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Voltammetric assay of anti-vertigo drug betahistine hydrochloride in sodium lauryl sulphate

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ABSTRACT

Assay and electrochemical behaviour of betahistine hydrochloride in Britton–Robinsons (BR) buffer of pH range 2.5–12.0 at a glassy carbon electrode have been investigated. Addition of anionic surfactant (sodium lauryl sulphate) to the betahistine hydrochloride solution containing electrolyte enhanced the reduction current signal while neutral surfactant (Tween-20) and cationic surfactant cetyl trimethylammonium bromide (CTAB) showed an opposite effect. Voltammograms of betahistine hydrochloride exhibited a single wave. Based on reduction behaviour of betahistine hydrochloride, a direct square-wave voltammetric method has been developed for the assay of betahistine hydrochloride in pharmaceutical formulation. The proposed method has been validated as per ICH guideline. System and method precision in terms of RSD were 1.88% and 1.60% respectively, whereas the method accuracy was indicated by the recovery of 97.6–101.9%. Reduction peak current was linear over the target concentration with correlation coefficient 0.998. The proposed method was successfully applied to the determination of betahistine hydrochloride in pharmaceutical formulation. The results were compared with those obtained by the reference high performance liquid chromatographic method. No significant differences were found between results of proposed and reference methods.

1. Introduction

Betahistine hydrochloride [*N*-methyl-2-(pyridin-2-yl) ethanamine hydrochloride] is an orally administered, centrally acting histamine H_1 receptor agonist with partial H_3 antagonistic activity and no H_2-binding effects (Scheme 1).

In the past, betahistine hydrochloride was clinically studied mainly as a vasodilator for conditions such as cluster headaches, vascular dementia and Meniere's disease, for which it is still used. In recent years, histamine was found to be a key neurotransmitter in the regulation of feeding behaviour. The unique pharmacologic properties of betahistine hydrochloride point to its potential future use as an antiobesity agent [1].

Few analytical methods have been reported to quantify betahistine hydrochloride in pharmaceutical formulation. Assay method in drug substance is mentioned in United States Pharmacopoeia (USP) [2]. Assay method for drug substance and pharmaceutical formulation is also mentioned in European Pharmacopoeia (EP) [3]. Spectrophotometric, atomic absorption spectrometric and high performance liquid chromatographic (HPLC) procedures have been reported for the determination of betahistine hydrochloride [4]. Stress degradation studies on betahistine hydrochloride performed by stability indicating assay method by HPLC [5]. Determination of betahistine hydrochloride in tablets and human urine was performed by amperometric detector in capillary electrophoresis [6].

Electrochemical methods such as square-wave voltammetry (SWV), stripping voltammetry (SV), differential pulse voltammetry (DPV) and differential pulse polarography (DPP) have been widely applied for the determination of pharmaceuticals [7–29]. Electrochemical techniques are time saving, cost effective, provide qualitative and quantitative information.

Surface active agents play great role in various fields of pharmaceutical analysis. Surfactants are often used as selective masking agent to improve not only sensitivity but also selectivity of electrochemical methods [30,31]. Surfactants help in solubilizing the organic compounds and provide specific orientation to the molecule at electrode interface.

A survey of literature reveals that there is no electro-analytical method present in the presence of either organic solvents or surface active agents for the determination of betahistine hydrochloride. The aim of this work is to develop and validate an electro-analytical method for determination of betahistine hydrochloride in pharmaceutical formulation in solubilized system vis-à-vis HPLC.

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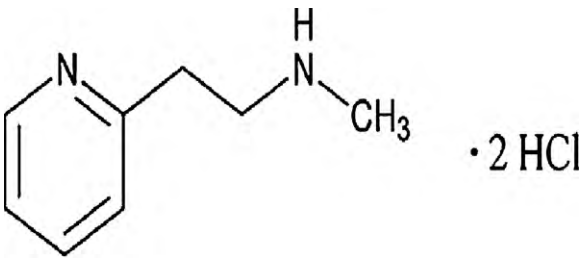

Scheme 1.

