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Simultaneous sensing of mesalazine and folic acid at poly (murexide) modified glassy carbon electrode surface

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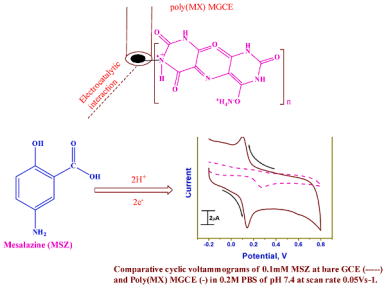
HIGHLIGHTS

- Demonstration of a simple method for the modification of glassy carbon electrode.
- The fabricated electrode was used for the electrochemical determination of mesalazine (MSZ) and folic acid (FA).
- The simultaneous determination of MSZ and folic acid by CV technique.
- The lower limit of detection was achieved.

GRAPHICAL ABSTRACT



Comparative cyclic voltammograms of 0.1mM MSZ at bare GCE (-----) and Poly(MX) MGCE (-) in 0.2M PBS of pH 7.4 at scan rate 0.05Vs-1.

ARTICLE INFO

Keywords:
Mesalazine
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ABSTRACT

The electro analytical determination of Mesalazine (MSZ) and Folic acid (FA) were done using a murexide-based sensor developed on a glassy carbon electrode. Electro oxidations for MSZ and FA were investigated in buffer (PBS) of pH 7.4 using cyclic voltammetry. This work was carried out to study the effect of change in the concentration of MSZ, scan rate, and pH of the electrochemical behaviour of MSZ on poly-murexide modified glassy carbon electrode [poly(MX) MGCE] surface. The limit of detection of MSZ was found to be 9.1×10^{-5} M in the linear concentration range of 2.5×10^{-4}M to 12.5×10^{-4}M. The modified electrode has also shown good sensitivity for detection of FA and simultaneous detection of MSZ and FA. The two distinct individual peaks at the corresponding peak potentials of MSZ and FA were obtained. The poly (MX) MGCE electrode showed a stable, reproducible, and sensitive result for MSZ and FA.

1. Introduction

For more than three decades, mesalazine (5-aminosalicylic acid; 5-ASA)(Scheme 1) has been used by practitioners to treat chronic inflammatory bowel disease (IBD) like ulcerative colitis (UC) and Crohn's disease [1,2]. Usually, both these diseases adversely affect the patients' quality of life [3]. Mesalazine at doses above 2.4 g/day works well to control Crohn's disease [4]. Colorectal neoplasia (CRN) is

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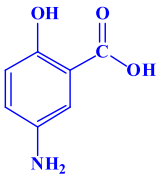


Scheme 1. Mesalazine (MSZ).

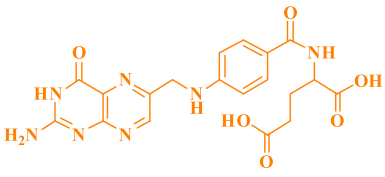
another recognized impediment of IBD. It is a primary medical concern worldwide not only for its dreadfulness but also for its considerable impact on healthcare costs. In recent years, it is also observed that colorectal adenocarcinoma caused enormous morbidity and mortality [5]. The much known 5-ASA agents like sulfasalazine, mesalazine, and balsalazide have been associated with a protective effect against the development of colorectal cancer [6]. Currently, many researchers are working on designing different methods to deliver sufficient 5-ASA at the sites of inflammation [7]. MSZ detection in different types of pharmaceutical preparations and biological samples using analytical techniques such as ultra-performance liquid chromatography [8], spectrophotometry [9], HPLC [10], HPLC-ESI-MS [11], fluorescence spectroscopy [12], LC-MS [13], and HPLC [14] are reported. However, these reported methods are less cost-effective, more time-consuming, and less sensitive. In contrast, electro analytical methods are proved to be more advantageous, simple, and accurate in comparison with other methods [15–21].

Folic acid (FA) (Scheme 2) controls many biological functions related to DNA replication and repair, nucleotide synthesis, regulation of vitamins, amino acids, etc. It also acts as a coenzyme that controls the generation of ferrochrome [22–24]. The insufficient amount of folates in human beings leads to the risk of the development of colorectal cancer and neural tube defects [25,26], heart attack, leucopenia, and psychosis [27,28]. All such health hazards demand different methods to determine FA accurately.

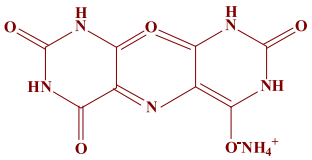
Murexide (MX), the ammonium salt of purpuric acid, is a reddish-purple powder (Scheme 3). Murexide is soluble in water, but we must freshly prepare the aqueous solution of Murexide every day as it is unstable. This dye has attracted the attention of researchers since it is widely used as a metal ion indicator to be employed in the EDTA complexometric titration [29]. It has been reported that the dye changes colour during titrimetric analysis due to the displacement of hydrogen ions from the four imido groups [30]. Murexide has also shown suitable scavenging activities for superoxide and hydroxyl radicals, and in recent times, it has been used as a chromogenic agent [31].

