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DPP direct and indirect estimation of sulfamethoxazole in pharmaceuticals using Schiff base derivative

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ABSTRACT

The research includes the development of a simple, sensitive and accurate DPP (differential pulse polarographic) method for the quantitative determination of sulfamethoxazole drug in pharmaceutical preparations and in their pure and commercial farms, also the electrochemical behavior using the dropping mercury electrode DME, as well as finding the values of the half-wave potential (E½) as qualitative value also the number of electrons that were transferred and participating in the reduction process. Synthesis of Schiff's base between sulfamethoxazole with 4-dimethylaminobenzaldehyde compound wherein the Sulfamethoxazole drug can be indirectly estimated. The sulfamethoxazole drug and the sulfamethoxazole Schiff's base derivative showed a clear reduction peak at a voltage of (-0.18) and (-0.49) volt under optimal conditions. The standard calibration curve prepared for the sulfamethoxazole and the sulfamethoxazole Schiff's base derivative at a concentration range of (10-100) and (50-1000) $\mu g.ml^{-1}$ gave a correlation coefficient of 0.9996 and 0.9999 respectively, also LOD and LOQ of the sulfamethoxazole drug 1.75 and 5.82 respectively, and The LOD and LOQ of sulfamethoxazole Schiff's base derivative 8.40 and 25.40 $\mu g.ml^{-1}$, respectively, also the average of the relative standard deviation RSD of the sulfamethoxazole drug was 0.52 % sulfamethoxazole Schiff's base derivative was 0.33% with recovery of the sulfamethoxazole drug 99.54% and 100.41% for the sulfamethoxazole Schiff's base derivative.

Capsule Summary: A simple, sensitive and accurate DPP method for the quantitative determination of sulfamethoxazole drug in pharmaceutical formulations was developed, which showed 99.54% and 100% recovery for sulfamethoxazole drug and sulfamethoxazole Schiff's base derivative, respectively.

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INTRODUCTION

Sulfamethoxazole (SMX) is [4-amino-N-(5-methyl-1,2-oxazol-3-yl) benzene sulfonamide] (Figure 1), discovered in 1932 and introduced into clinical use in 1935. a sulfonamide bacteriostatic antibiotic, where inhibits the bacterial enzyme dihydropteroate synthetase, also gets readily absorbed in the body (Kasule et al., 2018). Its basic activity is against sensitive forms of streptococcus, staphylococcus aureus,

escherichia coli, haemophilus influenzae, and oral anaerobes. It is usually used to treat urinary tract diseases and respiratory tract infections, also it can be used treat sinusitis. The human and veterinary medicine have relied on the antibiotic sulfamethoxazole to treat diseases (Ricken et al., 2017). Despite, high consumption of this compound culminates causes in environmental and community health problems, in addition, different techniques for estimate sulfamethoxazole in pharmaceutical preparations and biological fluids have been developed. Several techniques for determining sulfamethoxazole in pharmaceutical preparations and biological fluids have been developed, these methods include spectroscopic methods, chromatographic methods (Sayar et al., 2010), electrochemical methods, NMR spectrophotometric method (Salem, A.A., Mossab, H.A., Barsoumb, 2006), flow injection (Mohammed et al., 2020) and voltameteric (López et al., 2019).

Polarography is the study of the electrolysis of the oxidizable and reducible materials between a a dropping mercury electrode (DME) and a reference electrode (RE) (Joseph & Kumar, 2010). The distinguished characteristics of the polarographic wave are used in the quantitative and qualitative evaluation of the substance to be analyzed by measuring the diffusion current id (Heyrovský, 2012), which is directly proportional to the concentration of the studied substance as a quantitative estimation (S. A. H. Al-Ameri & Al-Waeli, 2016). The half-wave potential ($E_{1/2}$) is used for qualitative analysis of the matter. Among the many polarographic techniques, differential pulse polarography (DPP) method is the most commonly utilized (H. S. Al-Ameri, 2017). In this study, the estimation of sulfamethoxazole in its pure form and pharmaceuticals was done directly by differential pulsed polarography (DPP) method also indirectly estimation by synthesis Schiff's base (Latif et al., 2019) with (4-dimethylaminobenzaldehyde) (Latif et al., 2019; Lucida et al., 2000). Based on above mentioned facts, this research is focused on the development of a simple, sensitive and accurate DPP (differential pulse polarographic) method for the quantitative determination of sulfamethoxazole drug in pharmaceutical formulations.