2. Experimental

2.1. Reagents and chemicals

Betahistine hydrochloride standard (99% purity) was obtained as gratis from RFCL Ltd., New Delhi, India. Tablets containing betahistine hydrochloride (*Zevert*®) labeled 8 and 16 mg were obtained from commercial source. Ultra pure water, obtained from Milli-Q purification system (Millipore Corp., Milford, MA, USA), was used throughout the studies. KCl (1.0 M) solution was prepared in Milli Q water and used as supporting electrolyte. All chemicals used were of analytical reagent grade quality and employed without further purification.

2.2. Preparation of standard and test solutions

Stock solutions of betahistine hydrochloride standard (1500 μg mL^{-1}) were prepared in dimethylformamide (DMF), acetonitrile, 1,4-dioxane, water, 0.1% cetyl trimethylammonium bromide (CTAB), 0.1% sodium lauryl sulphate (SLS) and 0.1% Tween-20 solution. Ten tablets were grounded to fine powder. Sufficient amount of powder for preparation of a stock solution (1500 μg mL^{-1}) was weighed, transferred into 25 mL volumetric flask and made up the volume with organic solvent or 0.1% surfactant solution. Solutions were sonicated for 10 min and centrifuged. Clear supernatant liquid was withdrawn. Stock solutions of standard and sample were protected from light and stored at 1–10 °C. The solutions for recording of voltammograms were prepared by mixing appropriate volume of BR buffer, stock solution and KCl (1.0 M).

2.3. Voltammetric and chromatographic conditions

Electrochemical measurements were performed using a MICRO AUTOLAB TYPE III (Eco- Chemie B.V., Utrecht, The Netherlands) potentiostat–galvanostat with 757VA computrace software. The utilized electrodes were glassy carbon as working electrode, Ag/AgCl (3 M KCl) as reference electrode and a graphite rod as auxiliary electrode. All pH measurements were made on a Decible DB-1011 digital pH meter fitted with a glass electrode and a saturated calomel electrode as reference, which was previously standardized with buffers of known pH.

Chromatographic experiments were performed on the HPLC apparatus consisting of a UV variable wavelength detector (SPD-20AU, Prominence, Shimadzu Corporation, Japan), an isocratic pump (LC-20AD, Prominence) and an injection valve with a 20 μL sample loop (Model 7125, Rheodyne, Cotati, CA, USA). Separations were performed according to the method mentioned in European Pharmacopoeia, using YMC ODS column (250 mm × 4.6 mm, 5 μm) at a flow rate of 2.0 mL/min, detection at 254 nm with mobile phase {60:40::buffer solution (0.46%, w/v, of NaH_2PO_4, 0.27%, w/v, of sodium dodecyl sulphate and 0.4% hexylamine):acetonitrile}. Sample injections were performed with a Model 701 syringe (50 μL, Hamilton, Bonaduz, Switzerland). Data acquisition and processing were performed by Spinchrom CFR software.

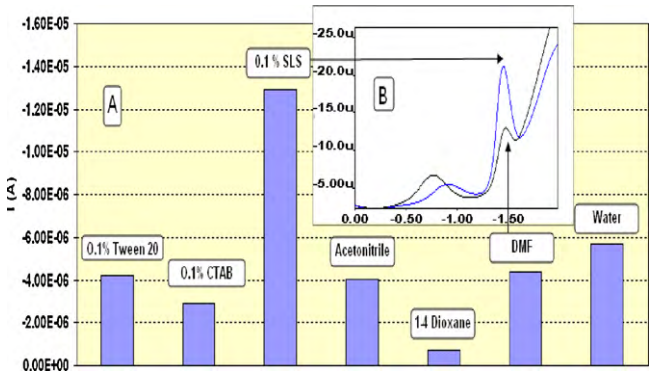

Fig. 1. (A) Comparison of cathodic peak current *I* (A) response of betahistine hydrochloride (700 μg mL^{-1}) in different organic solvents (acetonitrile, DMF and 1,4-dioxane), water and surfactants (0.1% Tween-20, 0.1% CTAB and 0.1% SLS). (B) Inset picture represents overlapped square-wave voltammograms of betahistine hydrochloride (700 μg mL^{-1}) in 0.1% SLS (maximum response in surfactants) and DMF (maximum response in organic solvents). *X*-axis shows potential *U* (V) and *Y*-axis represents cathodic peak current *I* (A).

