

Electrochemical behaviour of sertraline hydrochloride at a glassy carbon electrode and its determination in pharmaceutical products using osteryoung square wave voltammetry

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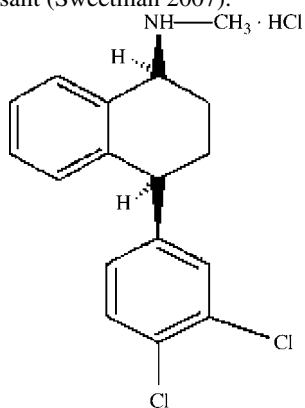
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In this study the electrooxidation of sertraline (STR) hydrochloride in pH 8 Britton-Robinson buffer (BRb) – methanol (MeOH) (1:1, v/v) supporting electrolyte was investigated using Osteryoung Square Wave Voltammetry (OSWV) with the glassy carbon electrode. OSWV is a rapid and sensitive electro-analytical technique for sertraline determination. This study indicated that sertraline was susceptible to oxidation. The effects of the supporting electrolyte, pH and scan rate on the anodic reactions performed in BRb and a scan rate interval 5 – 1000 mVs⁻¹ were investigated. Sertraline hydrochloride was oxidized irreversibly and diffusion controlled. OSWV was selected for the quantitative determination. Using optimized OSWV technique, the current was linear within a concentration range of 0.04 – 0.8 mM in pH 8 BRb which at the equivalent volume with MeOH. The applicability of the proposed method was shown by the successful analysis of sertraline in tablet dosage forms. Accuracy, precision, selectivity, sensitivity, within day and between days reproducibility of the method were investigated statistically. Application of the suggested method to pharmaceutical formulation is presented and compared with the UV spectrophotometric and HPLC methods. The results were found to be in a good agreement. No interference was observed from common pharmaceutical adjuvants.

1. Introduction

Sertraline hydrochloride (STR) is a selective serotonin (5-hydroxytryptamine, 5HT) re-uptake inhibitor (SSRI) (Auster 1993). Efficiency of Sertraline has been established in the treatment of depression, obsessive-compulsive disorder, depression relapse and social phobia (Stahl 2000).

Sertraline is available for pharmaceutical use as salt. Sertraline is a single stereoisomer and has a carbon side-chain containing an amino group. It is a secondary amine that exhibits two asymmetric centers, but has only a single enantiomer. This enantiomer is formed by N-demethylation and was also introduced as an antidepressant (Sweetman 2007).



Sertraline hydrochloride

Sertraline is naphthalenamine-derivative that differs structurally from classic tricyclic antidepressants (TCAs), and as effective as TCAs but has less side effects.

Recently, many methods have been developed for the determination of sertraline in biological specimens, such as plasma, blood, urine and some tissues. Almost all assays are based on the separation by GC and HPLC or in combination with mass spectrometry (MS) i.e. liquid chromatography and tandem mass spectrometry (LC-MS/MS) and GC-MS/MS. All the recent methods were based on HPLC with fluorimetric or UV detection, or gas chromatography with nitrogen phosphorus, electron capture, or mass spectrometric detection and on micellar electrokinetic capillary chromatography.

For this drug the literature reveals a variety of analytical methods such as spectrophotometry (Bebawy et al. 1999; Erk 2003; Darwish 2005), NMR (Salsbury and Isbester 2005), electrophoresis (Buzinkaiova and Polonsky 2000; Himmelsbach et al. 2005, 2006), GC (Logan et al. 1994; Martinez et al. 2002; LC (Logan et al. 1994; Rogowsky et al. 1994; Adams and Bergold 2001; Frahnert et al. 2003), TLC (Eap 1996; Novakova 2004), electrokinetic chromatography (Zhou and Foley 2004), GC-MS (Fouda et al. 1987; Rogowsky et al. 1994; Eap et al. 1998; Kim et al. 2002; Wille et al. 2005), LC-MS/MS (Jain et al. 2005; Chen et al. 2006), HPLC (Patel et al. 1996; Kobayashi et al. 2000; Lucca et al. 2000; Tournel et al. 2001; Duverneuil et al. 2003; Titier et al. 2003; Chen et al. 2004; Mandrioli et al. 2006; HPLC-ESI-MS (He et al. 2005), HPLC/ESI-MS/MS

