtNPs/polyfurfural film/GCE	DPV	BR pH 10	−0.65	–	–	2.5 – 500 μmol/dm^3	50 nmol dm^{-3}	Human Serum	[113]
polydopamine/MWCNTs –COOH/ GCE	DPV	PBS pH 10	−0.721	–	–	5 – 5000 μmol/dm^3	0.25 μmol/dm^3	Drugs	[114]
poly (*p*-ABSA)/GCE	DPV	PBS pH 7	–0.549	–	–	3 – 70 μM	0.373 μmol/L	Nidazol Tablet	[115]
β-CD-GNPs/poly(L-cys)/ GCE	LSSV	BR pH 7	−0.768	0.745	–	0.1–600 μmol/L	0.014 μmol/L	Injection	[116]
Cu-poly(Cys) film/GCE	LSSV	BR pH 9	−0.776	0.497	3.966×10^{-6}	0.5 – 400 μmol/dm^3	0.37 μmol/dm^3	Injection	[117]
Cysteic acid and PPDA-GN/GCE	LSV	BR pH 8	−0.672	–	1.29×10^{-6}	10 nM – 1 μM	2.3 nM	Human urine and Lake water	[118]
PDDA-GN/DNA/GCE	LSV	PBS pH 6	−0.63	0.421	3.021×10^{-6}	0.05 – 100 μM	24 nM	Human urine and Lake water	[119]
PCHAGCE	DPV	pH 6	−0.58	–	–	10 – 400 μmol/L	0.33 μmol/L	Drugs	[120]
3D-HPG/PTH/GCE	DPV	pH 11	−0.8	0.5	–	0.05–70 μM	0.001 μM	Water	[121]

transfer, chemical stability and physical rigidity, low toxicity, and enhanced sensitivity [125–128]. Therefore, there has been an increased interest to develop the MIPs for electrochemical determination of MTZ in biological and environmental fields. Firstly, Deng *et al.* [129] developed the magnetic MMIP modified electrode and it was used to analyse the MTZ in food products. The active surface area of MMIP modified had been found to be 0.025 cm^2 using Randles–Sevcik equation. As a result, the proposed system achieved better sensing performance towards MTZ detection by DPSV method with detection range of 5×10^{-8} to 1×10^{-6} M, LOD of 1.6×10^{-8} M, better stability and reproducibility. In addition Zhoa *et al.* [130] proposed an electrochemical sensing method for MTZ using graphene modified magnetic-controlled GCE. The developed sensor showed high efficiency for MTZ detection in serum and urine samples.

Madhuri *et al.* [131] fabricated AuNPs electrochemically incorporated into polyglutamic acid to have better electrode conductivity and surface area. The proposed sensor displayed excellent electrocatalytic behaviour towards MTZ detection with a broad dynamic response range, lower LOD, high sensitivity, selectivity, reproducibility as well as stability (Fig. 7). Li *et al.* [132] proposed a 3D nanoporous nickel covered by ultrathin MIP film by electrodeposition process. The fabricated MIP/3D nanoporous nickel modified gold electrode exhibited enriched electron transport ability with surface area which resulted in high electrocatalytic activity towards MTZ. Furthermore, the modified electrode has good anti-interference ability towards several co-existing substances and successfully applied to detect MTZ in drugs and fish tissues.

Detection of MTZ in drug formulations was studied based on a composite structure of MIP and MWCNTs by Li *et al.* [133].