Many research reports have suggested that the combination drug therapy of sulfasalazine and folic acid have a protective effect against colorectal cancer for patients who have had ulcerative colitis for a long time [32]. However, many patients were intolerant of sulfasalazine, so 5-aminosalicylic acid (5-ASA) or MSZ medications were developed to replace it. It has been reported that MSZ is better than sulfasalazine [4,33,34].

Vitamin B12 and folate deficiencies are common in patients with long-term IBD because the small intestine gets damaged by IBD and can't absorb the micronutrients. This fact is reported by Pan et al., where the amount of serum folate concentration in patients with ulcerative colitis (UC) was measured and seen to be much lower than the expected value [35]. A fixed-dose combination of MSZ and FA can improve the



Scheme 2. Folic acid(FA).



Scheme 3. Murexide (MX).

quality of IBD patients' life [36]. Also, not many reports have examined the compatibility of folic acid with 5-aminosalicylate drugs used in the treatment of inflammatory bowel diseases [37]. Although the electrochemical determination of MSZ was reported [2,38], only one report on the simultaneous determination of MSZ and FA using electrochemical analysis is available in the literature [39]. In this work, we have examined the interaction between MSZ and FA at poly (MX) modified glassy carbon electrode, and subsequent simultaneous determination of MSZ and FA was observed. Poly (MX) GCE has been selected as a modifier for the electrochemical determination as no dye-based electrodes were used to detect MSZ and FA earlier. The Modified ploy (MX) GCE showed good voltammetric sensing activity to determine MSZ and FA simultaneously. There was no interaction between MSZ and FA, as reported earlier, by using a different technique [40].

2. Materials and methods

2.1. Chemicals

Mesalazine (Mwt = 151.16 g/mol, purity >97%), Murexide (Mwt = 284.18 g/mol, purity >95%) and Folic acid(Mwt = 441.40 g/mol, purity ≥99.5%) were procured from Himedia and used directly without any further purification. All the solutions of MSZ (25×10^{-4} M), FA (25×10^{-4} M) and Murexide (25×10^{-3}M), phosphate buffer (PBS) of the desired pH were prepared using water doubly distilled. The Mesacol tablets were purchased from a local pharmacy for real sample analysis.

2.2. Instrumentation

In this work, we have used an electrochemical work station CHI-619E with three electrodes for cyclic voltammetry analysis. The reference, counter, and working electrodes were saturated calomel (SCE), platinum wire, and glassy carbon electrode (bare/modified), respectively.

2.3. Preparation of modified electrode [poly (MX)MGCE]

The GC electrode surface was modified by polymerizing the murexide monomer on its surface by employing ten reversible potential cycles in the range of −1.0 V to +2.0 V. The scan rate was maintained at 0.1 V/s, and the technique used was CV. The murexide monomer solution was prepared in 0.2 M PBS of pH 7.4. The polymerization of Murexide could be confirmed by observing stable voltammograms with ten repeated scans, as shown in Fig. 1. The poly(MX)MGCE sensor, thus obtained, was rinsed with DD water and used for the electro analysis of MSZ and FA [41].

2.4. Preparation of real sample

For preparation of real sample, five mesacol tablets were weighed and ground to a homogeneous fine powder in a mortar. An amount equivalent to prepare a stock solution of concentration of about 1.0 mM was accurately weighed and dissolved in distilled water. The contents were sonicated for 20 min for extensive dissolution. The excipient was separated by filtration and the residue was washed three times with distilled water. The solution was transferred into a 100 ml measuring flask and made up to the mark. Appropriate solutions were prepared by

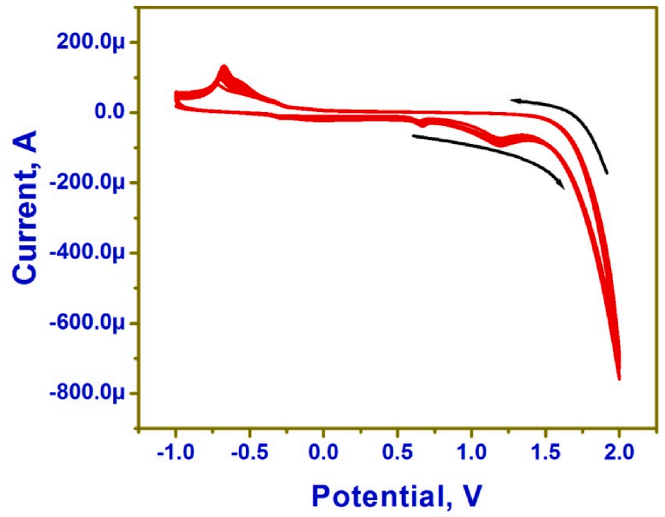


Fig. 1. The voltammograms obtained during polymerization of murexide monomer on GCE maintaining [MX] = 1.0 mM, pH = 7.4, and scan rate = 0.1Vs^{-1}.

taking suitable aliquots from this stock solution and diluting them with the phosphate buffer. Each solution was transferred to the voltammetric cell and analyzed by standard addition method.