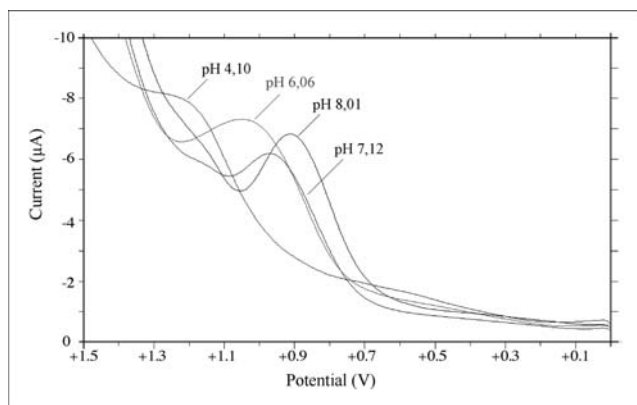


Fig. 1: Voltammograms of 5×10^{-4} M sertraline HCl by OSWV technique in BRb-MeOH (1:1) supporting electrolyte at different pHs

(Smyth et al. 2006), electrochemical (Vela et al. 2001; Nouws et al. 2005).

No official methods for sertraline hydrochloride determination have been reported in the British, United States and European Union Pharmacopoeias.

Until now, two publications on the electrochemical study and analysis of sertraline have been published. These studies focused on the electroreduction of sertraline in pharmaceutical products using square wave adsorptive stripping voltammetry under batch conditions. In the present paper, applying, OSWV for the determination of sertraline in pharmaceutical preparation was explored. It was possible to determine sertraline in flow at a high sample rate and reduced costs, opening the possibility to compete with the chromatographic methods generally used for this analysis.

In this study electrochemical examination of sertraline is performed by means of a solid electrode.

2. Investigations, results and discussion

The electrochemical behaviour of sertraline hydrochloride for oxidation with a glassy carbon electrode was investigated using cyclic voltammetry (CV) and OSWV methods. Square wave voltammetry technique which was observed of highest current and being more sensitive, was used for quantitation. Voltammetric test results revealed that the chemical structure of sertraline hydrochloride is electroactive. OSWV technique was found to be rapid, sensitive, definite, accurate and selective for the analysis of sertraline hydrochloride.

Effects of supporting electrolyte type, pH, the effect of solution concentration on the oxidation event were examined. The effect of pH was investigated with solution containing BRb which at the equivalent volume with MeOH. Figure 1 gives OSWV curves obtained within BRb solution at different pH. pH 8 BRb solution was chosen as supporting electrolyte and the best results were obtained in this solution with regard to repeatability.

Electrochemical examinations were performed at $5\text{--}1000\text{ mVs}^{-1}$ scanning speeds in pH 8 BRb-MeOH(1:1,v/v) solutions by CV technique. Cyclic voltammograms of 5×10^{-4} M STR obtained in pH 8 BRb (Fig. 2) shows one anodic peak at about 900 mV. When cyclic voltammograms were examined, it was found that current linearly increases with speed and potential was changed to positive potential up to 97 mV (Fig. 2). Being a peak, which demonstrating any reduction event, wasn't met on the direction of voltammograms rotation, shows that the event is irreversible.

Regression analysis shows that the relationship between $v^{1/2}$ and peak current (i_p) belong to sertraline alternate voltammograms

taken at different scanning speeds, with 5×10^{-4} concentration in pH 8 BRb-MeOH (1:1), was linear.