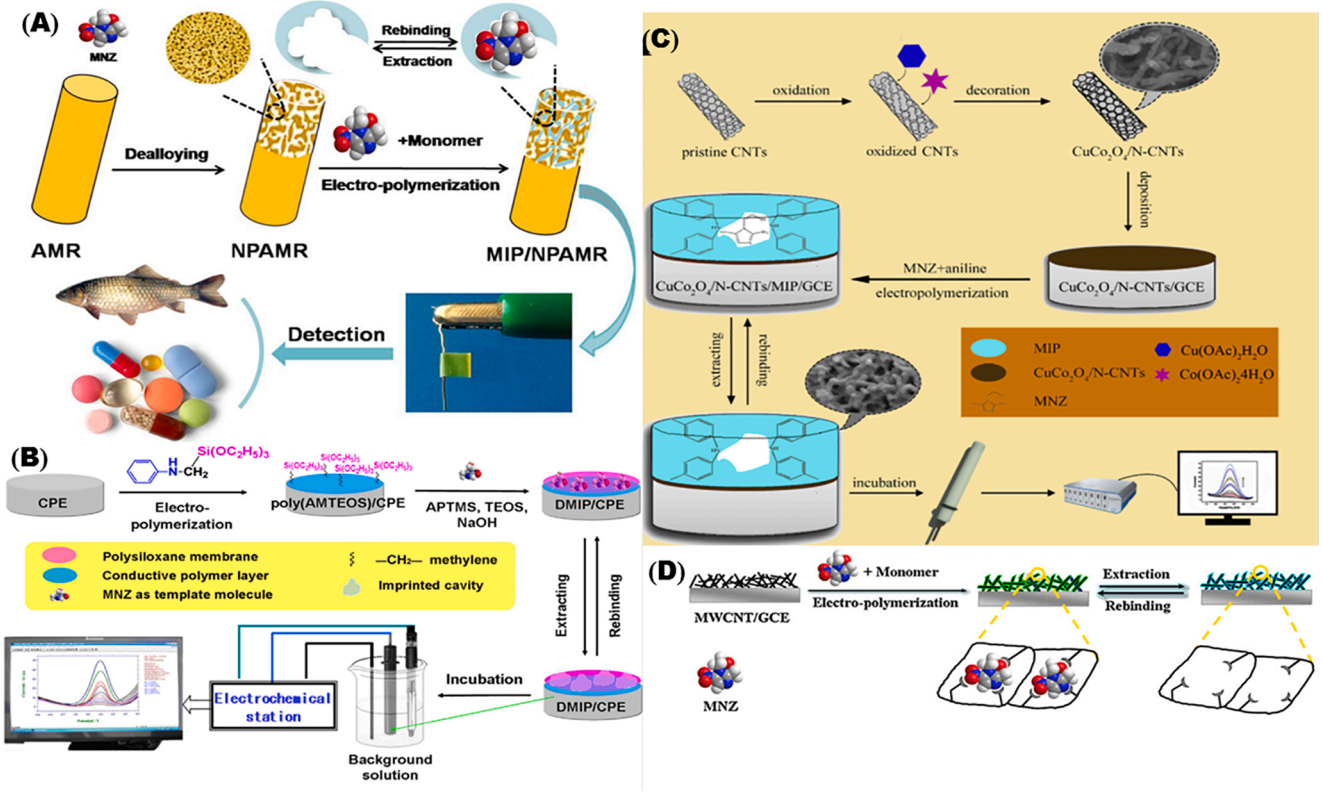

Fig. 7. Illustration for (A) Fabrication of MIP/NPAMR and detection of MTZ in drugs and fish tissues (reprinted from Ref. 136 with permission from Elsevier, copyright 2016), (B) Preparation of DMIP/CPE and recorded the sensitive MTZ detection (reprinted from Ref. 142 with permission from Elsevier, copyright 2016), (C) Preparation of $CuCo_2O_4$/N-CNTs/MIP/GCE and electrochemical determination of MTZ (reprinted from Ref. 138 with permission from Elsevier, copyright 2019), and (D) Synthesis of MNZ-MIP/MWCNT/GCE (reprinted from Ref. 132 with permission from Elsevier, copyright 2015).

Electropolymerization of DA in the presence of MTZ on the electrode surface was carried out by voltammetry technique. The sensor provided unique merits like enlarged surface area with high electronic property and increased sensitivity towards MTZ. The linear calibration plot was achieved in the range of $1.71 \times 10^{-4} - 2.05 \times 10^{-1}$ mgL^{-1} with LOD of 4.92×10^{-5} mgL^{-1}. Selectivity coefficient and *t*-test confirmed the significant difference of sensor response towards MTZ analogues.

Glassy carbon electrode modified with MIP for electrochemical sensing of MTZ either by MIP/catalysis or MIP/gate effect was reported elsewhere [134]. Both methods could detect MTZ in a good precision with small difference of LOD. Nonetheless, MIP/gate effect detected a wide range of substances independent of their electroactivity and ensuing beneficial in applications. This sensor has specific recognition towards MTZ detection in presence of interferents and structural analogues. MIP functionalized nanoporous Au-Ag alloy micro-rod had been prepared by electropolymerization and it resulted simultaneous identification and quantification of MTZ (Song *et al.*) [135]. Anson equation predicted the electrode surface area (0.74 cm^2) by chronocoulometry method which is higher after dealloying, resulted better signal amplification and sensitivity enhancement. Ensafi *et al.* [136] fabricated MIP on the surface of graphene quantum dots (GQDs) by sol–gel method. To improve the sensitivity and selectivity, GNPs were dropped on the GCE before dropping GQDs-MIPs. Modified electrode offered excellent synergistic effect from GNPs and MIPs with enhanced electrochemical response of MTZ. At GQDs-MIPs/GNPs/GCE, the reduction peak current of MTZ had 5.3 times higher than bare electrode and it resulted high electrical conductivity and large surface area. Specifically; GQDs-MIPs enhanced the accumulation of MTZ on the electrode surface. Significant enhancements of the reduction peak current with lower detection current and superior repeatability are the best advantage of this method.