3. Result and discussion

3.1. Characterization of poly(MX)MGCE

The pattern of the voltammograms as shown in Fig. 2 has revealed that there is a remarkable improvement in the electron transfer process at poly(MX)MGCE (solid line) when compared with bare GCE (dashed line). The total active surface area available for the reaction of species in solution has been estimated by the Randles-Sevcik equation [17]. For poly (MX) MGCE the electroactive surface area is maximum (0.01953 cm^2) as compared with bare GCE (0.01752 cm^2).

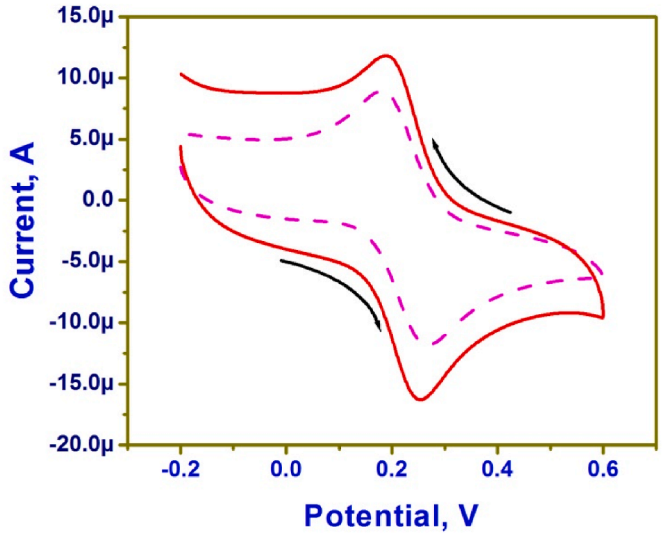


Fig. 2. Enhanced peak current of 1.0 mM potassium ferrocyanide at poly(MX) MGCE (solid line) at a scan rate of 0.1 Vs^{-1}against that at bare GCE (dashed line).

3.2. Electro-oxidation of MSZ at poly(MX)MGCE

This work investigated the nature of the peak current of oxidation of 0.1 mM MSZ at bare GCE and modified GCE surfaces using the CV technique. Before we started the investigation with mesalazine, the bare and modified electrodes were tested with buffer (PBS) without the analyte to ensure that the reaction is electrocatalytic. The supporting voltammograms are attached in the supplementary file (S1). The solution pH was maintained at 7.4 and the scan rate used was 0.05 Vs^{-1}. At bare GCE, an oxidation peak potential for MSZ was obtained at 0.2475 V, whereas the oxidation peak of MSZ at poly(MX)MGCE was obtained at 0.1417 V. The two cyclic voltammograms in Fig. 3 clearly shows that the peak current has been increased substantially at poly(MX)MGCE indicating a faster electron transfer as compared to bare GCE. The improved current response at a lesser potential value confirms superior electro catalytic activity or better electro-oxidation of MSZ at poly(MX) MGCE surface. The probable mechanism of electro-oxidation of mesalazine is shown below (Scheme 4).

3.3. Influence of variation of scan rate on the peak current of MSZ

In this work, we have investigated the influence of scan rate for the oxidation of 0.1 mM MSZ in 0.2 M PBS of pH 7.4 at poly(MX)MGCE surface (Fig. 4A) by maintaining a range of 0.01 Vs^{-1} to 0.21 Vs^{-1}. It has been observed that the anodic peak current gradually increased with the increase of scan rate, and this observation was at par with the Randles-Sevcik equation. The two plots of Ipa vs. υ (Fig. 4B) and Ipa vs. $\upsilon^{1/2}$ (Fig. 4C) showed a linear relationship with correlation coefficients (r^2) of 0.9778 and 0.9984, respectively. These results suggest that the electrode phenomenon is diffusion-controlled [42,43].

3.4. Variation of solution pH value

As various electro analytical reports suggest that the oxidation of biologically active compounds depends on solution pH [2,44], therefore, in this work, we have investigated the effect of variation of solution pH on the electro-oxidation of 0.1 mM MSZ at poly(MX)MGCE by using CV technique. The pH range was varied in the range of 5.5–8.0 in increasing order (Fig. 5A). The result shows, by increasing the pH of 0.2 M PBS, the oxidation peak potential was shifted to more negative side. This indicates the pH of the supporting electrolyte has significant effect on the