3. Results and discussion

Assay and electrochemical behaviour of betahistine hydrochloride on glassy carbon electrode were determined by using square-wave and cyclic voltammetry in presence of 0.1% SLS. In proposed square-wave voltammetric method betahistine hydrochloride gave one well defined reduction peak in surfactants and organic solvents at glassy carbon electrode.

3.1. Optimization of operational parameters

3.1.1. Response enhancement effect of anionic surfactant

Square-wave voltammetric response of betahistine hydrochloride in organic solvents (acetonitrile, DMF and 1,4-dioxane), water and surfactants (a neutral, a cationic and an anionic type) was recorded. Results show substantial increase in peak current in anionic surfactant SLS. While neutral and cationic surfactants showed an opposite effect. Cathodic peak responses of betahistine hydrochloride in various solvents are shown in Fig. 1.

3.1.2. Effect of pH on reduction wave

The shape and characteristics of voltammograms were dependent on various electrolyte and pH of the medium. For controlling pH various buffers such as phosphate, acetate, borate, citrate and BR buffer were used. The best results with respect to sensitivity accompanied with better peak shape and stable response were obtained with BR buffer. The effect of pH on the peak current of betahistine hydrochloride was studied in pH range 2.5–12.0. Peak current decreases as pH shifted to higher value. pH 2.5 is found suitable in terms of better peak shape and stable response. With the rise in pH the peak potential shifted towards more negative potential indicating the participation of protons in the electrode process.

3.1.3. Influence of frequencies

Increment in a linear pattern was found between the intensity of peak current and frequency of the signals up to 90 Hz but the most stable response was obtained at 50 Hz Hence the frequency of 50 Hz was chosen for entire analysis.

Table 1
Operational parameters of proposed square-wave voltammetric method.

Parameter	Value
Buffer	BR buffer
pH	2.5
Purge time (s)	15
Stirring rate (rpm)	2000
Equilibration time (s)	10
Frequency (Hz)	50
Cleaning potential	0.7
Conditioning cycle	3

3.2. System suitability evaluation

After optimization of operational parameters of proposed method (Table 1), system suitability tests (SST) were performed.

It was shown that surfactants are highly effective in stabilizing the voltammetric response of analyte by protecting the electrode surface from fouling [32]. Stable voltammetric response is very essential for result reproducibility and acceptable SST.

Here the purpose of SST is to ensure that the complete testing system (including instrument, reagents, electrodes, and analyst) is suitable for the intended application. Five replicate voltammetric readings of betahistine hydrochloride standard solution (1500 μg mL^{-1}) were used in the system suitability evaluation. Data from five replicate reading were used to calculate the relative standard deviation (%RSD). 0.1% SLS was chosen the suitable surfactant due to the lesser value of %RSD in comparison with other surfactants and organic solvents.

3.2.1. System suitability with and without cleaning potential

The cleaning potential can be used to clean solid state electrodes with a stationary surface which are contaminated with the products of the electrode redox processes. Six sets of system suitability were performed, three with cleaning potential and another three without cleaning potential. After applying cleaning potential in voltammetric method lower %RSD is obtained in comparison to without cleaning potential. It clearly indicates the role of cleaning potential, hence decided to include cleaning potential in method parameters.