$CuCo_2O_4$ nanoparticles modified with nitrogen doped carbon nanotubes loaded MIP modified GCE was prepared by hydrothermal and electropolymerization using aniline monomer (Zhao *et al.*) [137]. The composite exhibited higher catalytic performance and large surface area which lead for sensing the electro-reduction of antibiotic drug. After electropolymerization, the modified GCE surface offered higher peak current response with good resorption capacity against MTZ detection. Long-term storage, reproducibility, repeatability and stability of this composite have tested at room temperature and provided effective quantitative analysis of MTZ in human urine and serum samples. However, the limitation of the small number of molecularly imprinted cavities has to be resolved. Also, Hu *et al.* [138] reported surface imprinted vertically cross-linking 2D Sn_3O_4 nanoplates used to determine the MTZ reduction in honey bee samples. MIP/2D Sn_3O_4 nanocomposite also effectively catalysed the MTZ reduction, in terms of decreased over-potential and increased reduction peak current. DPV measurement confirmed excellent analytical performance with linear dynamic range (0.025–2.5 μM) and very low LOD (0.0032 μM). Conversely, porous structure of NPGL decorated onto MIP through electropolymerization designed by Yingchun *et al.* [139]. Modified electrode offered excellent synergistic effect between NPGL and MIPs which lead to obviously enhanced the electrochemical response of MTZ. It can displayed excellent analytical capability in terms of broad linear detection and low LOD of MTZ, improved stability and high selectivity. This group firstly reported the coupling of molecular imprinting technology and NPGL for establishing ultra-sensitive detection of MTZ in fish meat and tablet.

A selective voltammetric sensor of MTZ was designed using synthesized MIP incorporated into CPE [140] and it was explored to detect MTZ using cathodic stripping voltammetric method; as a result, improved peak current, wider linear range and lower LOD. Moreover, the mechanism for the electrocatalytic reduction of MTZ was suggested as four-electron reduction of $–NO_2$ to –NHOH. Concentration of MTZ was measured at 1.37×10^{-2} mg/L, therefore, good repeatability was perceived with RSD <5% (n = 7). This is appreciable for quality control analysis of drug samples and biological fluids. Deng *et al.* [141] fabricated duplex MIP hybrid film modified CPE for sensitive electrochemical reduction of MTZ. A polymeric film was initially deposited on CPE and then MIPS membrane was covered covalently on the film by sol–gel method. Hybrid film offered more advantage in signal transformation between target molecule and transducer. Enhanced recognition capabilities as well as mass transfer were achieved. The electrochemical response signal was linear to MTZ concentration varying from 4.0×10^{-7} to 2.0×10^{-4} mol L^{-1} with a low LOD of 9.1×10^{-8} mol L^{-1}. No interference was observed for MTZ detection with some similar structural analogs and other coexistent molecules (dimetridazole, ronidazole, tryptophan, tyrosine, proline, histidine and phenylamine). The hybrid film sensor has been meritoriously analysed for the determination of MTZ in human plasma, serum, urine, and tablets with good accuracy and excellent sensitivity and selectivity. Recent developments on the MIP sensors for the quantification of MTZ are summarized in Table 5.

6. Metal and metal oxide nanoparticles modified electrodes

Over the past decades, various transition elements/metal oxide/bimetallic composites modified electrode have been recognized for plentiful sensing applications [142–146]. These electrodes offered higher electrocatalytic activity with large surface-to-volume ratio, reduced cross-interference, non-toxicity, low-cost, improved sensitivity and selectivity [147,148]. Here, we have discussed about the electrochemical behaviour of MTZ using various transition metal/metal oxide/bimetallic nanocomposites-based electrodes.

Especially, GNT possess several unique properties along with biological compatibility and they have been used in molecular detection and diagnosis. Ghorbani *et al.* [149] designed an electrochemical sensor based on the electrodeposition of 3D GNT inside polycarbonate pores and offered better electrochemical response toward redox probe. The sensor efficaciously resolved a strong response toward MTZ in SWASV method. This modified electrode exhibited high peak current with low concentration level and a linear plot of peak current against square root of sweep rate suggested diffusion-controlled electron transfer process. A rapid and powerful SWV technique was used to optimize the pH and maximum peak current. LOD was calculated using S/N = 3 for MTZ reduction and the 3D GNT modified electrode was reported to have good repeatability and reproducibility with RSD values of 2.17 % and 1.84 % which indicated very good accuracy and precision for the prepared electrode in MTZ detection. Likewise, nanoscale zero-valent iron nanoparticles modified screen printed electrode was used to detect antibiotic drug in tablets using amperometric method in flow injection system (Rodriguez *et al.*) [150]. Detection limit was attained at micromolar level with a broad detection range and high sensitivity. Tucek *et al.* [151] synthesized Hagg carbide nanoparticles (χ-Fe_5C_2) from iron oxide via simple thermal method which exhibited low charge transfer resistance and tremendous electrochemical sensing property against MTZ detection. The stable χ-Fe_5C_2 nanoparticles modified GCE gave enhanced electrochemical peak current and peak potential at −0.65 V, lower LOD and LOQ, reproducibility, etc. at SWV method (Fig. 8).

