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ORIGINAL ARTICLE

Validated electroanalytical determination of flavoxate hydrochloride and tolterodine tartrate drugs in bulk, dosage forms and urine using modified carbon paste electrodes

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KEYWORDS

Flavoxate HCl;
Tolterodine tartrate;
Carbon paste electrode;
Ferrocene;
Polyethylene glycol

Abstract Simple, precise, inexpensive and sensitive voltammetric methods have been developed for the determination of flavoxate HCl (FLXHC) and tolterodine tartrate (TOLT) in the bulk, pharmaceutical dosage forms and human urine using ferrocene modified carbon paste electrode (FMCPE) for FLXHC and polyethylene glycol modified carbon paste electrode (PEGMCPE) for TOLT. The electrochemical behavior of FLXHC and TOLT showed irreversible diffusion-controlled oxidation processes in Britton-Robinson (BR) buffer over the entire pH range from 2 to 6 for FLXHC and from 2 to 9 for TOLT. The peak current was evaluated as a function of some variables such as pH, scan rate and number of cycles of ferrocenium solution and PEG concentration. The linear ranges were 7.8×10^{-6}–1.2×10^{-4} mol L^{-1} and 7.6×10^{-7}–2.2×10^{-4} mol L^{-1} for FLXHC and TOLT, respectively. The limits of detection and quantification were 5.9×10^{-7} and 2×10^{-6} for FLXHC and 8.6×10^{-8} mol L^{-1} and 2.9×10^{-7} mol L^{-1} for TOLT. The percentage recoveries were found in the following ranges: 99.2–101.1% and 99.7–101.1% for FLXHC and TOLT, respectively.

1. Introduction

Flavoxate HCl (FLXHC) is described as a smooth muscle relaxant but it also has antimuscarinic effects. It is a tertiary amine and is used for the symptomatic relief of pain, urinary frequency and incontinence associated with inflammatory disorders of the urinary tract (Sweetman, 2009).

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Tolterodine tartrate (TOLT) is a muscarinic receptor antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. TOLT was the first drug to be developed specifically for the treatment of overactive bladder (Malhotra et al., 2007).

Literature survey reveals that chromatographic methods for FLXHC (El-Gindy et al., 2008; Attimarad, 2010; Attimarad et al., 2012; El-Shaheny et al., 2014; Yunoos et al., 2014; Rathod et al., 2015; Attia et al., 2016b) and TOLT (Krishna et al., 2009; Rao et al., 2010; Ramathilagam et al., 2012; Shetty and Shah, 2011a; Mhamunkar et al., 2012; Yanamandra et al., 2012; Kumar et al., 2013; Parveen et al., 2014; Attia et al., 2016b), spectrophotometric methods for FLXHC (Attimarad, 2011, 2012) and TOLT (Shetty and Shah, 2011b; Vanilatha et al., 2011; Fraihat and Khatib, 2013), potentiometric methods for the determination of FLXHC (Rizk and Abdel-Haleem, 2010; Ismail, 2016) and TOLT (Sakr and El Nashar, 2012), spectrofluorimetric method for TOLT (Nassar et al., 2013) and electrochemical voltammetric methods for the determination of FLXHC at mercury electrode (Ghoneim et al., 2007) and TOLT at glassy carbon electrode (Kul, 2014) and boron doped diamond electrode (Macikova et al., 2013) were reported for the determination of these drugs in bulk, dosage forms and biological fluids.

Electrochemical methods are sensitive, accurate and low-cost techniques used for determination and monitoring electro-active species in industrial, environmental analysis, biological and pharmaceutical analysis (Beitollahi et al., 2008a,b, 2012; Beitollahi and Sheikhshoaie, 2011a,b,c; Molaakbari et al., 2014; Beitollahi and Mostafavi, 2014; El-Ries et al., 2008; Rizk et al., 2015; Elshal et al., 2013; Elshal and Attia, 2013; Attia and Saber, 2011; Attia, 2010; Attia et al., 2011, 2014, 2015, 2016a; Tasdemir, 2016; Raj et al., 2016; Filik et al., 2016).

There is a need to determine drugs at high sensitivity than the reported methods; therefore, the aim of work was the development of rapid, economical, simple, precise and sensitive voltammetric method for the determination of FLXHC and TOLT at modified carbon paste electrodes in bulk, dosage forms and urine using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques showing very low detection limits.