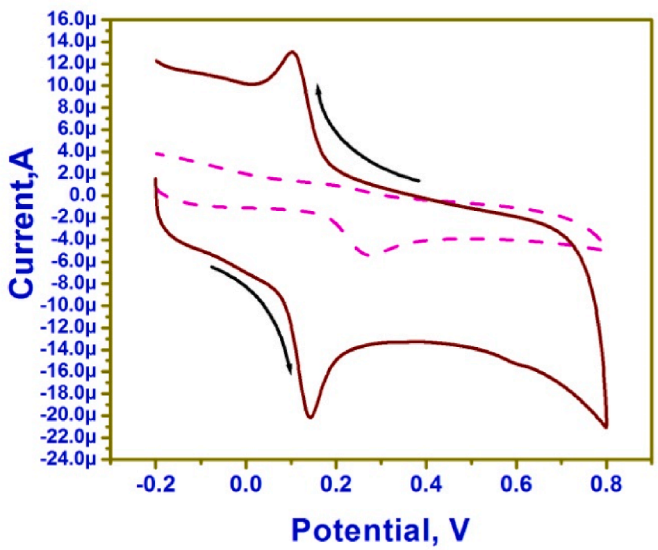
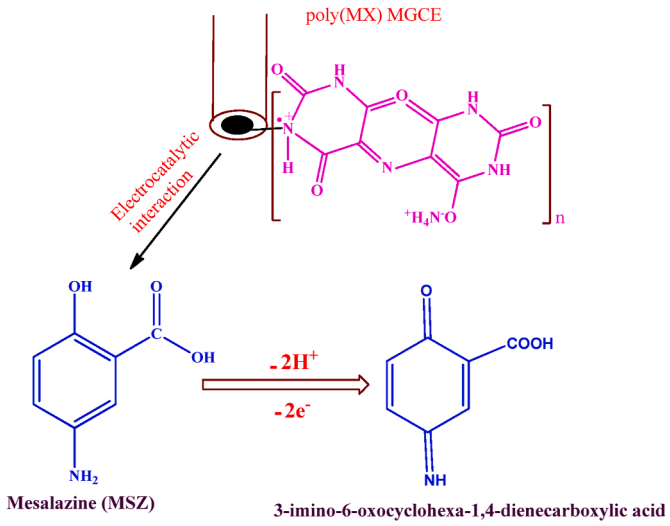


Fig. 3. Comparative cyclic voltammograms of 0.1mM MSZ at bare GCE (———) and Poly(MX) MGCE (–) in 0.2 M PBS of pH 7.4 at scan rate 0.05Vs^{-1}.



Scheme 4. Probable electro-oxidation of mesalazine.

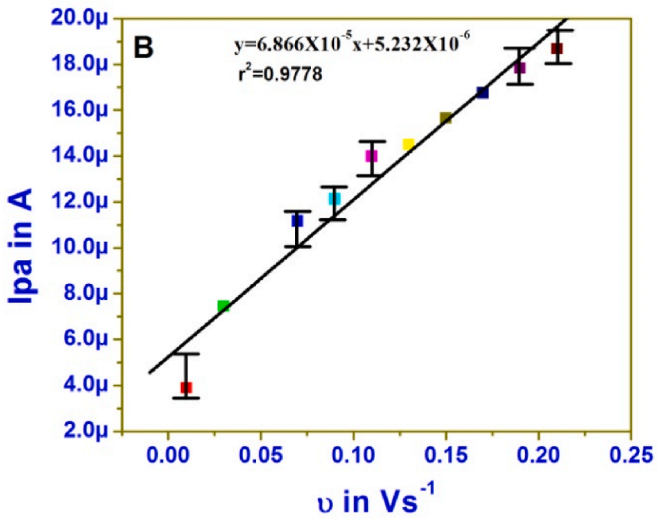


Fig. 4B. Anodic peak current (Ipa) vs. scan rate (υ) plot.

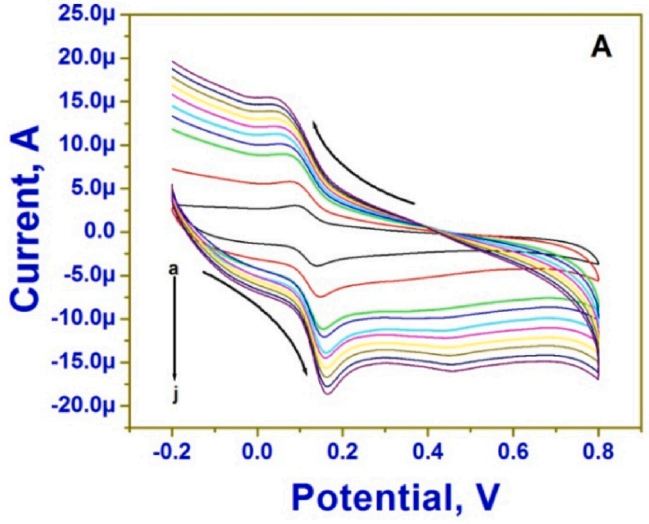


Fig. 4A. Electro oxidations of 0.1 mM MSZ at poly(MX)MGCE in 0.2 M PBS of pH 7.4 at various scan rates(a-j range: 0.01Vs^{-1} to 0.21 Vs^{-1}).