On the other hand, the cheapest transition metal oxide or functionalized metal oxide have been explored for electrochemical biosensors due to its interesting products such as large surface area, high electroconductivity, antitoxic nature *etc*. The electrodeposited CuO nanoparticle on graphene/β-CD composite with homogeneous morphology was developed by Vijayalakshmi *et al.* [152]. Curiously, this composite displayed excellent catalytic activity and lower reduction potential towards MTZ detection. A sharp amperometric i-t curve indicated the lower detection limit, wider linear response and high sensitivity. Moreover, this composite modified electrode result good selectivity towards MTZ over the interfering nitro compounds such as nitrobenzene, nitrophenol, nilutamide, flutamide, amino acids and neurotransmitters. Similarly, Fe_3O_4 nanoparticle modified with MWCNTs was fabricated by Guo *et al.* [153] and it helped to overcome the aggregation issue of

Table 5
Electroanalytical performance on MTZ reduction using various MIP based electrodes.

Electrode	Method	pH	E_{pc}(V)	A (cm^2)	Scan range (V)	Dynamic range	LOD	RSD (%)	Sample	Ref
MMIP/MGCE	DPSV	BR pH 5	−0.65	0.025	+0.5 to −0.3	0.05 – 1 μM	0.016 μM	4.8	Milk and Honey	[129]
mag-MIPs (4-VP) /r-GO/ MCGCE	DPV	PBS pH 6.2	−0.65	0.122	−0.1 to −1.0	0.03 –3.4 μmol/L	1.22 nmol/L	5.0	Human Serum and Urine	[130]
AuNPs/PGA/ PGE	DPSV	PBS pH 7	−0.6	0.074	+0.5 to −0.2	9.87 ng/L – 130 mg/L	1.0 ng/L	1.5	Tablets	[131]
MIP/NPNi/GE	CV	PBS pH 7	−0.75	–	+1.0 to −1.0	6×10^{-5} – 4×10^{-3} M	2×10^{-5} M	1.12	Drugs and fish tissue	[132]
MTZ-MIP/ MWCNT/ GCE	CV	Redox probe	–	–	+1.0 to −1.0	0.17 –205.39 μg/L	0.049 μg/L	0.6	Tablet and fish meat	[133]
MIP/GCE	DPV	PBS pH 7	−0.48	–	+1.0 to −1.0	2.0×10^{-9} – 1.0×10^{-7} M	6.67×10^{-10} M	2.0	Mouse serum	[134]
MIP/NPAMR/GCE	CV	Redox probe	–	–	+1.0 to −1.0	8×10^{-8} – 1.0 μM	2.7×10^{-8} μM	0.8	Tablet and fish tissue	[135]
GQDs-MIPs/ GNPs/ GCE	DPV	PBS pH 7	−0.62	–	0.0 to –1.0	0.005 – 10 μmol/L	0.52 nmol/L	3.4	Human Plasma	[136]
$CuCo_2O_4$/N-CNTs/ MIP/GCE	DPV	PBS pH 10	−0.74	–	−1.0 to −0.5	0.1 – 100 μM.	0.48 nM	3.2	Human serum and urine	[137]
MIP/2D Sn_3O_4/GCE	DPV	PBS pH 6	−0.37	–	−0.6 to −0.2	0.025–2.5 μM	0.0032 μM	4.78	Honey bee	[138]
MIP/NPGL/GE	CV	PBS pH 6	–	–	+1.0 to −1.0	5×10^{-5} – 1.4 μmol/L	0.018 nM	0.8	Fish meat and tablet	[139]
MIP/CPE	DPASV	PBS pH 7	−0.68	–	+0.2 to −0.35	5.64×10^{-5} – 7.69×10^{-1} mg/L	3.59×10^{-5} mg/L	<4.0	Human Serum and Urine	[140]
DMIP/CPE	DPV	BR pH 5	−0.40	–	−0.1 to −0.9	4×10^{-7} – 2×10^{-4} mol/L	9.1×10^{-8} mol/L	5.52	Human Serum, Urine and drug	[141]