MATERIAL AND METHODS

Materials, reagents and apparatus

A polarographic analyzer type 797VA Computrace Metrohm, Herisau, Switzerland was used for electrochemical analysis. It was employed with a working electrode in DME mode, a reference electrode (RE) in Ag/AgCl mode and an auxiliary electrode in (Pt) wire mode. All of the trials were carried out at a temperature of 25 °C. The pH was measured using a WTW inoLab® IDS – Benchtop pH meter (Germany).

The analyses were achieved via applying analytical grade reagent, chemicals substances and solvents. Ethanol was used to preparing the standard solution and commercial drug sample. The pure form sulfamethoxazole (SMX) standard material was achieved from the state company for drug industries - Samara Iraq (SDI). The Septrin tablet was obtained from local pharmacies. A 100 mg of the SMX was used to prepare a standard solution 1000 $\mu g.ml^{-1}$ by dissolving in 100 ml volumetric flask with ethanol. The standard solutions were prepared by sequential dilution with ethanol.

Supporting electrolytes of 1M lithium chloride (LiCl) was prepared a by dissolving 2.1 g in 50 ml of deionized water with continuous stirring also (0.1 and 0.01) M of lithium chloride (LiCl) was prepared by diluting 5 and 0.5 ml respectively of lithium chloride 1M in 50 ml of deionized water with continuous stirring (Al-Ameri and Al-Mayahi, 2016). The acetate buffer solution (pH= 6,7.4 and 8.1) was prepared by dissolving 6.8 g of sodium acetate salt($C_2H_3NaO_2$) in an appropriate volume of deionized water and add a volume of 2.8 ml of glacial acetic acid and transfer it to a volumetric flask of 1000 ml and the volume to be completed with deionized water to the mark, than adjusted the pH value by adding drops of sodium hydroxide 1 N or hydrochloric acid 1 N and monitoring the change in the pH value with a pH meter (Bunnell & Mock, 1990) .

Sulfamethoxazole standard calibration

An aliquot volumes of 1000 $\mu g.ml^{-1}$ sulfamethoxazole standard solution were transferred to 20 ml volumetric flasks, and 1 ml of 0.1M acetate buffer at pH 8.1 was added, along with 0.2 ml of LiCl (0.01M) as a supporting electrolyte, and diluted to the mark with ethanol. Each sample was transferred to a polarographic cell and degassed with high purity nitrogen for 300 s to purge the oxygen and analysis at scan rate 5 mVs^{-1} with pulse amplitude 50.

Synthesis of Schiff's bases of sulfamethoxazole

In 50 ml of ethanol, a solution of 4-dimethyleaminobenzaldehyde (0.149 g, 1 mmol) and sulfamethoxazole (0.253 g, 1mmol) was refluxed at temperature of 78 ^{0}C for 4 hours. After 24 hours, the reaction mixture was cooled, the precipitate was filtered, washed with cold distillate water and dried for 1 day at room temperature. A stock standard 1000 $\mu g.ml^{-1}$ sulfamethoxazole Schiff's base derivative solution was prepared by dissolving 100 mg weight in an appropriate volume of ethanol in a 50 mL beaker and transfer the solution to a 100 ml volumetric flask and the volume was completed by adding ethanol.

Preparation of sulfamethoxazole Schiff's base derivative

An aliquot volume of 1000 $\mu g.ml^{-1}$ sulfamethoxazole Schiff's base derivative solutions were transferred to 20 ml volumetric flasks, and 1 ml of 0.1M acetate buffer at pH 8.1 was added, along with 0.2 ml of LiCl 0.01 M as a supporting electrolyte, and diluted to the mark with ethanol. Each sample was transferred to a polarographic cell and degassed with high purity nitrogen for 300 s to purge the oxygen and analysis at scan rate 5 mVs^{-1} with pulse amplitude 50.