2. Experimental

2.1. Apparatus

All voltammetric measurements were performed using AEW2 electrochemistry workstation with ECprog3 electrochemistry software, manufactured by Sycopel Scientific Limited (Tyne & Wear, UK). Glass cell with the three electrodes was connected to the electrochemical workstation through a C-3-stand. A platinum wire was employed as auxiliary electrode. All the cell potentials were measured with respect to Ag/AgCl (3 mol L^{-1} NaCl) reference electrode. All electrodes and the C3 stand were obtained from BASi (Indiana, USA). Solutions were degassed using pure nitrogen prior and throughout the

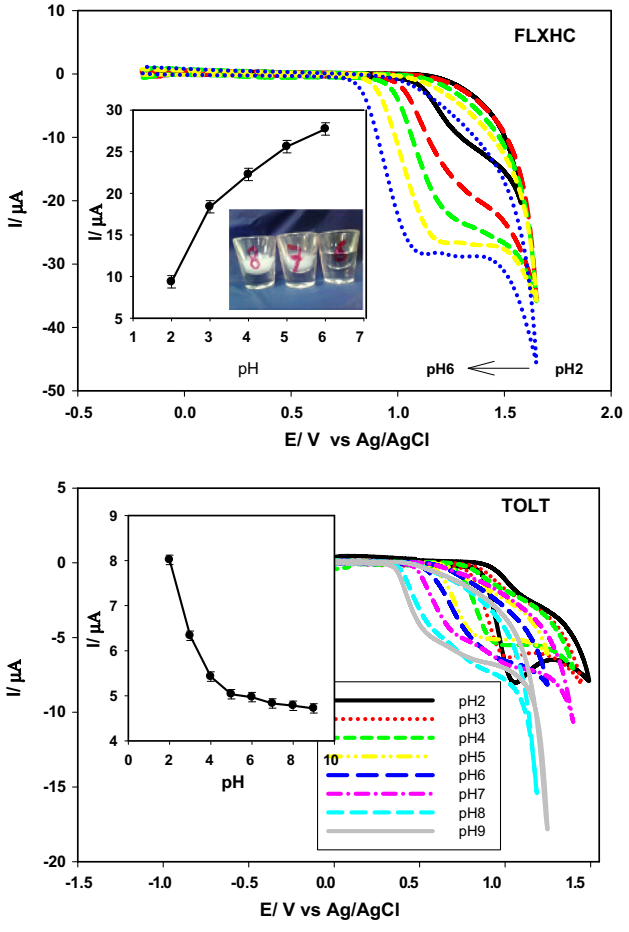

Figure 1 Cyclic voltammograms of the effect of solution pH on the oxidation of FLXHC and TOLT (1×10^{-3} mol L^{-1}) at CPE using BR buffers at scan rate of 100 mV s^{-1}. The inset: plot of anodic peak currents as a function of pH for FLXHC and TOLT at CPE.

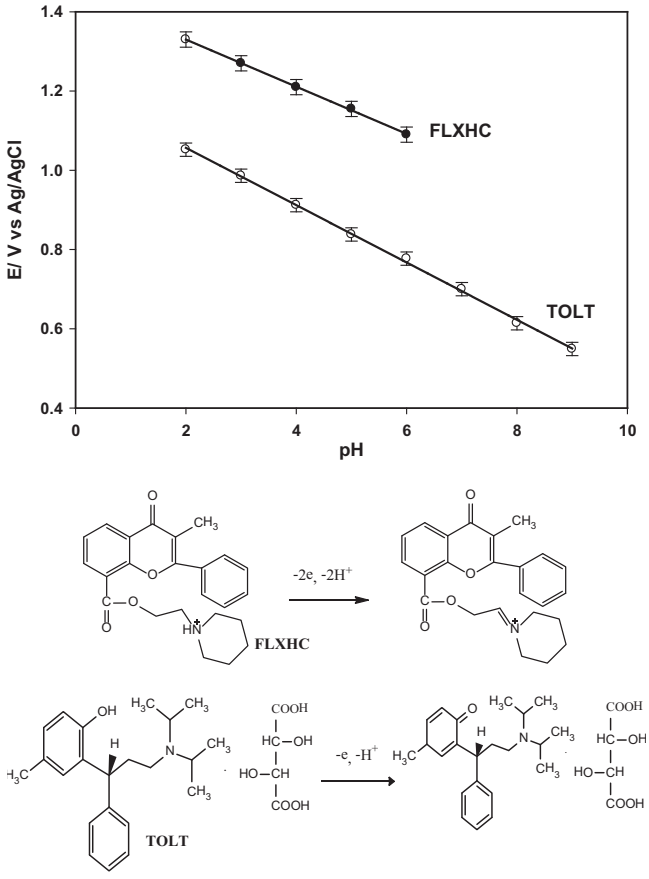

Figure 2 Plot of peak potentials as a function of pH for FLXHC and TOLT at CPE. The oxidation mechanism of FLXHC and TOLT.

electrochemical measurements. A JENWAY 3510 pH meter (Staffordshire, England) was used for pH measurements. All the electrochemical experiments were performed at an ambient temperature.