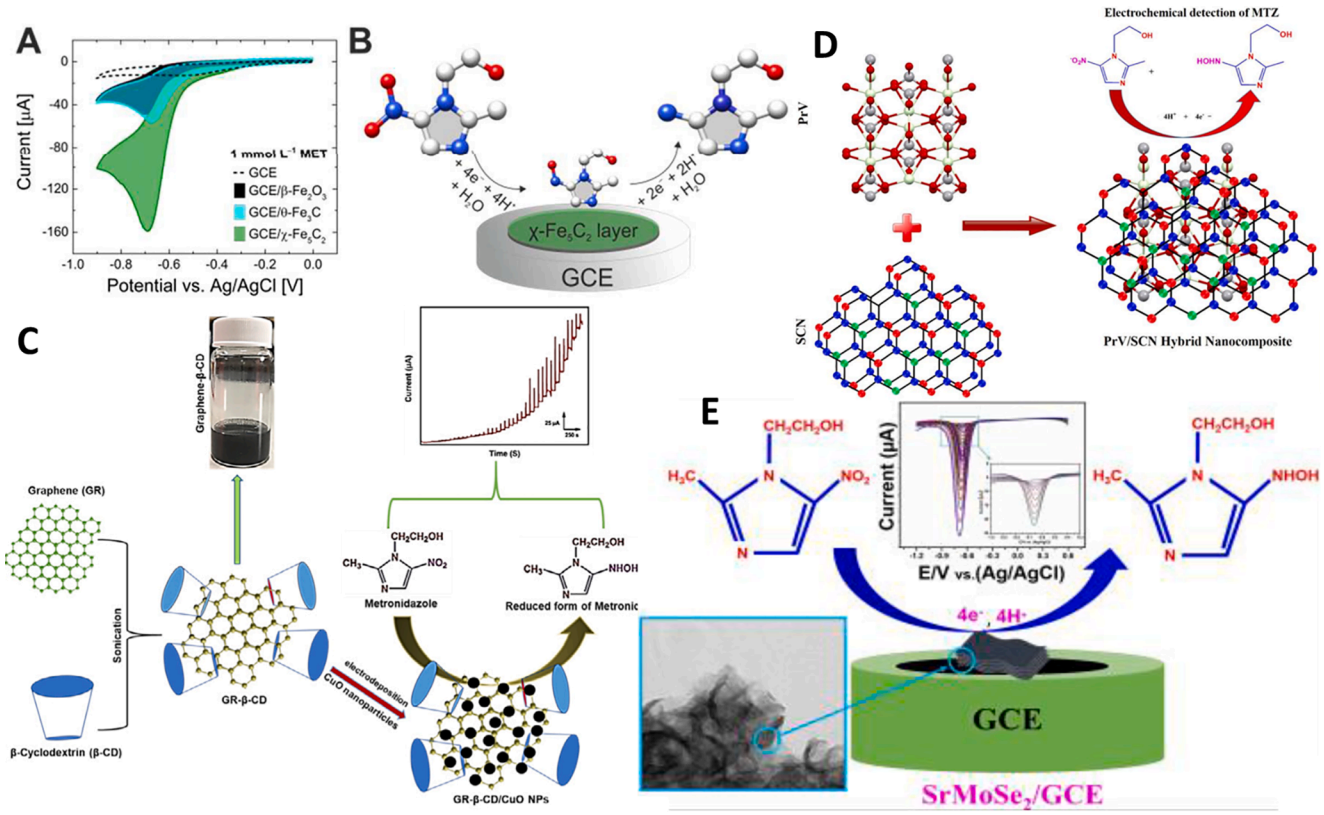

Fig. 8. (A) Schematic represents the cyclic voltammograms of bare GCE, GCE modified with β-Fe_2O_3, θ-Fe_3C, and χ-Fe_5C_2, (B) Electrocatalytic reduction of MTZ using χ-Fe_5 (reprinted from Ref. 152 with permission from Royal Society of Chemistry, copyright 2017), (C) Preparation of GR-β-CD/CuO NPs composites and amperometric determination of MTZ (reprinted from Ref. 153 with permission from Elsevier, copyright 2018), (D) Electrochemical determination of MTZ using PrV/SCN hybrid nanocomposite (reprinted from Ref. 155 with permission from American Chemical Society, copyright 2019), and (E) Electrocatalytic reaction mechanism for the analysis of MTZ using $SrMoSe_2$/GCE (reprinted from Ref. 156 with permission from American Chemical Society, copyright 2018).

Fe_3O_4. This nanocomposite enhanced the conductivity and electrochemical performance because of synergistic effect from Fe_3O_4/N/C and MWCNTs. Surface area of the nanocomposite was calculated to be 0.134 cm^2 using Sevcik equation. The designed sensor exhibited outstanding analytical performance for detecting antibiotic drug involving low E_{pc} (−0.69 V), wide linear range (1–725 μM), high sensitivity (2.57 μA/μM·cm^2), low LOD (0.19 μM), free-from interference and good reproducibility.

Nowadays bimetallic nanocomposites have superior electrocatalytic performance owing to their synergistic catalytic effect as compared to individual metal composites. Chen *et al.* [154] synthesized praseodymium vanadate anchored to sulphur-doped carbon nitride and electrochemical sensing performance of MTZ was determined. Interestingly, PrV/SCN modified electrode resulted higher electrocatalytic ability towards MTZ reduction due to the formation of π–π stacking interactions. Admirable electrochemical performances such as high surface concentration (3.1×10^{-6} mol cm^2), wider concentration range (0.001–4338 μM), lower LOD (0.8 nM), higher sensitivity (1.386 μA/μM cm^2), strong anti-interference property, good reproducibility, repeatability and long-term stability were observed. The developed sensor was effectively explored to determine the MTZ in urine and water samples with excellent reliability. Similarly, a two-dimensional $SrMoSe_2$ nanosheet was fabricated via a simple hydrothermal process [155]. The Sr^{2+} successfully increased the surface area and electrocatalytic performance for the reduction of MTZ. Modified electrode showed low charge transfer resistance because of incorporation of Sr^{2+} in $MoSe_2$. The active electrode surface area and charge transfer coefficient of nanosheet modified electrode have been determined using Randles-Sevick equation and Tafel plot. DPV method was utilized to detect the electrochemical response of MTZ, lower LOD (1 nM), higher sensitivity (1.13 μA/μM cm^2) and good reproducibility with RSD value of 3.7 % was observed. The fabricated sensor was used to determine MTZ concentration in human urine samples.