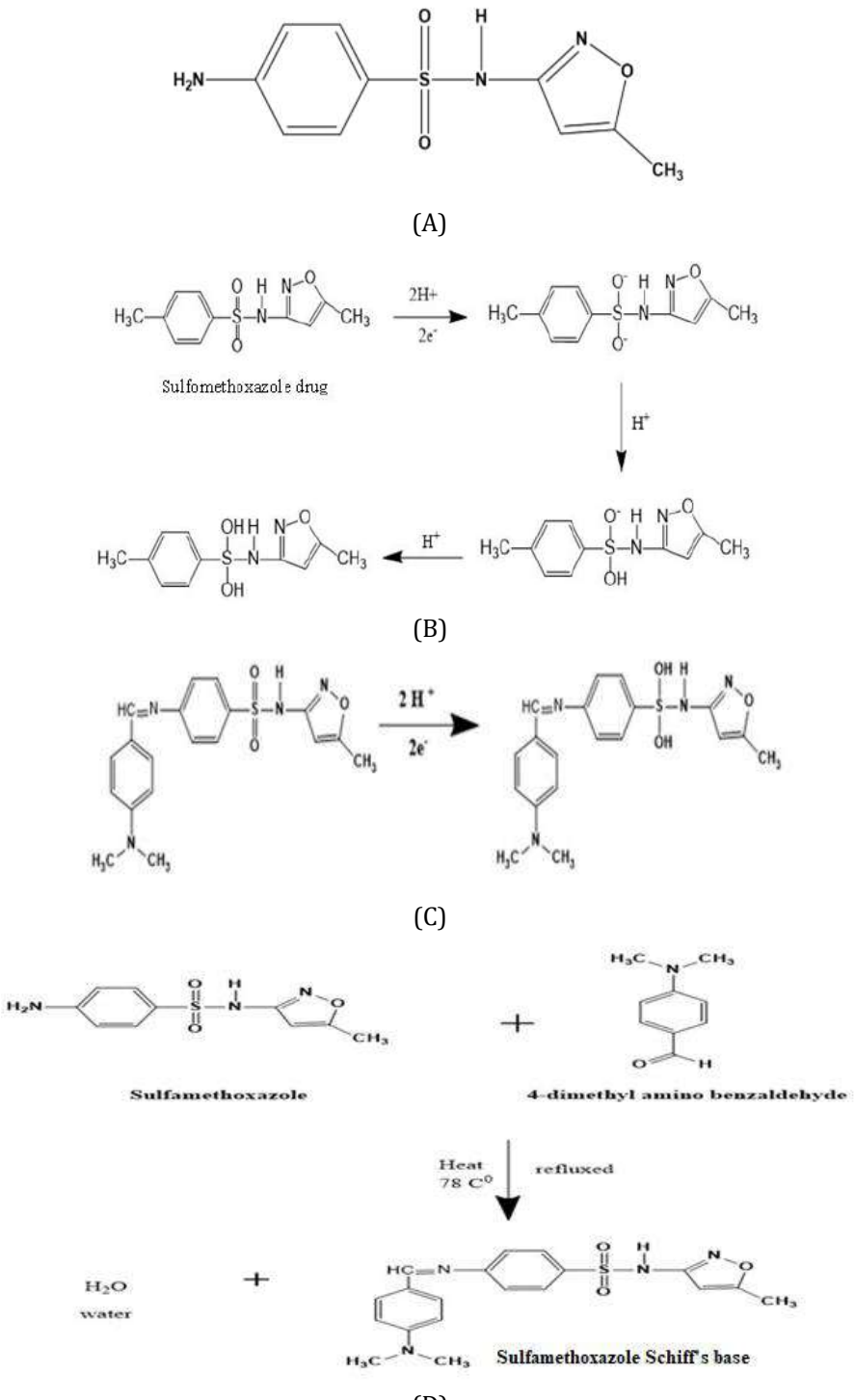

Fig. 1: (A) Sulfamethoxazole structural, (B) reduction mechanism of sulfamethoxazole drug, (C) reduction mechanism sulfamethoxazole Schiff base and (D) reaction mechanism of sulfamethoxazole and 4-dimethylamenobenzaldehyde sulfamethoxazole Schiff's base derivative synthesis