Equations demonstrating the current linearly alternating with square root of scanning rate and obtained from calculations performing at the scanning rates of $5\text{--}1000\text{ mVs}^{-1}$, were as follows.

$$i_p = 0.8725 v^{1/2} - 1.411 (r^2 = 0.9940, n = 12) \quad (1)$$

$$\log i_p = 0.5576 \log v - 0.265 (r^2 = 0.9969, n = 12) \quad (2)$$

This linear relationship shows that the reaction is diffusion-controlled. When the graphs of $\log v - \log i_p$ (Fig. 3) at the same speed range and obtained straight line equation are examined, the slope value of 0.55 demonstrates that the reaction is diffusion-controlled. If it is purely diffusion-controlled and the solution is suitable for this substance, the slope of the reaction equation is 0.5; if it is purely adsorption-controlled and the used electrode is suitable for the electrochemical case, the slope is 1 (Laviron et al. 1980).

When drug voltammograms in BRb-MeOH (1:1,v/v) pH 8 solution were taken in the $4 \times 10^{-5} - 8 \times 10^{-4}$ M concentration range using OSWV technique by means of a glassy carbon electrode, (Fig. 4) the method exhibited good linearity with a correlation coefficient of 0.996. Evaluation of these curves revealed that quantitative determination of STR could be made by OSWV and the optimal operational parameters were found to be 25 mV pulse amplitude, 15 Hz frequency. Under these conditions the peak current of the OSWV curve is linearly dependent on concentration. Statistical treatment of this dependence is given in Table 1. Reproducibility of OSWV peak current and peak potential was tested by repeating ten experiments at 5×10^{-4} M.

The validation of the procedures was carried out by evaluation of the limit of detection (LOD), limit of quantitation (LOQ), repeatability, recovery, specificity and robustness.

The LOD and LOQ were calculated using the following equations (USP 2003): $\text{LOD} = 3S_b/m$ and $\text{LOQ} = 10S_b/m$, where S_b is the standard deviation of the intercept and m is slope of the calibration curve. The values of LOD and LOQ were 1.04×10^{-5} M (for OSWV), 9.8×10^{-6} M (for UV-spec.) and 1.02×10^{-6} M (for HPLC) and 3.72×10^{-5} M (for OSWV), 3.26×10^{-5} M (for UV-spec.) and 3.41×10^{-6} M (for HPLC), respectively. The achieved quantitation limit of STR was low enough to reach its concentration at minimum levels.

Repeatability and recovery were examined by performing five replicate measurements of the concentration of 6×10^{-5} M STR and a mean recovery of 98.6% for OSWV was achieved.

After the voltammetric techniques for sertraline hydrochloride active substance were validated, these were applied also for sertraline quantitation in Lustral® tablets. Tablet solutions with appropriate concentration were prepared and these voltammograms were taken under the same experimental conditions. Test results demonstrate that excipients in the tablet are not electroactive and therefore will not effect the voltammetric analysis. It was concluded that the developed voltammetric method was considerably specific for sertraline hydrochloride active substance and is applicable as direct, easy and rapid method to quantify sertraline hydrochloride in tablet dosage forms (Fig. 5). The intra- and inter-assay reproducibilities of the assay were investigated in terms of accuracy and precision, as shown in Table 2. Accuracy of the procedure was expressed as bias% within and between days less than (0.41%) at low and high concentrations.

In order to show the accuracy of the developed OSWV method, this analysis method which is also applicable to tablet dosage forms of the drug, was compared to drug analysis results, performed by UV-spectrophotometric and HPLC methods by means of Student's t-test at a 95% confidence level (Table 3).