2.2. Reagent and solutions

FLXHC and TOLT were obtained from Unipharma Pharmaceutical Company, Egypt, and Pfizer Pharmaceutical Company, Egypt, respectively. The dosage forms, FLXHC: Nephroflam and Genurin tablets (200 mg per tablet) and TOLT: Tolterodine tablets (2 mg per tablet) and Detrusitol capsules (4 mg TOLT per capsule) were purchased from Unipharma Pharmaceutical Company, Egypt, Medical Union Pharmaceutical Company, Egypt, Sabaa Pharmaceutical Company, Egypt, and Pfizer Pharmaceutical Company, Egypt, respectively.

Stock solutions of 1×10^{-3} mol L^{-1} of FLXHC and TOLT were prepared by dissolving the calculated weights of these drugs in deionized water.

Britton-Robinson (BR) buffer solutions (pH 2–9) were used as supporting electrolytes. BR buffers were made in a usual way (i.e. by mixing a solution of 0.04 mol L^{-1} phosphoric acid, 0.04 mol L^{-1} acetic acid and 0.04 mol L^{-1} boric acid). Buffer solutions were adjusted by adding the necessary amounts of 2 mol L^{-1} NaOH solution to obtain the appropriate pH. Graphite powder, paraffin oil, ferrocene and tetrabutylammonium hexafluoro-phosphate were obtained from Sigma–Aldrich, Taufkirchen, Germany. Acetonitrile and polyethylene glycol (PEG) 300 liquid were purchased from Poch, Poland, and Algomhoria Company, Egypt, respectively. All solutions were prepared from pure analytical grade chemicals.

2.3. Preparation of modified carbon paste electrodes

a. Carbon paste electrode (CPE) was prepared by mixing graphite powder (0.5 g) with paraffin oil (nearly 0.3 mL) in a mortar. The carbon paste was packed into the hole of the electrode body and smoothed on a filter paper until it had a shiny appearance.
b. FMCPE was prepared through the electrodeposition of ferrocene from 0.01 mol L^{-1} ferrocenium solution (ferrocene was dissolved in 0.01 mol L^{-1} tetrabutylammonium hexafluoro-phosphate which was prepared in acetonitrile) by applying 10 repeated cycles in a potential range from −400 mV to 1200 mV at CPE.
c. PEGMCPE was prepared by adding 10 μL from 1.5% w/v PEG on the surface of CPE then leave this surface to dry in air.

2.4. Determination of FLXHC and TOLT in bulk

Aliquots of FLXHC and TOLT solutions (1×10^{-3} mol L^{-1}) were added to the electrolytic cell containing 5 mL of BR buffer of pH 6 for FLXHC and pH 2 for TOLT. The solution was stirred for 5 s at open circuit conditions. The voltammetric analyses were carried out and the voltammograms were recorded at scan rate = 10 mV s^{-1}, pulse width = 25 ms and pulse amplitude = 50 mV at FMCPE for FLXHC and PEGMCPE for TOLT.

2.5. Determination of FLXHC and TOLT in dosage forms

Ten tablets or capsules of FLXHC and TOLT were weighed and the average mass of per tablet or per capsule was determined. A portion of the finely grounded material needed to prepare 1×10^{-3} mol L^{-1} FLXHC and TOLT solutions were transferred into 50 mL calibrated flask containing 30 mL of deionized water for FLXHC and into 25 mL calibrated flask containing 15 mL of deionized water for TOLT. The flasks were sonicated for about 20 min and made up the volume with deionized water. The solutions were filtered to separate out the insoluble excipients. Aliquots of the drug solutions were introduced into the electrolytic cell and the voltammograms were recorded.

2.6. Determination of FLXHC and TOLT in urine

Urine (1 mL), obtained from healthy volunteer, was mixed with 9 mL of BR buffer of pH 6 for FLXHC and pH 2 for TOLT. Aliquots of FLXHC and TOLT solutions (1×10^{-3} mol L^{-1}) were added to the voltammetric cell containing 5 mL of the prepared mixture. The differential pulse voltammetric procedure was carried out as for the pure drugs.