Nejati *et al.* [156] proposed the detection of MTZ using electrodeposited thin film Ni/Fe-LDH. In past few decades, LDH have been used for electrochemical sensor because of its sensitivity, simplicity, wider linear range, low cost and adsorption properties. The Ni/Fe-LDH/GCE showed higher peak current and decreased over-potential for MTZ reduction with wide detection range, LOD and higher sensitivity are 5.0×10^{-6} to 1.61×10^{-3} M, 58 μM and 19.099 μA mM^{-1}, respectively. The modified electrode was evaluated for MTZ in tablets using standard additions method. Furthermore, detection of MTZ in tablets has been reported based on glycosylated metalloporphyrin incorporated into CPE by Yu *et al.* [157]. It was fabricated by active material of glycosylated metalloporphyrin in epoxy resin-graphite matrices which resulted better selectivity, sensitivity and reproducibility. In addition, interesting electrochemical sensing performance of MTZ was observed in titanocene/Nafion®-modified graphite felt electrode developed by Geneste *et al.* [158].

7. Other nanocomposites-based electrode system

Sadeghi *et al.* [159] designed a homemade disposable SPCE consisting of graphite and CA printing ink modified with IL (1-octyl-3-methylimidazolium hexafluorophosphate) ([OMIM][PF_6]) and AgNPs (AgNPs/IL/CA-SPCE) for electrochemical determination of antibiotic drug. In AgNPs/IL/CA-SPCE, improved conductivity and enhanced surface area was observed. Morales *et al.* [160] attempted to incorporate α–CD through electropolymerization over a CPE and observed the electroreduction response of MTZ. Under optimized experimental conditions, the proposed MTZ sensor resulted diffusion controlled and irreversible reduction reaction with wider concentration range and lower LOD along with strong stability. Meenakshi *et al.* [161] developed a chitosan protected tetrasulfonated copper phthalocyanine thin-film by a simple chemical method. This film showed higher electrocatalytic performance towards MTZ because of strong electrostatic interaction between chitosan with CuTsPc. Reduced electrode fouling and lower LOD with high sensitivity was observed. Similarly, Ranganathan *et al.* [162] synthesized a biocompatible chitosan-pectin biopolyelectrolyte (CS-PC BPE) complex which showed fast electron transfer process and electrocatalytic reduction of MTZ due to the ionic interaction between CS and PC as well as electrostatic interaction between biopolyelectrolytes. The developed sensor effectively performed the electroreduction of MTZ with lower LOD (0.007 μM) ensued admirable biocompatible and biodegradable properties (Fig. 9). Kalaiyarasi *et al.* [163] prepared egg shell like alumina hollow sphere by hydrothermal method and carbon sphere used as template. The stability and reproducibility of the electrode was tested using amperometric method. The fabricated electrode displayed excellent electrocatalytic reduction response towards MTZ detection with a dynamic linear range from 0.6×10^{-6} to 20×10^{-5} M with correlation coefficient of 0.9993, low LOD (0.18 nM), higher sensitivity (18.20 μA μM^{-1} cm^{-2}), and excellent selectivity as well as stability.

Recently, zeolite modified electrodes (ZMEs) have been received more attention to determine organic, inorganic and pharmaceutical samples as compared to CMEs. Especially, ZMEs unveiled high cation-exchange capacity and it's loaded to transition metals which exhibited high conductivity and surface area. Here, Ejhieh *et al.* [164] designed zeolite modified CPE based copper exchanged clinoptilolite nanoparticles (Cu(II)-CNP/CPE). The modified sensor offered good repeatability, reproducibility, long lifetime statistical reports and high selectivity for the determination MTZ in pharmaceutical drugs. Table 6 summarizes the details of various transition elements/metal oxide/bimetallic and other composites studied for MTZ detection.

8. Conclusion

This work focused to offer the overview of electrochemical method of detection using chemically modified electrodes (CMEs) for the drug, metronidazole (MTZ) which has been reported to have harmful effects. MTZ has a nitro-group which acts as a redox centre and hence it could be monitored electrochemically. In the initial part of this article, we have discussed about the bare electrodes (HMDE, Au, BFE, UTGE, BDD, CPE and SPCE *etc.)* based MTZ detection and their disadvantages. In order to produce electrochemical sensor for MTZ with extraordinary performance, various research works have been reported in this context. Especially, CMEs based MTZ sensors are the more attractive systems and various types of materials such as carbon, polymer, molecularly imprinted polymer and metal/metal oxide/bimetallic/nanomaterial modified electrodes have been explored for MTZ detection worldwide. Various methods such as SWV, ASW, DPV, LSV and DPASV were used in these studies.