Septrin commercial sulfamethoxazole drug samples

A commercial sample of tablets was prepared by taking 10 tablets of the Septrin drug and grinding well in a fine powder with a mortar and a ceramic hammer and mixing homogeneously and taking a weight equal to the weight of one tablet in a 50 ml beaker A volume of 20 ml of ethanol was added with good stirring, then the mixture was filtered and a

clear solution was obtained, and transferred to a volumetric bottle of 50 ml and the volume was completed to the mark by adding ethanol.

RESULTS AND DISCUSSION

Optimization of DPP

Sulfamethoxazole drug has been studied using the differential pulse polarography (DPP) method. In order to obtain the best performing conditions that provide the best results, by carrying out the analyses at different conditions and selecting the one that resulted in highest value for the diffusion current, the effect of pH solutions, buffers and supporting electrolyte were chosen in this work (Gupta, 2016; Knoth et al., 2019).

Sulfamethoxazole drug, preliminary experiments were conducted to evaluate the behavior of the active groups in it and the extent of the best effort to work using (DPP) technique, and the use DEM with 99% pure ethanol solvent. Sulfamethoxazole drug showed a distinguished peak at (-0.18) V applied potential in 0.08 M acetate buffer at pH 8.1 as a best buffer solution, also 0.01 M LiCl was found to be the most excellent supporting electrolyte compared with KNO_3 and KCl, where causes precipitation of the sulfamethoxazole drug in solution (Figure 2). The synthesis of the sulfamethoxazole Schiff's base derivative was verified at a concentration of 50 $\mu g.ml^{-1}$ using DPP by the appearance of a polarographic peak at (-0.49) V while the sulfamethoxazole drug showed a polarographic peak at (-0.18) V and 4-dimethylamenobenzaldehyde polarographic peak (-1.29) V (Figure 3). Sulfamethoxazole Schiff's base derivative showed a distinguished peak at (-0.49) V applied potential versus in 0.08 M Acetate buffer at pH 8.1 as a best buffer solution, also 0.01 M LiCl was found to be the most excellent supporting electrolyte Figure 4. Also, the proposed mechanism reaction for the sulfamethoxazole Schiff's base derivative prepared with 4-dimethylamenobenzaldehyde Figure 5.

Method validation

Under optimal measurement conditions, a standard calibration curve prepared via measured diffusion current of sulfamethoxazole with the corresponding drug concentration values within the concentration range 10 – 100 $\mu g.ml^{-1}$, Figure 6. And a standard calibration curve prepared via measured diffusion current of sulfamethoxazole Schiff's base derivative with the corresponding drug concentration values within the concentration range 50 – 1000 $\mu g.ml^{-1}$ Figure 6. The results showed a linear equation statistically treated using the least squares method (Menke, 2015).

The statistical data for the standard curve showed a straight-line equation well suited for the analysis of sulfamethoxazole drug and sulfamethoxazole Schiff's base derivative and it was used to find the drug concentration in