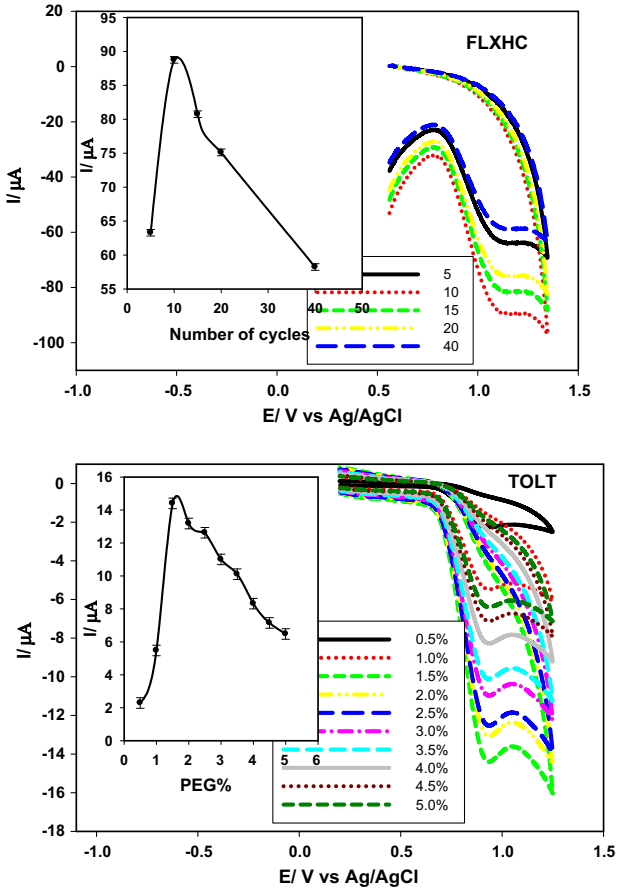

Figure 3 Cyclic voltammograms of the effect of number of cycles and PEG concentration on the oxidation of FLXHC and TOLT (1×10^{-3} mol L^{-1}) in BR buffer of pH 6 and 2, respectively. Scan rate of 100 mV s^{-1}. The inset: plots of anodic peak currents as a function of number of cycles and PEG concentration at CPE.

3. Results and discussion

3.1. Effect of pH

Fig. 1 shows the electrochemical behavior of 1×10^{-3} mol L^{-1} FLXHC and TOLT at CPE in BR buffer at different pH values ranging from 2 to 6 for FLXHC and from 2 to 9 for TOLT, exhibiting an anodic peak for each drug, with no peak on the reverse scan over the entire pH range, suggesting the irreversible nature of the electrode reaction for each drug. Well-defined anodic peaks of maximum current values were obtained at pH 6 for FLXHC (27.73 μA) and at pH 2 for TOLT (8.016 μA). In case of FLXHC, the anodic current increases with the increase of pH until pH 6, then the drug was precipitated as shown in Fig. 1. In case of TOLT, the anodic current shows its maximum value at pH 2 then decreases by increasing pH up to pH 9. The broadness of the peak increases as the pH increases. Therefore, pH 6 and pH 2 were chosen as the optimum pH values for determination of FLXHC and TOLT, respectively. Fig. 1 shows that the anodic peak potential (E) shifted negatively with the increase of the pH of the solution indicating that protons have taken part in the oxidation process of the drugs.

Fig. 2 shows linear relations between the anodic peak potential and the pH of the solution giving the following equations $E = 1.45–0.06$ pH and $E = 1.21–0.072$ pH for FLXHC and TOLT, respectively. The slopes of 60 and 72 mV per pH unit indicate that the oxidation processes of the two drugs involve the same number of electrons and protons (Pontinha et al., 2012).

The electrons involved in the reaction can be calculated using the formula of $\omega_{1/2} = 62.4/\alpha n$ (Bard and Faulkner, 2001), where $\omega_{1/2}$ is the peak width at half height, n is the number of electrons transferred and α is the transfer coefficient of an electron which is often between 0.4 and 0.6. The number of