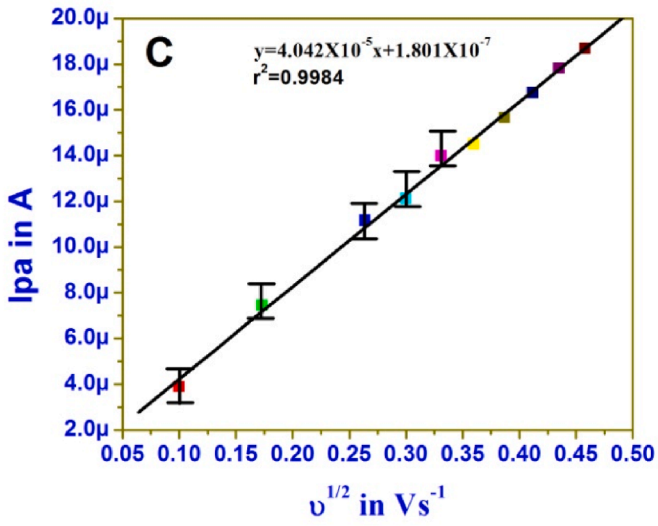


Fig. 4C. Plot of Ipa vs. square root of scan rate.

oxidation of the MSZ at poly(MX)MGCE surface as shown in Fig. 5B.

3.5. Influence of variation of MSZ concentration

The concentration of MSZ was varied from 2.5 × 10^{-4}M to 12.5 × 10^{-4}M to investigate its effect on the electro-oxidation at poly(MX)MGCE surface. The pH was maintained at 7.4 with a scan rate at 0.05Vs^{-1}, as shown in Fig. 6A. It has been observed that the peak current (Ipa) increased with an increase in the concentration of MSZ, while anodic peak potential Epa has a positive shift. Ipa vs [MSZ] graph also revealed a straight line indicating a superior correlation between Ipa and the MSZ concentration (Fig. 6B). The detection limit was calculated and found to be 9.1 × 10^{-5} M for MSZ at poly(MX)MGCE and we compared this value with other reported values as shown in Table 1. Our work is comparable with other reported methods [2,44–51].

3.6. Electrocatalytic response of FA at poly(MX)MGCE

The electro-oxidation of 1.0 × 10^{-4}M FA was studied on both the surfaces of BGCE and poly (MX)MGCE in 0.2 M Phosphate buffer of pH 7.4 with the 0.05 Vs^{-1} scan rate(Fig. 7). The irreversible oxidation of FA at BGCE was almost flat and without any anodic peak potential. At the same time, in the identical conditions, there was an enhancement in peak current at poly(MX)MGCE surface. A sharp oxidation peak for FA at poly (MX)MGCE was obtained at 0.6312 V, and hence, we can conclude that the fabricated poly(MX)MGCE was responsive towards the determination of FA.

3.7. Variation of FA concentration at poly (MX)MGCE

The electrocatalytic oxidation of FA with different concentrations in the range of 2.5 × 10^{-4}M to 10.0 × 10^{-4}M in PBS (0.2 M) of pH 7.4 was investigated using the CV technique (Fig. 8A). A steady rise in Ipa has been observed as the concentration of FA was increased along with a positive shift in Epa. A plot of Ipa versus concentration of FA was plotted to obtain a straight line with satisfactory linearity (r^2 = 0.9764), as shown in Fig. 8B. The linear regression equation was obtained as follows:

Ipa (10^{-5}A) = 0.0535(C_o10^{-4}M/L)+1.494

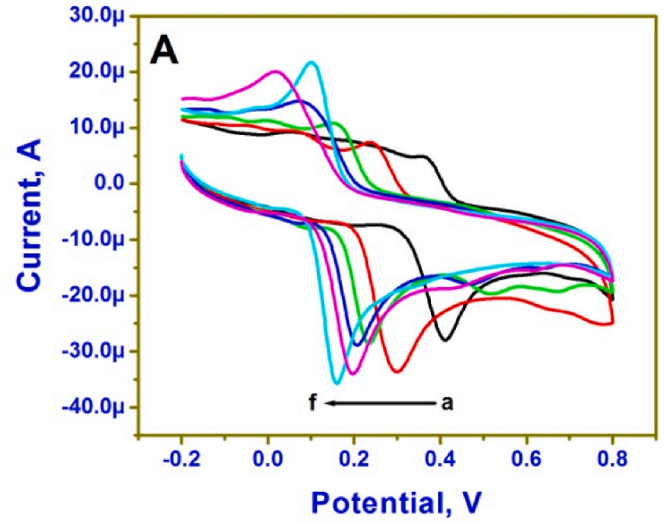


Fig. 5A. Cyclic voltammograms of the poly(MX) MGCE in 0.2 M PBS solution at different pH values (a–f: 5.5 to 8.0), scan rate = 0.05 Vs^{-1}.

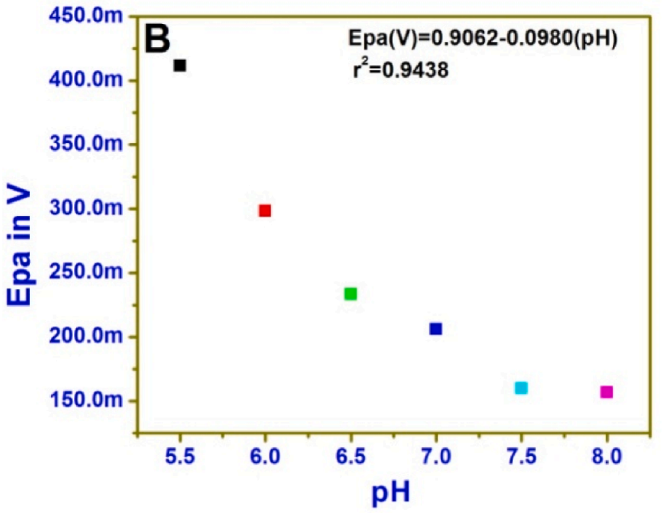


Fig. 5B. The effect of pH on the peak potential response of MSZ in 0.2 M PBS solution.