Reasonable research findings based on carbon materials (CMs) tailored CMEs are available in literature. It was noted that the LOD ranges from 0.015 nM to 0.06 μM in these systems. Moreover, among them significant concentration range of 0.05–4500 μM was observed in p-GR-Ag composite modified electrode. Most of CMs based electrodes are resulted the reduction of MTZ with very less negative potential at neutral pH and in the SWCNT modified GCE, reduction potential was −0.15 V. Similarly, polymer-modified electrodes (PMEs) are the attractive electrode systems have been also explored for MTZ determination. Out of the variety of PME based CMEs reported for MTZ, composite film of cysteic acid and PDDA functionalized graphene made electrode resulted a very low detection limit (2.3 nM). Moreover, PMEs based sensors were studied for a wide concentration range of MTZ and at polydopamine/MWCNTs–COOH/GCE, 5–5000 μmol/dm^3 of the drug was examined.

In addition, CMEs based on molecularly imprinted polymers (MIPs) are having the specific binding sites and recognition capacity for target molecules also utilised for the determination of MTZ. In the most of the MIP based electrodes, the reduction of the antibiotic was carried out at the pH range of 6 – 7. Significant LOD was reported for $CuCo_2O_4$/N-

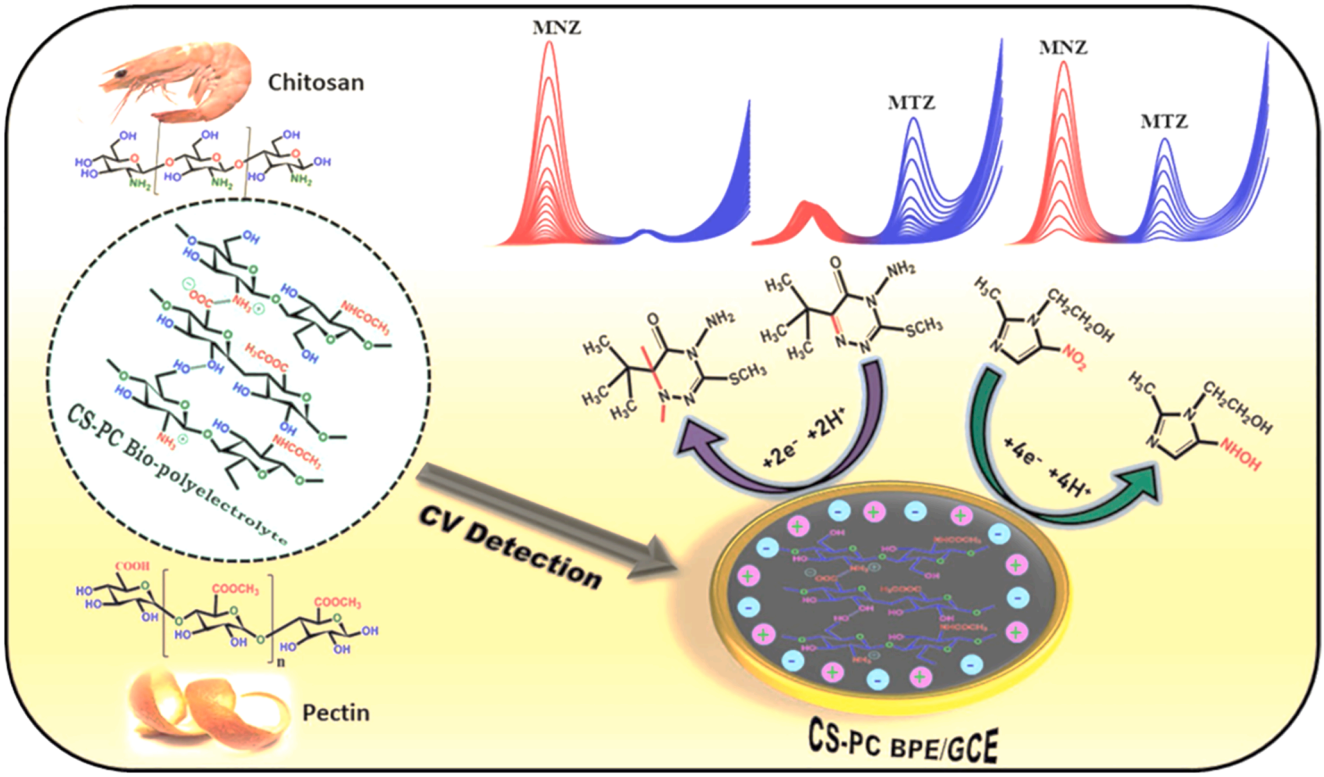

Fig. 9. Schematic represents the preparation of CS-PC BPE and its electroreduction reaction mechanism of MNZ and MTZ (reprinted from Ref. 163 with permission from Elsevier, copyright 2019).