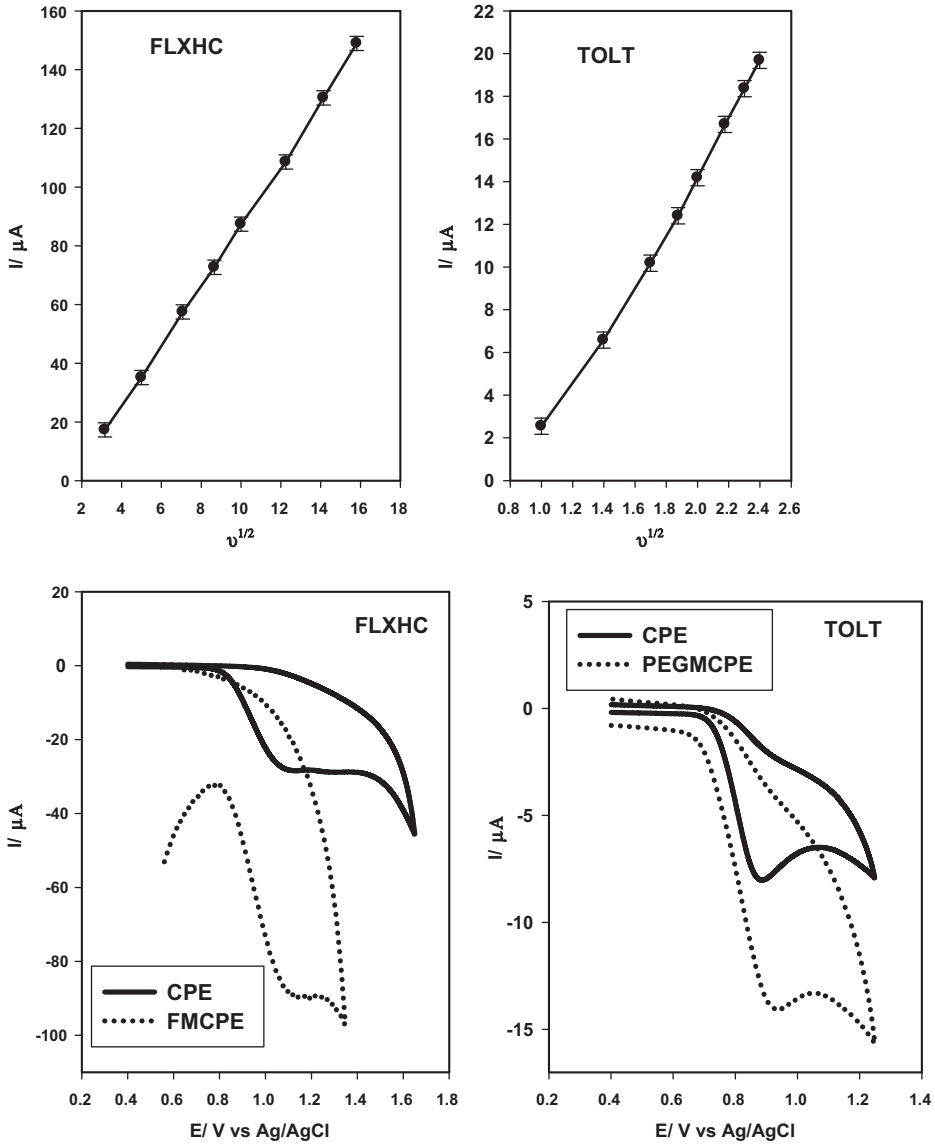

Figure 4 Effect of scan rate on 1×10^{-3} mol L^{-1} FLXHC (at FMCPE) and 1×10^{-3} mol L^{-1} TOLT (at PEGMCPE) in BR buffer of pH 6 and 2, respectively. Cyclic voltammograms of FLXHC and TOLT at CPE and modified electrodes.

electrons transferred ($\alpha = 0.5$) was calculated to be $n = 2.25$ and 1.22 for FLXHC and TOLT, respectively. Hence, the number of electrons assumed to be $n \approx 2$ for FLXHC and $n \approx 1$ for TOLT. The oxidation process of FLXHC takes place at the piperidine ring through the loss of one electron and one proton from the nitrogen atom and another electron and proton from adjacent carbon atom to form double bond with the nitrogen atom. The oxidation process of TOLT occurs at the phenolic group forming ketonic group through the loss of one proton and electron. The proposed oxidation mechanisms are shown in Fig. 2.

3.2. Effect of number of cycles

The electrochemical behavior of 1×10^{-3} mol L^{-1} FLXHC in BR buffer of pH 6 was studied at FMCPE which is prepared using different number of cycles of 0.01 mol L^{-1} ferrocenium solution at CPE. Fig. 3 shows that the peak current increases up to 10 cycles then decreases as the number of cycles increases. Therefore, 10 cycles were chosen as the optimum number of cycles needed to form ferrocene layer at CPE giving the maximum current value of 88.76 μA.

3.3. Effect of PEG concentration

The electrochemical behavior of 1×10^{-3} mol L^{-1} TOLT in BR buffer of pH 2 was studied by putting different concentrations of PEG varying from 0.5% to 5% onto CPE surface. The experimental results show that the peak current increases as the PEG concentration (PEG%) increases up to 1.5% showing the maximum peak current of 14.4 μA then decreases as PEG % increases (Fig. 3). Thus 1.5% of PEG was chosen as the