3.8. Simultaneous determination of MSZ and FA

The binary mixture of 0.1 mM MSZ and 0.1 mM FA in 0.2 M PBS of pH 7.4 was subjected to CV analysis, maintaining the scan rate at 0.05 Vs^{-1}. The CV response of the binary mixture at BGCE (dashed line) did not show any significant sensitivity, and the signals for electro oxidations of both the analytes were suspected to be merged. However, when we examined the CV response of the binary mixture at the poly(MX) MGCE, we obtained enhanced current responses for the selective oxidation of MSZ and FA (Fig. 9). The oxidation potentials were located at 0.1835 V and 0.6644 V for MSZ and FA, respectively, similar to their oxidation potentials. The reproducibility and stability tests were done by repeating thirty reversible potential cycles in the range of −0.2 V to +0.8 V. The results are acceptable for reproducibility and stability. The supporting voltammogram is attached in the supplementary file (S2). Thus, we can conclude that the poly(MX)MGCE can be used for the individual as well as simultaneous detection and determination of MSZ and FA in a binary mixture.

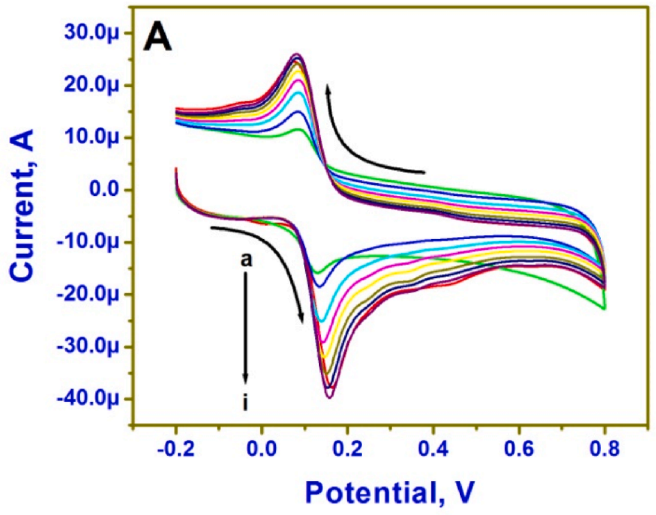


Fig. 6A. The cyclic voltammograms obtained on variation of MSZ concentration (a–f: 2.5 × 10^{-4}M, 4.54 × 10^{-4}M, 6.25 × 10^{-4}M, 7.69 × 10^{-4}M, 8.92 × 10^{-4}M, 10.0 × 10^{-4}M, 10.93 × 10^{-4}M, 11.76 × 10^{-4}M and12.5 × 10^{-4}M), scan rate = 0.05 Vs^{-1}.

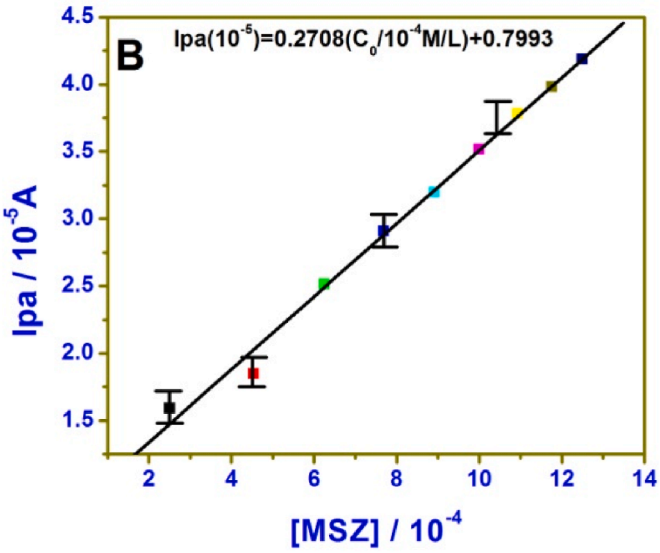


Fig. 6B. Plot of anodic peak current vs. MSZ concentration.

3.9. Real sample analysis of MSZ

To evaluate the efficiency of poly(MX)MGCE, the electrode was subjected to the determination of MSZ content in commercial tablets (Mesacol 400 mg MSZ/tablet). The CV method was used to study the recovery of the sample of MSZ in the concentration range from 1.0 × 10^{-5} M to 1.0 × 10^{-4} M. As shown in Table 2, we have obtained a good recovery with acceptable SD ± RSD at poly(MX)MGCE. The results show that the modified electrode works efficiently as an electrochemical sensor for the quantitative determination of MSZ in commercially available tablets.