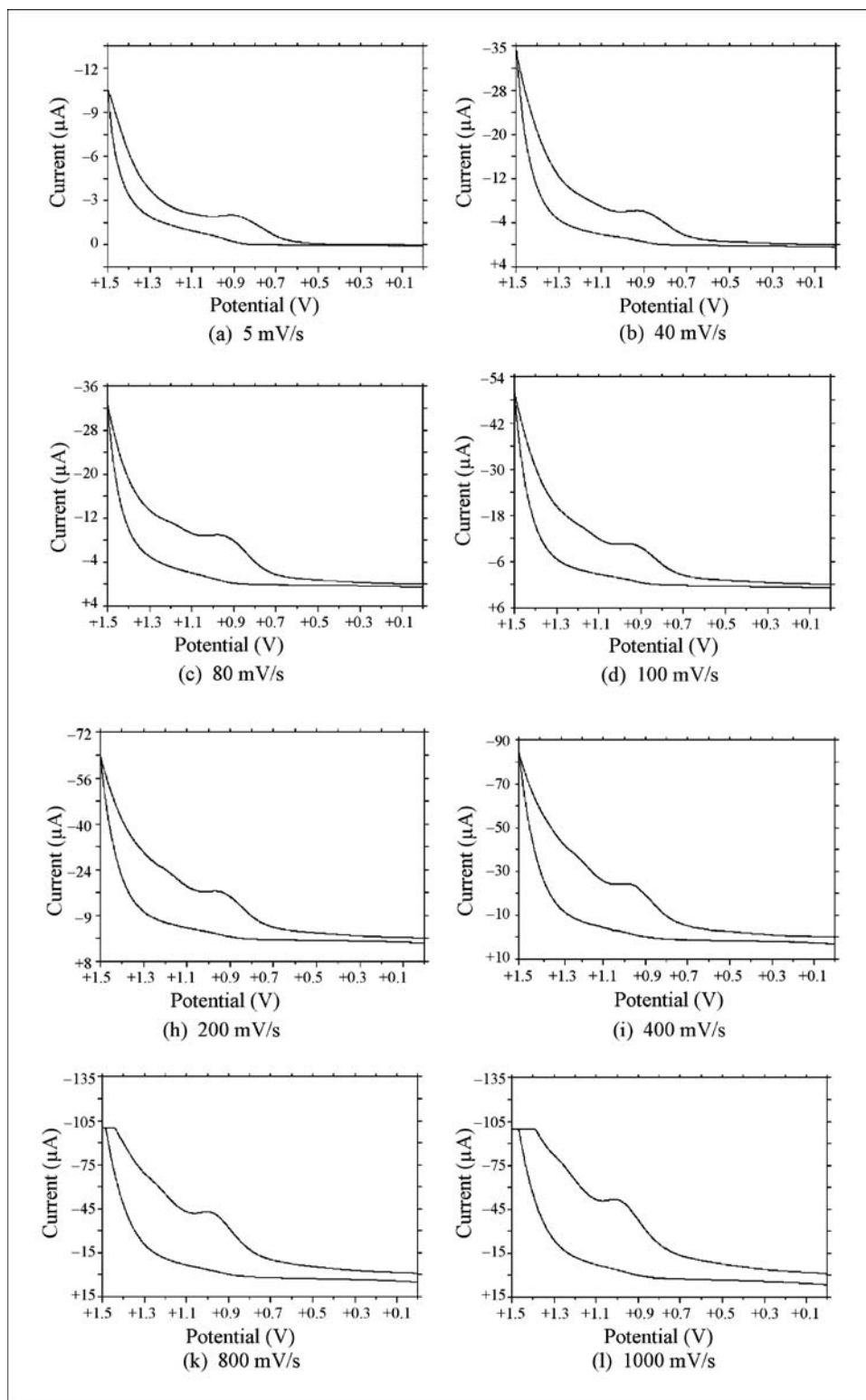


Fig. 2: Voltammograms of 5×10^{-4} M sertraline HCl in pH 8 BRb-MeOH (1:1,v/v) supporting electrolyte obtained 5-1000 mVs⁻¹ scanning speed

The calculated t-test and F-values are less than the corresponding theoretical values indicating that there is no significant difference between the results obtained by the proposed procedure and those of UV-spectrophotometric and HPLC methods with respect to accuracy, precision and repeatability.

It was shown that the developed OSWV analysis method can be easily, accurately and sensitively applied to pharmaceutical dosage forms containing sertraline. Results from this study demonstrate that the proposed analysis method is suitable for quality control and routine analysis of sertraline hydrochloride.