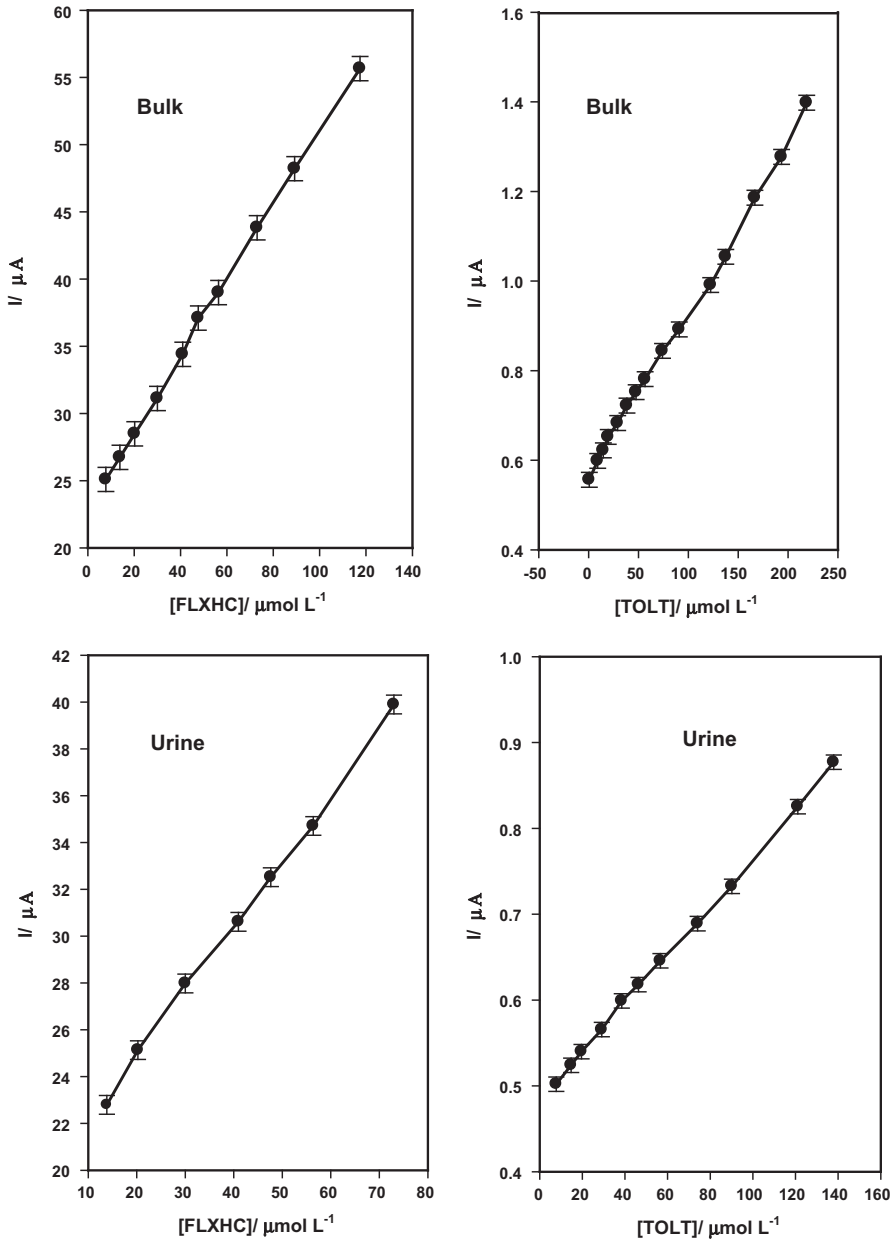

Figure 5 The plots of the oxidation peak current vs. the concentration of FLXHC and TOLT in bulk and in urine.

Table 1 Robustness of the proposed method.

Robustness	Drug (mol L^{-1})		Mean ± SD[a]	
Parameter	FLXHC	TOLT	FLXHC	TOLT
pH of buffer				
5.8/1.8	1.215×10^{-5}	1.527×10^{-5}	$1.233 \times 10^{-5} \pm 2.32 \times 10^{-7}$	$1.546 \times 10^{-5} \pm 2.87 \times 10^{-7}$
6.0/2.0	1.224×10^{-5}	1.580×10^{-5}		
6.2/2.2	1.259×10^{-5}	1.533×10^{-5}		
Scan rate				
9	1.244×10^{-5}	1.617×10^{-5}	$1.230 \times 10^{-5} \pm 1.35 \times 10^{-7}$	$1.584 \times 10^{-5} \pm 3.12 \times 10^{-7}$
10	1.224×10^{-5}	1.580×10^{-5}		
11	1.219×10^{-5}	1.555×10^{-5}		
No. of cycles				
9	1.220×10^{-5}	–	$1.245 \times 10^{-5} \pm 2.490 \times 10^{-7}$	
10	1.224×10^{-5}	–		
11	1.270×10^{-5}	–		
PEG%				
1.3%	–	1.542×10^{-5}		$1.550 \times 10^{-5} \pm 3.580 \times 10^{-7}$
1.5%	–	1.580×10^{-5}		
1.7%	–	1.530×10^{-5}		

SD: Standard deviation.
[a] Mean of three different determinations.