3.10. Interference study

Different salts are selected to check the interfering effects on the voltammetric response of 1.0 × 10^{-4} M MSZ. The experimental results are shown in Table 3. The voltammetric signal of MSZ was not affected

Table 1
Comparative analysis of linear range and detection limits of present work with other works available in the literature.

Electrochemical methods	Modified Electrodes	Linear working range (M)	Detection limits (M)	Refs.
SWV	Pencil graphite electrode	9.8×10^{-7} - 7.3×10^{-5}	2.1×10^{-8}	[44]
Sona LSV	Glassy carbon electrode	1.0×10^{-6}- 5.7×10^{-5}	3.0×10^{-7}	[45]
CV	CTAB immobilized modified CPE	60×10^{-6}-140×10^{-6}	1.9×10^{-9}	[2]
DPV	Glassy Carbon Electrode	2.0×10^{-6}- 1.0×10^{-4}	8.2×10^{-7}	[46]
DPV	Graphene Oxide composite modified GCE	2.0×10^{-6}- 20×10^{-6}	0.97×10^{-6}	[47]
DPV	Poly (Methylene blue)-Carbon nanotube composite modified GCE	5.0×10^{-6}-100×10^{-6}	7.7×10^{-9}	[48]
CV	Copper tungstate nanosheet MGCE	0.005×10^{-6}-367×10^{-6}	0.0012×10^{-6}	[49]
CV	Phosphomolybdic acid MGCE	0.02×10^{-6}- 0.16×10^{-3}	79.50×10^{-7}	[50]
CV	Poly (glutamic acid) MGCE	0.0×10^{-6}- 0.5×10^{3}	23.94×10^{-9}	[51]
CV	Poly(MX)MGCE	2.5×10^{-4}- 12.5×10^{-4}	9.1×10^{-5}	Present work

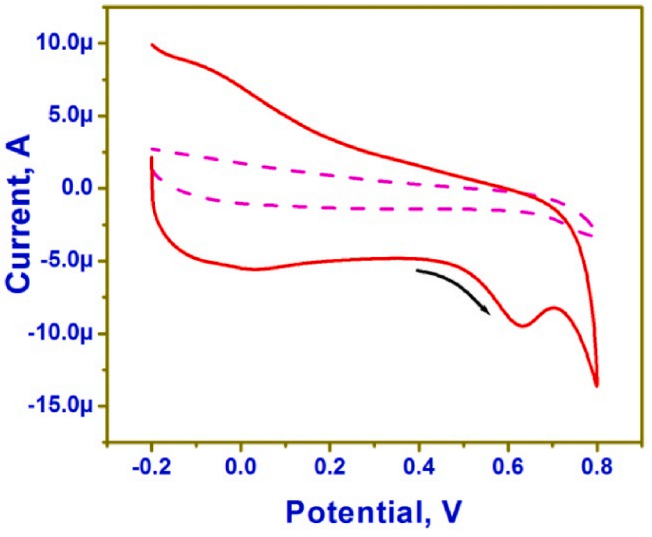


Fig. 7. Cyclic voltammograms for 1.0×10^{-4}M FA at BGCE and poly(MX) MGCE in PBS of pH 7.4.

by ten-time higher concentrations of potassium chloride, sodium carbonate, magnesium chloride, and ammonium chloride. However, the result is not the same with calcium chloride and starch.

4. Conclusion

In the present work, we have demonstrated a simple method to develop an electrochemical sensor by electro polymerization of murexide on glassy carbon electrode surface to detect MSZ and FA using CV technique. Further, the fabricated electrode was used to separate MSZ and folic acid voltammetrically. The influence of variation of different parameters such as scan rate, pH, and concentration on the electro-oxidation process of the analytes were examined. The modified electrode could detect the lowest concentration, 9.1×10^{-5} M of MSZ. This modified electrode is also used to determine MSZ in the commercially available tablet sample. Hence, we can conclude that our work could develop a sensor to assess mesalazine and folic acid separately and simultaneously.

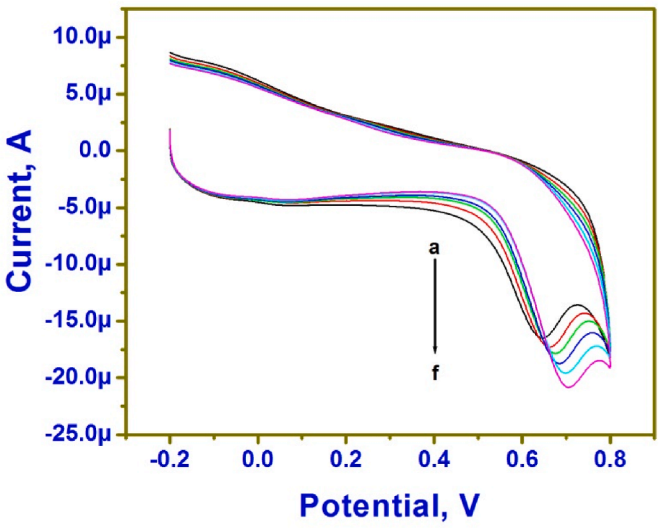


Fig. 8A. Concentration variation of FA in PBS solution of pH 7.4 at poly(MX) MGCE with different concentrations (2.5×10^{-4}M, 4.54×10^{-4}M, 6.25×10^{-4}M, 7.69×10^{-4}M, 8.92×10^{-4}M, 10.0×10^{-4}M) at scan rate of 0.05 Vs^{-1}.