3. Experimental

3.1. Apparatus

Voltammetric measurements were made using a BAS 100 W/B electrochemical analyzer. The three-electrode system comprised of a BAS MF 2012 glassy carbon disc working electrode, a BAS MF 1063 type silver/silver chloride/saturated KCl reference electrode and a BAS MV 1032 platinum wire auxiliary electrode.

A double beam, Shimadzu model 1601 spectrophotometer with a fixed slit width (2 nm) connected to an IBM-PC computer was used. The UV spectra of standard and test solutions were recorded in 1 cm quartz cells.

Table 1: Determination of STR by OSWV UV-spectrophotometry and HPLC

Parameters	OSWV	UV-Spectrophotometry	HPLC
Range (M)	$4 \times 10^{-5} - 8 \times 10^{-4}$	$4 \times 10^{-5} - 1 \times 10^{-3}$	$3.65 \times 10^{-6} - 2.2 \times 10^{-5}$
Regression equation (Y) ^a			
Slope (b)	6883.8	1022.4	7012.6
Std.dev.on slope (S _b)	289.52	6.33	157.11
Intercept (a)	3.0123	0.0145	52.116
Std.dev.on intercept (S _a)	0.12	0.0033	76.48
Regression coefficient (r ²)	0.996	0.999	0.999
LOD (M)	1.04×10^{-5}	9.78×10^{-6}	1.02×10^{-6}
LOQ (M)	3.72×10^{-5}	3.26×10^{-5}	3.41×10^{-6}

^a Y = a + bC where C is concentration in M and Y in absorbance, current and peak area units for UV- spectrophotometric, voltammetric and HPLC methods, respectively

Table 2: Accuracy and precision test results of voltammetric analysis (OSWV) method for sertraline HCl in bulk form

Intra-day (n=6)					
Concentration (taken) (M)	Concentration (found) (M)	Recovery %	S.D.	Precision R.S.D. %	Accuracy bias %
6×10^{-4}	6.03×10^{-4}	100.46	0.128	1.78	0.46
1×10^{-4}	9.82×10^{-5}	98.27	0.056	1.52	-1.73
6×10^{-5}	5.92×10^{-5}	98.62	0.024	0.70	-1.38
	X _{mean}	99.12			
	S.D.	1.18			
	R.S.D.	1.19			
Inter-day (n=6)					
Concentration (taken) (M)	Concentration (found) (M)	Recovery %	S.D.	Precision R.S.D. %	Accuracy bias %
6×10^{-4}	6.02×10^{-4}	100.41	0.002	0.028	0.41
1×10^{-4}	9.82×10^{-5}	98.17	6.7×10^{-4}	0.018	-1.83
6×10^{-5}	5.89×10^{-5}	98.10	3.6×10^{-3}	0.106	-1.90
	X _{mean}	98.89			
	S.D.	1.31			
	R.S.D.	1.33			

X_{mean}: Mean value

S.D.: Standard deviation

R.S.D.(%): Relative standard deviation

Inter-day: Consecutive days

Intra-day: Within the day

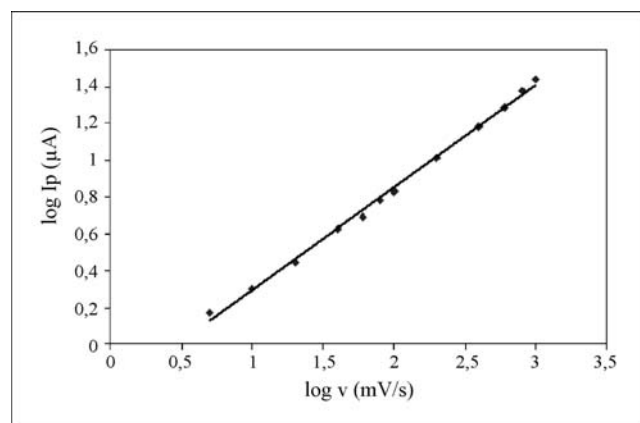


Fig. 3: $\log v$ - $\log i_p$ graphic of voltammograms of 5×10^{-4} M sertraline HCl in pH 8 BRb – MeOH(1:1) obtained 5-1000 mV/s⁻¹ scanning speed

An Agilent 1100 model liquid chromatograph was equipped with a model series of G13 79A degasser, 613 11A quaternary pump, G13 13A auto sampler, 61315B DAD detector, was used for chromatographic measurements. The chromatograms were recorded and the peaks were quantitated using its automatic integrator. The chromatograms were carried out at 40 °C temperature on Nova-Pak[®] C18 Column of 3.9 × 150 mm (4 μm particle size).