3.2.2. System suitability with and without purging

Purging means saturation of the analysis solution with an inert gas (nitrogen) and is used to remove the electrochemically active and hence interfering oxygen. With the inert gas flow rate of 20 L/h purging time of 3–5 min usually suffices. For an effective purging of the analysis solution, the solution should also be stirred. To evaluate the importance of purging in method performance six sets of system suitability were performed, three with purging and another three without purging. No significant difference was found between results of both sets hence purging time reduced from 3 to 5 min to only 15 s. Reduction in purging time played a major role in decreasing the total run time of voltammogram.

3.3. Calculation for assay determination of betahistine hydrochloride in pharmaceutical formulation

Assay value of betahistine hydrochloride has been calculated by using the formula

$$\text{Assay (mg per tablet)} = \frac{HT}{HS} \times \frac{DS}{DT} \times \frac{P}{100} \times C$$

where HT is the height of betahistine hydrochloride peak in the test voltammogram or chromatogram, HS is the height of betahistine hydrochloride peak in the standard voltammogram or chromatogram, DS is the dilution factor for standard solution, DT is the dilution factor for test solution, *P* is the potency of betahistine hydrochloride standard, on as is basis, and C is the label claim of betahistine hydrochloride in mg per tablet.

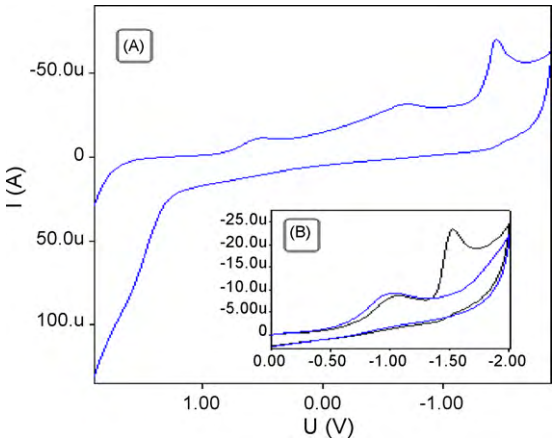

Fig. 2. (A) Cyclic voltammogram of betahistine hydrochloride (4000 μg mL^{-1}) in 0.1% SLS shows the irreversibility of electrode process. (B) Inset picture represents overlapped cyclic voltammograms of blank and standard solution containing betahistine hydrochloride (2750 μg mL^{-1}) in 0.1% SLS. *X*-axis shows potential *U* (V) and *Y*-axis represents cathodic peak current *I* (A).

3.4. Cyclic voltammetric behaviour

The reversibility of the reduction process was investigated using cyclic voltammetry. The cyclic voltammogram of betahistine hydrochloride in BR buffer (pH 2.5) at glass carbon electrode exhibits one well defined reduction peak at –1.45 V. No peak could be observed in anodic direction of the reverse scan suggesting the irreversible nature of the electrode process (Fig. 2).

3.5. Validation of square-wave voltammetric method

A validation study was conducted for assay of betahistine hydrochloride in pharmaceutical formulation as per ICH guideline [33].

3.5.1. Specificity

The specificity of the assay procedure for estimation of betahistine hydrochloride was examined in presence of various excipients like microcrystalline cellulose, mannitol, citric acid monohydrate, colloidal anhydrous silica and talc. No interferences found at reduction potential of betahistine hydrochloride. Additionally different concentrations of these excipients were added to solution containing betahistine hydrochloride (1500 μg mL^{-1}) and analyzed by proposed method. The obtained percentage recoveries (99.3–101.0%) based on the three replicate measurements showed no significant interference from excipients. Thus the proposed procedure can be considered specific.

3.5.2. Linearity of response

Linearity exercise was performed by standard addition method. Linearity of response for betahistine hydrochloride was determined in the range of 250–3500 μg mL^{-1}. Data in Fig. 3 and Table 2 indicate that the response is linear over the specified range.

3.5.3. Precision

3.5.3.1. System precision. Six replicate cathodic peak current readings of standard solution were taken, %RSD was calculated and data shown in Table 2 indicate an acceptable level of precision for the voltammetric system.