Table 2 Results of determination of FLXHC and TOLT in pharmaceutical dosage forms.

Dosage form	Drug	Label claim, mg	Found, mg	%Recovery	RSD%[a]
Genurin tablet	FLXHC	200	201.1	100.55	1.64
Nephroflam tablet		200	198.4	99.20	1.81
Detrusitol capsules	TOLT	4	4.03	100.75	1.74
Tolterodine tablet		2	2.03	101.50	1.88
Parameter	Proposed method	Reported method (Attimarad, 2010)	Proposed method	Reported method (Ramathilagam et al., 2012)	
	FLXHC		TOLT		
SD[a]	1.22	1.29	1.34	1.34	
Std. Error	0.52	0.50	0.51	0.54	
F-value	1.60	–	0.91	–	
t-value	1.15	–	0.58	–	

Tabulated *F* and *t* values at 95% confidence limit: 6.39 and 2.77, respectively.
[a] Mean of five different determinations.

optimum concentration of PEG needed to give the maximum current.

3.4. Effect of scan rate

The effect of different scan rates (ν ranging from 10 to 250 mV s^{-1}) on the oxidation current response of 1×10^{-3} mol L^{-1} FLXHC and TOLT was studied at FMCPE in BR buffer (pH 6) and at PEGMCPE in BR buffer (pH 2). Fig. 4 shows linear relationships between the square root of scan rates and the oxidation peak currents over the entire scan rate range, suggesting that the oxidation processes of the two drugs take place under diffusion controlled process (Gosser, 1993).

Diffusion coefficients of the used drugs were calculated using Randles–Sevcik equation: $I = (2.99 \times 10^5)\, n\, \alpha^{1/2}\, A\, C_o^*\, D_o^{1/2}\, \upsilon^{1/2}$ where I is the anodic peak current, D_o is the diffusion coefficient of the electroactive species, υ is the scan rate, n is the number of electrons exchanged during the oxidation process, A is the electrode surface area and C_o^* is the concentration of drug (Eggins, 2003). The diffusion coefficients for FLXHC and TOLT were found to be 1.18×10^{-4} and 7.75×10^{-6} $cm^2\ s^{-1}$, respectively.

Fig. 4 shows the cyclic voltammograms of FLXHC and TOLT (1×10^{-3} mol L^{-1}) at CPE, FMCPE and PEGMCPE in BR buffer of pH 6 and 2 in case of FLXHC and TOLT, respectively. The figure shows the enhancement effect of the modifiers on the anodic peak current of these drugs. The peak current values increased from 27.73 and 8.016 μA at CPE to 88.76 μA at FMCPE and 14.4 μA at PEGMCPE for FLXHC and TOLT, respectively.

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Table 3 Comparison of the mentioned reported methods for the determination of FLXHC and TOLT.

Method	FLXHC (mol L^{-1})	Ref	TOLT (mol L^{-1})	Ref
Voltammetry (μg/mL)	7.8×10^{-6}–1.2×10^{-4} (3.34–50.07)	This work	7.6×10^{-7}–2.2×10^{-4} (0.362–103.68)	This work
Electrochemistry	1×10^{-5}–2.5×10^{-4} (DCP)	Ghoneim et al. (2007)		
Chromatography (μg/mL)	10–60	Yunoos et al. (2014)	10–60	Parveen et al. (2014)
	10–60	Rathod et al. (2015)	10–30	Ramathilagam et al. (2012)
Potentiometry	1.39×10^{-5}–1×10^{-2} (PTA) 1×10^{-5}–1×10^{-2} (TPB)	Ismail (2016)	1×10^{-5}–2×10^{-2} (PTA) 5×10^{-5}–2×10^{-2} (STA)	Sakr and El Nashar (2012)
Spectrofluorimetry (μg/mL)			0.5–8	Nassar et al. (2013)
Spectrophotometry (μg/mL)			30–180	Shetty and Shah (2011b)
			2–14	Vanilatha et al. (2011)
			5–18	Fraihat and Khatib (2013)

DCP: DC Polarography.
PTA: Phosphotungstic Acid.
TPB: Tetraphenylborate.
STA: Silicotungstic Acid.