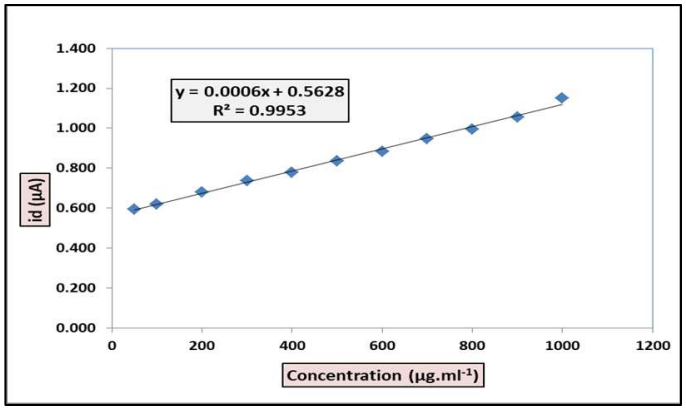

Fig. 2: Standard calibration curve for sulfamethoxazole Schiff's base derivative

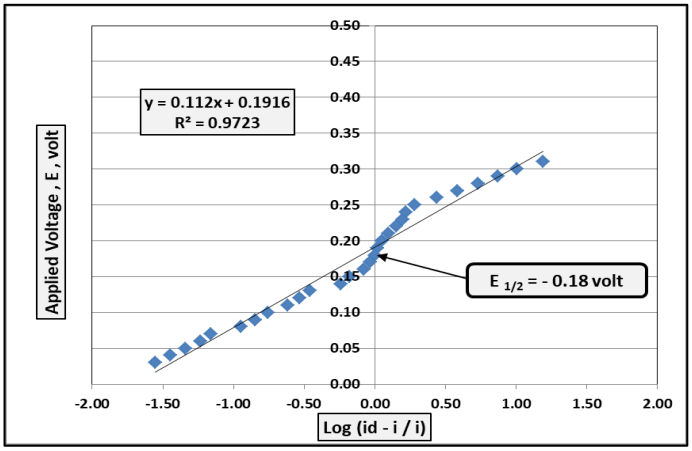

Fig. 3: Correlation between log (id-i)/i verses E for (10 µg. ml-1) sulfamethoxazole drug

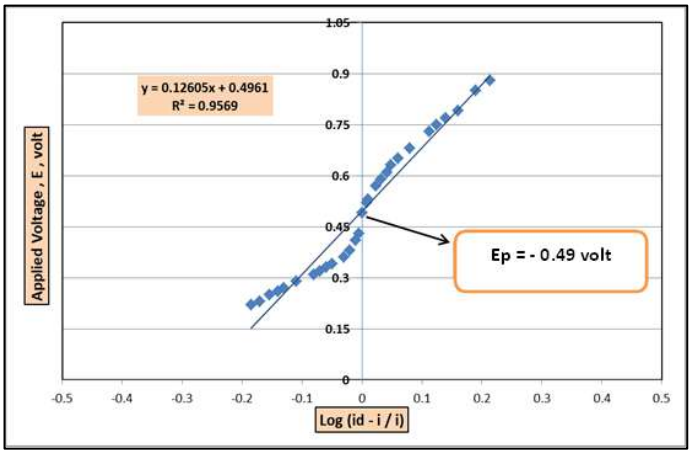

Fig. 4: Correlation between log (id-i)/i verses E for (10 µg. ml^{-1}) sulfamethoxazole Schiff's base derivative

samples. The results show that the LOD and LOQ found for sulfamethoxazole drug was equal to 1.75 and 5.82 $\mu g.ml^{-1}$ Table 1, while 65.33 and 218.67 $\mu g.ml^{-1}$ for sulfamethoxazole Schiff's base derivative Table 2 (Singh, 2020).

Table 2: Analytical results of standard sulfamethoxazole samples

Initial Conc. ($\mu g.ml^{-1}$)	Found Conc. ($\mu g.ml^{-1}$)	Absolute Error	Relative Error (%RE)	Recovery %	Standard Deviation (SD)	(RSD%)	C.L $= \bar{X} \pm ts/(\sqrt{n})$
30	29.39	-0.25	-0.83	99.17	0.14	0.48	29.75±0.14
50	49.39	-0.61	-1.21	98.79	0.35	0.70	49.39±0.35
70	70.46	0.46	0.66	100.66	0.27	0.38	70.46±0.27
n = 5				$t_{n-2} = 2.57$			

Table 3: Analytical results of standard sulfamethoxazole Schiff's base derivative samples