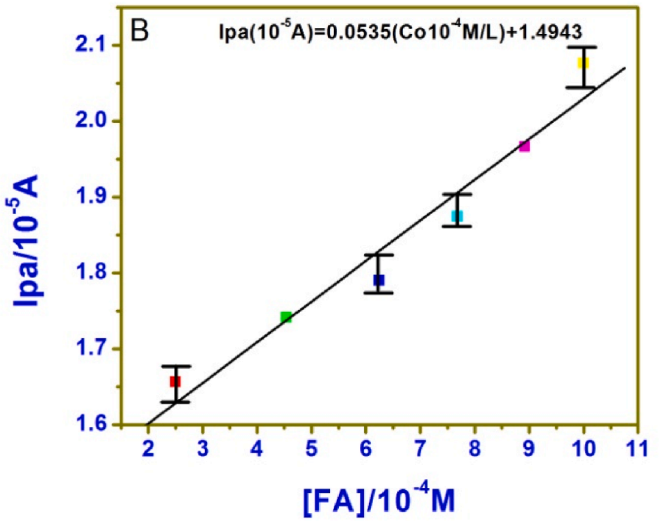


Fig. 8B. Graph of anodic peak current versus concentration of FA.

CRediT authorship contribution statement

Kailash S. Chadchan: performed the experiments, Formal analysis, Writing – original draft. **Amit B. Teradale:** performed the experiments, Formal analysis, Writing – original draft. **Pattan S. Ganesh:** Conceptualization, equally contributed, Formal analysis, Writing – original draft. **Swastika N. Das:** Conceptualization, equally contributed,

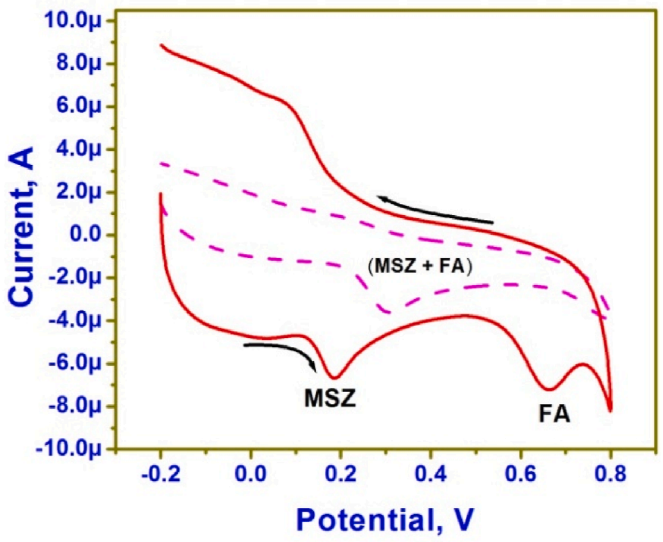


Fig. 9. Cyclic voltammograms for simultaneous determination of 1.0×10^{-4} M MSZ and 1.0×10^{-4}MFA at BGCE (dashed line) and poly(MX)MGCE(solid line) at a scan rate of 0.05 Vs^{-1}.

Table 2
Determination of MSZ in commercial tablet sample.

Formulation Sample	MSZ added (M)	Detected (M)	Recovery (%)	SD ± RSD (%)
Tablet (Mesacol)	–	Not detected	–	–
	1.0×10^{-5}	1.072×10^{-5}	107.2	0.0721 ± 0.0051
	3.0×10^{-5}	2.908×10^{-5}	96.93	0.0650 ± 0.0464
	5.0×10^{-5}	5.012×10^{-5}	100.24	0.0084 ± 0.0060
	7.0×10^{-5}	7.019×10^{-5}	100.27	0.0134 ± 0.0095
	9.0×10^{-5}	9.101×10^{-5}	101.12	0.0714 ± 0.0510
	1.0×10^{-4}	0.969×10^{-4}	95.9	0.0466 ± 0.0333

Table 3
Effect of different interferants on the cyclic voltammetric response of 1.0×10^{-4} M MSZ at scan rate of 0.05 Vs^{-1} at poly(MX)MGCE.

Interferents	Concentration (mM)	Signal Change (%)
Calcium chloride	1.0	2.48%
Potassium chloride	1.0	0.84%
Sodium carbonate	1.0	1.67%
Magnesium chloride	1.0	0.78%
Ammonium chloride	1.0	1.74%
Starch	1.0	4.97%

performed the experiments, Formal analysis, Writing – original draft, All authors agreed to the final version of the manuscript.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.matchemphys.2022.126538.

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