Table 6
Electroanalytical performances on MTZ reduction using Metal/Metal oxide/Bimetallic and other composites based electrodes.

Sensor Electrode	Method	pH	E_{pc} (V)	LRE of pH vs. E_{pc}	Conc. Range (μM)	LRE of I_{pc} vs. conc. MTZ	LOD (μM)	RSD (%)	Sample	Ref
Metal/Metal oxide/Bimetallic composites										
3D GNT/ CPE	SWASV	7.0	+ 0.25	E_{pc} = –0.052 pH + 0.574	0.001 – 2	I_{pc} = 19.253 μM + 13.766	0.0001	2.17	Tablet	[149]
χ-Fe_5C_2/ GCE	SWV	7.0	–0.65	–	10 – 100	I_{pc} = 0.594 μM – 0.0547	2.8	3.01	–	[151]
GR-β-CD/CuO NPs/GCE	Amp	7.0	–0.60	E_{pc} = –0.045 pH – 0.219	0.002 – 210.0	I_{pc} = 0.6958 μM + 2.709	0.0006	2.1	Tablet	[152]
Fe_3O_4/N/C@MWCNTs-2–600/GCE	DPV	7.0	–0.60	E_{pc} = –0.053 pH – 0.225	1 – 725	I_{pc} = –0.345 μM – 0.680	0.19	5.0	Urine &serum	[153]
PrV/SCN/GCE	Amp	7.0	−0.59	E_{pc} = −0.046 pH – 0.246	0.001–2444	–	0.0008	2.3	Urine & water	[154]
$SrMoSe_2$/GCE	DPV	7.0	−0.72	–	0.05–914.92	I_{pc} = 0.0832 μM + 10.227	0.001	1.64	Urine	[155]
Ni/Fe-LDH/GCE	CV	13.0	−0.74	–	5–161.0	–	58	4.0	Tablet	[156]
Other nanomaterial composites										
AgNP/IL/CA-SPCE	DPV	10.0	−0.72	–	3.3 –1300	I_{pc} = 0.07080 μM + 45.73	0.4	3.2	Tablet, urine & serum	[159]
$CPE_{α\text{-}CD}$	DPV		−0.37	–	0.5–103.0	I_{pc} = 0.1193 μM + 0.0971	0.28	3.71	Injection	[160]
Chit/CuTsPc/GCE	DPV	1.0	−0.45	E_p = −0.0445 pH – 0.42	0.0008 – 720	I_{pc} = −0.7340 nM – 0.761	0.00041	<5%	Tablet & urine	[161]
CS-PC BPE/GCE	DPV	5.0	−0.63	E_{pc} = − 0.045 pH –0.467	0.01–465	I_{pc} = −0.0273 μM – 0.4492	0.009	2.25	Serum & soil	[162]
Nafion Al_2O_3/GCE	Amp	7.0	−0.70	E_{pc} = −0.060 pH – 0.288	0.006–213	I_{pc} = 5462 μM + 0.1807	0.0018	3.9	Tablet & urine	[163]
$Cu(II)_{0.5}$-CNP/CPE	SWV	6.0	−0.70	–	0.02–1.6	I_{pc} = 18.9 μM + 70.1	0.0041	<5%	Tablet	[164]

CNTs/MIP/GCE and less negative potential for MTZ reduction was observed at MIP/2D Sn_3O_4/GCE. Comparing to the above-mentioned CMEs, the detection limit of MTZ was very less in metal/metal oxide/bimetallic/nanomaterial composites systems and in majority of these systems, the reduction behaviour of MTZ was reported at neutral pH.

Each CMEs based MTZ sensors reported in the literature have their own advantages and limitations. Almost all the materials discussed in this piece of writing showed excellent electrode surface area (A), charge transport, diffusion coefficient (D), sensitivity, high peak current, long term stability, reproducibility and also repeatability. Moreover,

majority of the CMEs offered simultaneous determination of MTZ and other nitroimidazole derivatives (ranitidine, chloramphenicol, 10-sulfonamide, tinidazole and ornidazole *etc*). Several interference studies (ronidazole, 1, 2 dimethylimidazole, dimetridazole, 4-nitroimidazole) were also investigated.

Despite of numerous advantages, there are few limitations in some CMEs. In order to attain fine-tuned senor systems for the MTZ detection, drawbacks need to be focused. Only a few CMEs based MTZ sensors were explored for a wide range of drug concentration and in the most of these systems, there was a high LOD and negative reduction potential. Moreover, details on electrode surface area (A), diffusion coefficient (D), electron transfer coefficient, rate constant, LOQ and electrode stability have not been reported in some studies. Apart from this, sensitivity was lacking for real sample analysis in various CMEs. Hence bringing out a more sensitive CME based electrochemical device for real sample analysis could be the more challenging work. Moreover, avoiding the costly materials and finding out the more eco-friendly methods and materials are highly essential. Hence, some more investigations and modifications which are needed to be brought out for the sensitive determination of MTZ electrochemically using CMEs are the opportunities in this field for making sensor devices.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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