Initial Conc. ($\mu g.ml^{-1}$)	Found Conc. ($\mu g.ml^{-1}$)	Absolute Error	Relative Error (%RE)	Recovery %	Standard Deviation (SD)	(RSD%)	C.L $= \bar{X} \pm ts/(\sqrt{n})$
50	50.33	0.33	0.67	100.66	0.19	0.38	50.33±0.19
200	203.67	3.67	1.93	101.83	2.12	1.06	203.67±2.12
400	399.50	-0.50	-0.12	99.88	0.29	0.07	399.50±0.29
n = 5				$t_{n-2} = 2.57$			

Table 4: Results of the analysis of a commercial sulfamethoxazole (400 mg)

Sample of drugs $\mu g.ml^{-1}$	Measured Current id (μA)	Found Conc. $\mu g.ml^{-1}$	Amount Found (mg)	Recovery (%)	RE (%)	Standard Deviation (SD)	RSD (%)
	0.223	49.75	398.00	99.50	-0.50	0.14	0.29
	0.221	49.04	392.29	98.07	-1.93	0.56	1.12
50	0.222	49.39	395.14	98.79	-1.21	0.35	0.70
	0.223	49.75	398.00	99.50	-0.50	0.14	0.29
	0.223	49.75	398.00	99.50	-0.50	0.14	0.29
mean	0.223	49.54	396.29	99.07	-0.93	0.27	0.54

The accuracy and precision of the method for the determination of sulfamethoxazole and sulfamethoxazole Schiff's base derivative were confirmed. Various standard samples were prepared and analysis (n=5), Table 3 and 4 respectively (Shazalia et al., 2015). The proposed DPP method was applied to the determination of the sulfamethoxazole drug in the commercial pharmaceutical Septrin tablet with the active ingredient of 400 mg of sulfamethoxazole drug. The method demonstrated a good precision and accuracy and the pharmaceutical drug concentration was estimated in the range of 398 to 392.29 mg, which is within the actual concentration depending on the pharmaceutical drug composition and international standards for a value of 400 mg. The results of the analysis are summarized in Table 5.

The number of transferred electrons and actual $E_{1/2}$

The Ilkovic -Heyrovsky equation was used to calculate the number of electrons transferred during the reduction on the electrode and the actual value for the half-wave potential ($E_{1/2}$) at 25 °C. This equation explains the polarographic wave as reversible/irreversible reaction when the number of electrons is integer and irreversible while (n) is non-integer (Al-Ameri and Al-Ameri, 2017). Number of electrons (n) can be calculating from the plot of log (i/id -i) versus applied voltage (E) at set group concentrations (Al-Rufaie and Hussain, 2014).

$$E_{applied} = E_{1/2} - (0.0591/n) \log (i/id - i)$$

The actual half-wave potential ($E_{1/2}$) calculated of sulfamethoxazole and sulfamethoxazole Schiff's base derivative were -0.18 and -0.49 V and two electrons were required for the reduction Figures (8 and 9). In sulfamethoxazole and sulfamethoxazole Schiff's base derivative have two Sulfonamide group is one of the active groups with electrochemical activity (Apaydın & Török, 2019; Gulçin and Taslimi, 2018)., this group can be electrically reduced at the surface of the Mercury electrode, resulting in the appearance of the electrical diffusion current at the cathode, the results showed easily Sulfonamide group reduced to give two electrons transfer Figure (10 and 11).

CONCLUSIONS

A facile, sensitive and accurate differential pulse polarographic method for the quantitative determination of sulfamethoxazole drug in pharmaceutical preparations was developed. The developed method showed promising efficiency for the determination of sulfamethoxazole drug in simulated as well as commercial formulations. The method has illustrated that the DPP technique has several advantages that make it appropriate, for estimating sulfamethoxazole in pharmaceutical formulations also this method proved to be accurate, quick and precise, thus it might be used for pharmaceutical analysis and same can also be extended for the determination of other relevant pharmaceutical formations.