Table 3: Comparative studies of sertraline formulations

Formulation ^a (tablet)	Analysis techniques		
	HPLC	UV Spectrophotometry	Voltammetry (OSWV)
X _{mean} (mg) ^b	49.73	49.97	50.21
t-test		0.81 ^c	0.89 ^c
F-test		1.93 ^c	1.77 ^c

X_{mean} = mean value.

^a Tablet, 50 mg per tablet

^b Each value is the mean of six experiments

^c NS, not significant

t_{table} = 2.57 (p=0,05)

F_{table} = 5,05 (p=0,05)

3.2. Reagents

STR was used without prior purification. Lustral[®] tablets containing a 50 mg dose were obtained from local drugstores. Analytical grade phosphoric acid, and Merck grade methanol were purchased from Merck&Co. All other chemicals were of analytical- reagent grade and were used as received.

3.3. Solution preparation

A stock solution of 10⁻³ M STR was prepared by dissolving 86 mg STR in 125 mL of methanol and diluting it to 250 mL with BRb (pH 8). Working

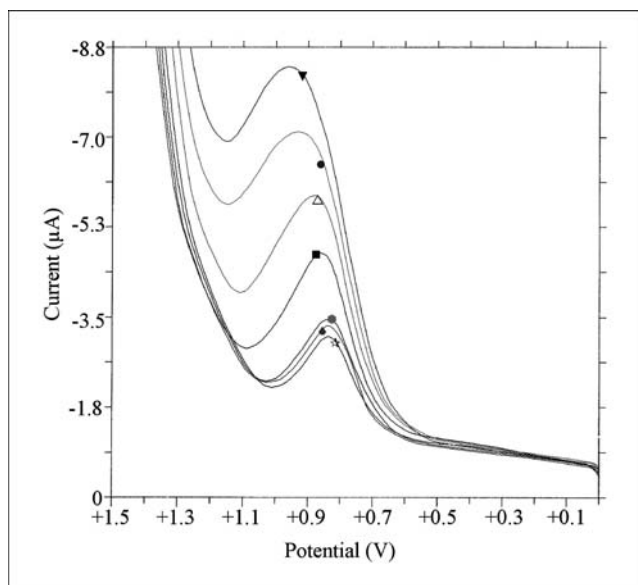


Fig. 4: OSWV curves obtained (pH 8 BRb: MeOH (1:1,v/v)), solution having various sertraline HCl concentration.

- ★ → 4×10^{-5} M;
- ◆ → 6×10^{-5} M;
- → 8×10^{-5} M;
- → 2×10^{-4} M;
- △ → 4×10^{-4} M;
- → 6×10^{-4} M;
- ▼ → 8×10^{-4} M

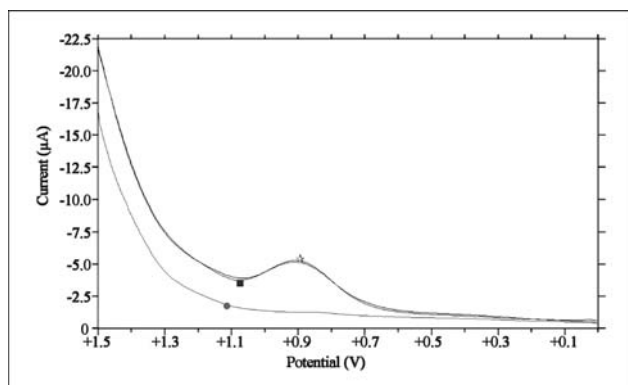


Fig. 5: Voltammograms of 3.265×10^{-4} M STR (bulk form and tablet formulations) in supporting electrolyte (pH 8 BRb: MeOH(1:1,v/v)).