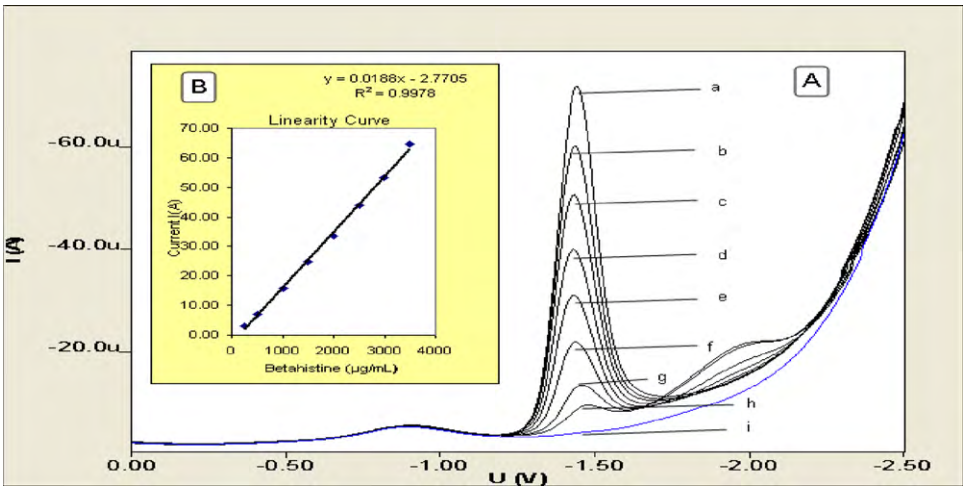

Fig. 3. (A) Overlapped square-wave voltammograms of betahistine hydrochloride at different concentrations: (a) 3500 μg mL^{-1}, (b) 3000 μgm L^{-1}, (c) 2500 μgm L^{-1}, (d) 2000 μg mL^{-1}, (e) 1500 μg mL^{-1}, (f) 1000 μg mL^{-1}, (g) 500 μg mL^{-1}, (h) 250 μg mL^{-1} and (i) blank solution. (B) Inset picture represents linearity curve of betahistine hydrochloride at different concentrations.

Table 2
Square-wave voltammetric method validation parameters.

Parameters	Results
Linearity	
Slope	0.019
Standard deviation	0.0004
Intercept	−2.770
Standard deviation	0.749
Correlation coefficient	0.998
Standard error of estimation	1.11
Sum of squares of regression	3426.13
Sum of squares of residuals	7.43
Precision	
System precision	1.88 (%RSD)
Method precision	1.60 (%RSD)
Accuracy	
Recovery level-1	97.6 (% recovery)
Recovery level-2	101.1 (% recovery)
Recovery level-3	101.9 (% recovery)
Stability in analytical solution	
Standard solution at 1–10 °C	At least 6 h, 1.27 (%RSD)
Sample solution at 1–10 °C	At least 6 h, 1.43 (%RSD)
Robustness	1.92 (overall %RSD)

3.5.3.2. Method precision. Six samples of single batch of betahistine hydrochloride tablets of 8 mg strength were prepared and analyzed. Data are incorporated in Table 2 .The %RSD value indicate that this method has an acceptable level of precision.

3.5.4. Accuracy

Different amounts of various excipients were taken and spiked with known amount of betahistine hydrochloride standard at three different levels each in triplicate. Solutions were prepared and analyzed; result shown in Table 2 clearly indicates that the method has acceptable accuracy.

3.5.5. Stability in analytical solution

Standard and test solutions were prepared and kept at room temperature as well as 1–10 °C. The standard and sample solutions were analyzed initially and at different time points. Cumulative %RSD of 6 time points up to 6 h shows that the solutions were stable at 1–10 °C as well as at room temperature. Results are given in Table 2.

3.5.6. Robustness

The robustness was examined by evaluating the influence of small change of some of the most important method parameters including pH of BR buffer, strength of KCL, without purging of nitrogen, equilibration time and strength of SLS solution. Test solutions were prepared, analyzed under each condition and assay of betahistine hydrochloride was determined. %RSD of different determinations has been tabulated in Table 2. Robustness of method is indicated by the cumulative RSD value. The obtained results provided the reliability of the proposed procedure for the assay of betahistine hydrochloride and hence it can be considered robust.