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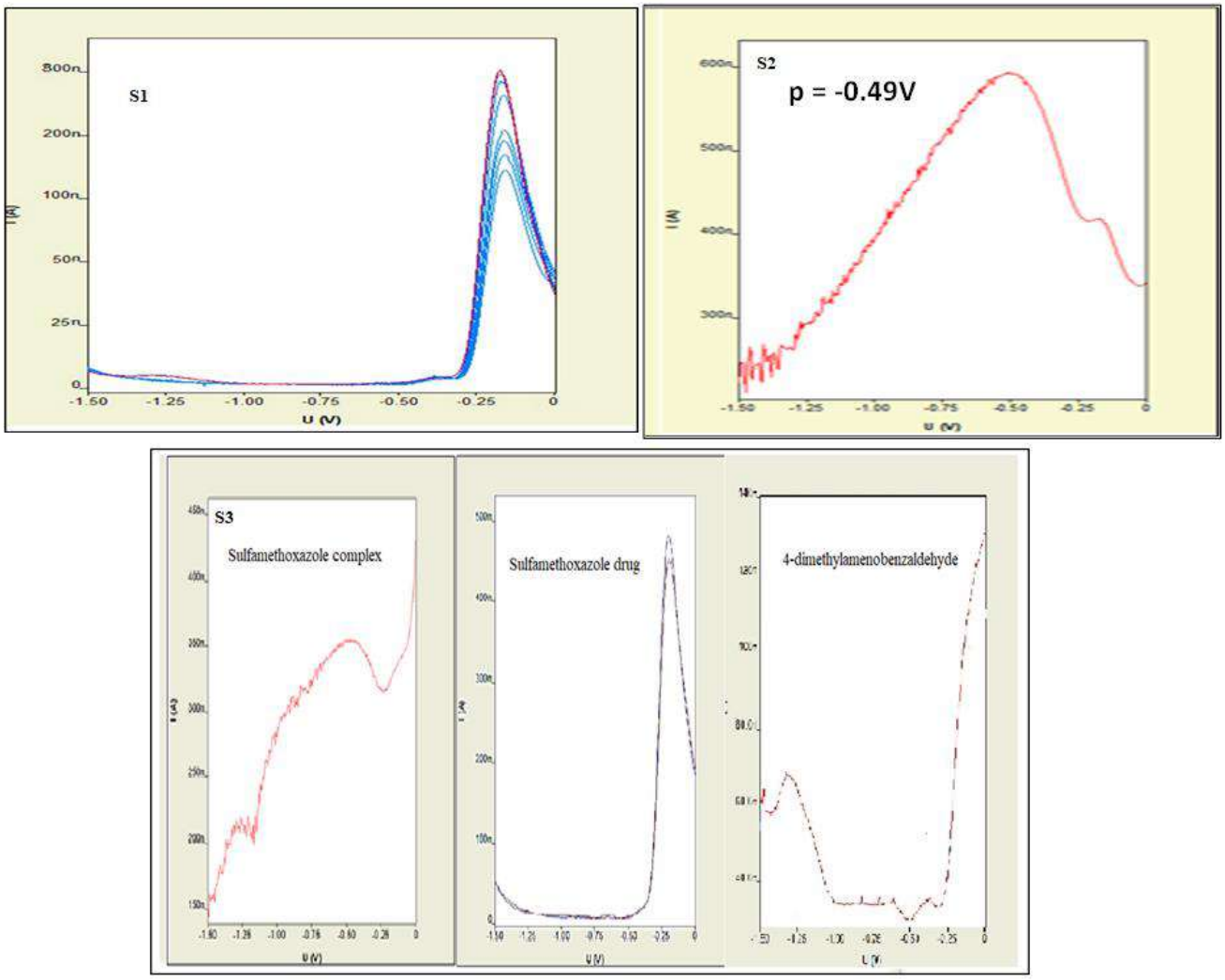
SUPPLEMENTARY DATA



Supplementary data: (S1) DPP polarograms of standard solutions of different concentrations of sulfamethoxazole drug at pH 8 using acetate buffer and the supporting electrolyte LiCl (0.01) M, (S2) DPP polarogram of the reduction of sulfamethoxazole Schiff's base derivative and (S3) DPP polarograms of aqueous sulfamethoxazole Schiff's base derivative, sulfamethoxazole drug and 4-dimethylamenobenzaldehyde.