- ★ : Pure drug in supporting electrolyte
- : Supporting electrolyte (pH 8 BRb-MeOH (1:1,v/v))
- : Drug in tablet formulations in the supporting electrolyte (tablet/500 mL)

standard solutions were prepared daily by appropriate dilution of the stock solution with BRb. Britton Robinson and Phosphate buffer were prepared according to the literature (Britton 1952) and USP pharmacopoeial procedure, respectively.

3.4. Pretreatment of the working electrode

The glassy carbon electrode was polished with $0.5 \mu\text{m}$ alumina powder on a polishing cloth prior to each measurement. Then, it was thoroughly rinsed with methanol and double distilled water, and gently dried with a paper tissue.

3.5. Procedure

Stock solutions in concentrations 4×10^{-5} – 8×10^{-4} M, 4×10^{-5} – 1×10^{-3} M and 3.65×10^{-6} – 2.2×10^{-5} M were prepared in (pH 8) BRb: MeOH/1:1 v/v, MeOH and (pH8) phosphate buffer:acetonitrile/65:35,v/v) and stored in dark bottles at $+4^\circ\text{C}$. The working solutions for voltammetric, spectrophotometric and chromatographic investigations were prepared by

dilution of the stock solution. The STR concentration does not change with time. All working solutions were prepared freshly every day.

3.6. UV Spectrophotometry

Absorption spectra of STR in MeOH were determined by UV spectrophotometry of this drug in tablet forms. For determination of STR measurement of the peak-zero amplitude in the zero order spectra at 272.8 nm was used.

3.7. HPLC

Chromatographic separation was achieved on an Nova-Pak® C18 column (particle size $4 \mu\text{m}$, 3.9×150 mm) at a column temperature of 40°C using mobile phase of 0.085 M pH8 phosphate buffer and acetonitrile (65:35,v/v) at a flow rate of 2 mL/min. The sample injection volume was $10 \mu\text{L}$ and the wavelength of detection was 232 nm chromatographic measurements.

3.8. Analysis of tablets

3.8.1. Voltammetric method

A commercial pharmaceutical preparation was assayed. Ten tablets of Lustral® (containing 50 mg STR hydrochloride) were accurately weighed and finely powdered.

The correct amount of powder was dissolved in 50 mL methanol into a 50 mL volumetric flask and then 15 min of ultrasonic shaking, 5 mL of this solution was filtered through a $0.45 \mu\text{m}$ membrane filter in a 50 mL volumetric flask and was added about 20 mL methanol. The volume was made up to 50 mL with the pH 8 BRb supporting electrolyte. All the test solutions were obtained by diluting this stock solution with the selected supporting electrolyte. The voltammograms were recorded following the already outlined voltammetric procedure.

3.8.2. Spectrophotometric method

The content of ten tablets were weighed and thoroughly powdered. The average of one tablet was weighed and transferred into a 50 mL volumetric flask and was dissolved in the methanol, the flask was left in a ultrasonic bath for 15 min. After 15 min of ultrasonic shaking, 5 mL of this solution was filtered through $0.45 \mu\text{m}$ membrane filter. The volume was made up to 50 mL with the methanol. All the test solutions were obtained by diluting this stock solution with the methanol and UVspectrums were recorded at 272.8 nm.

3.8.3. Chromatographic method

Ten tablets were weighed and thoroughly powdered. The average of one tablet was weighed and transferred into a 100 mL volumetric flask and was dissolved in pH 8 phosphate buffer – acetonitrile (65:35,v/v), the flask was left in a ultrasonic bath for 10 min. After 10 min of ultrasonic shaking, 1 mL of this solution was filtered through a $0.45 \mu\text{m}$ membrane filter. The volume was made up to 100 mL with the mobile phase. All the test solutions were obtained by diluting this stock solution with the mobile phase and chromatograms were recorded.

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