3.6. Application of proposed square-wave voltammetric method

3.6.1. Assay determination of betahistine hydrochloride in pharmaceutical formulation by proposed method

The proposed square-wave voltammetric method was successfully applied to the assay of betahistine hydrochloride in pharmaceutical formulation (commercial dosage form, tablet *Zevert*®) .The assay results incorporated in Table 3 are in good agreement with those obtained with reference method.

Table 3
Determination of betahistine hydrochloride in *Zevert*® tablets by the proposed voltammetric and reference HPLC methods.

Label claim (mg)	Proposed method[a]			Reference method[b]		
	Mean[c]	Error (%)	RSD (%)	Mean[c]	Error (%)	RSD (%)
8	8.11	1.4	1.76	8.05	0.6	0.71
16	15.90	0.6	1.87	16.11	1.1	0.10

[a] Proposed method – voltammetric method developed in-house.
[b] Reference method – HPLC method mentioned in European Pharmacopoeia (EP).
[c] Mean of three determinations of each strength.

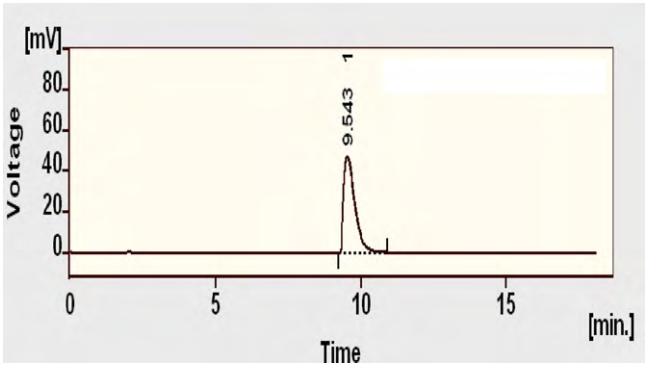

Fig. 4. Representative chromatogram of betahistine (320 μg mL^{-1}) using YMC ODS column (250 mm × 4.6 mm, 5 μm) at a flow rate of 2.0 ml/min, detection at 254 nm with mobile phase {60:40::buffer solution (0.46%, w/v, of NaH_2PO_4, 0.27%, w/v, of sodium dodecyl sulphate and 0.4% hexylamine):acetonitrile}.

Result indicates that method could be applied to determination of betahistine hydrochloride in pharmaceutical formulation.

3.6.2. Assay determination of betahistine hydrochloride in pharmaceutical formulation by reference method

Reverse phase HPLC method was also applied for determination of assay in betahistine hydrochloride in pharmaceutical formulation. Experimental details for chromatographic system were based on assay method mentioned in European Pharmacopoeia. The assay results are tabulated in Table 3. Representative chromatogram of target concentration is mentioned in Fig. 4.

Mean assay values obtained from proposed square-wave voltammetric and reference HPLC methods were compared. Percent differences between results of both methods were less than 2%.

4. Conclusion

As no electrochemical data were available concerning its voltammetric behaviour, the electrochemical reduction of betahistine hydrochloride was studied in a broad pH range (2.5–12.0) in surfactants. The electrochemical reduction of betahistine hydrochloride under the condition described in this work is an irreversible process. The proposed square-wave voltammetric method has distinct advantage over other existing methods. The proposed method is rapid, requiring less than 3 min to run a sample. Run time is approximately 5–6 times lesser than reference method. Solution preparations in proposed method are simple and less expensive than tedious and expensive preparation of mobile phase for reference method. No usage of toxic organic solvent makes proposed method more environment friendly than reference method. Consequently, the proposed method has a potential of a good analytical alternative for determining betahistine hydrochloride in pharmaceutical formulation and it can be adopted for routine analysis in Quality Control and Research & Development laboratories.

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