3.5. Determination of FLXHC and TOLT

The drugs were determined in linear ranges of 7.8×10^{-6}–1.2×10^{-4} mol L^{-1} and 7.6×10^{-7}–2.2×10^{-4} mol L^{-1} with correlation coefficient of 0.9995 and 0.9990 for FLXHC and TOLT, respectively (Fig. 5). The limits of detection (LOD) and quantification (LOQ) were calculated using the following equations: LOD = 3 SD/m and LOQ = 10 SD/m, where SD is the standard deviation of the intercept of the calibration curve and m is the slope of the calibration curve (Miller and Miller, 1993). The limits of detection were found to be 5.9×10^{-7} and 8.6×10^{-8} mol L^{-1} and the limits of quantification were found to be 2×10^{-6} and 2.9×10^{-7} mol L^{-1} with linear regression equations: I (μA) = 0.282 C (μmol L^{-1}) + 22.95, R (correlation coefficient) = 0.9995 and I (μA) = 0.0037 C (μmol L^{-1}) + 0.564, R (correlation coefficient) = 0.9990 for FLXHC and TOLT, respectively. The percentage recoveries were found in the following ranges: 99.2–101.1% and 99.7–101.1% for FLXHC and TOLT%, respectively. The relative standard deviations (RSDs) were found in the following ranges: 0.85–1.37% for FLXHC and 0.74–1.17% for TOLT.

The repeatability of the proposed DPV procedure was investigated on the basis of five measurements of 8×10^{-6} FLXHC and 1×10^{-5} mol L^{-1} TOLT solutions, and the relative standard deviations (RSD) were found to be 1.41% and 0.49% indicating good results for FLXHC and TOLT respectively.

3.6. Robustness

The robustness of a method is the ability to remain unaffected by small changes in parameters. To determine the robustness of the developed method, experimental conditions were purposely altered for FLXHC (1.224×10^{-5} mol L^{-1}) and TOLT (1.58×10^{-5} mol L^{-1}). The pH and PEG% values were changed by ±0.2 units and the number of cycles and scan rate were changed by ±1. The results are provided in Table 1. Form these results, it was observed that there was no significant changes obtained which demonstrate that the proposed methods developed were robust.

3.7. Assay of FLXHC and TOLT in dosage forms

Assay of FLXHC and TOLT content in pharmaceutical formulations was carried out using the proposed DPV procedure at FMCPE and PEGMCPE, respectively showing good recovery and RSD values as shown in Table 2.

Student's t- and F-tests (at 95% confidence level) were applied and the results showed that the calculated t- and F-values did not exceed the theoretical values which excluded any significant differences between the proposed method and the reported published methods based on accuracy and precision as shown in Table 2.

The proposed voltammetric methods for the determination of FLXHC and TOLT are more sensitive than some reported methods such as electrochemical, chromatographic, potentiometric, spectrofluorimetric and spectrophotometric methods as shown in Table 3.

3.8. Determination of FLXHC and TOLT in urine

Successive additions of 1×10^{-3} mol L^{-1} FLXHC and TOLT were added to the voltammetric cell containing 5 mL of the previously diluted urine and the voltammograms were recorded at the scan rate of 10 mV s^{-1} using DPV at FMCPE for FLXHC and PEGMCPE for TOLT. The calibration curves (Fig. 5) show straight lines in the range from 13.8×10^{-6} to 7.3×10^{-5} mol L^{-1} with linear regression equations: I (μA) = 0.278 C (μmol L^{-1}) + 19.27, R = 0.9980 for

FLXHC and in the range from 7.8×10^{-6} to 1.37×10^{-4} mol L^{-1} with linear regression equations: I (μA) = 0.0028 C (μmol L^{-1}) + 0.484, R = 0.9993 in case of TOLT.

The LOD values were found to be 2.3×10^{-6} and 6.4×10^{-7} mol L^{-1} for FLXHC and TOLT, respectively and LOQ values were 7.7×10^{-6} and 1.6×10^{-6} mol L^{-1} for FLXHC and TOLT, respectively. The relative standard deviations were 1.34% and 0.943% for FLXHC and TOLT, respectively. The percentage recoveries were found in the following ranges: 98.46–101.92% and 99.07–101.53% for FLXHC and TOLT, respectively.

4. Conclusions

In the present work, FMCPE and PEGMCPE were used for electrochemical determination of FLXHC and TOLT, respectively. The advantages of these modified electrodes are low cost, easily preparation and the significant enhancement of the CPE sensitivity. The experimental conditions such as pH, number of cycles, PEG% and scan rate were optimized to find the highest sensitivity for the determination of FLXHC and TOLT with good precision, accuracy and low detection limits sufficient for routine analyses. The results showed that the methods were simple and sensitive enough for the determination of FLXHC and TOLT in bulk, dosage forms and in human urine.

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