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RESEARCH ARTICLE

Development and Validation of First Order Derivative Method for Estimation of Betahistine Dihydrochloride and Prochlorperazine Maleate in Tablet Dosage Form Patel Vishvas D¹*, Patel Paresh U¹

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ABSTRACT

A simple, precise, and accurate method was developed for the estimation of Betahistine Dihydrochloride (BET) and Prochlorperazine Maleate (PRO) in Tablet dosage form using first order derivative spectrophotometry. Wavelengths selected for quantitation were 252.9 nm for Betahistine Dihydrochloride (zero crossing point for PRO) and 260.15 nm for Prochlorperazine maleate (zero crossing point for BET). The method was validated with respect to linearity, accuracy, precision, limit of detection and limit of quantitation in accordance with the International Conference on Harmonisation (ICH) guidelines. Linearity was observed in a concentration range of 4-24µg/ml and 3-18µg/ml for Betahistine Dihydrochloride and Prochlorperazine maleate, respectively. The limit of detection and limit of quantitation were found to be 0.29µg/ml and 0.95µg/ml for Betahistine Dihydrochloride and Prochlorperazine maleate. The percentage recovery of Betahistine Dihydrochloride and Prochlorperazine maleate was found to be 99.38% and 99.11% respectively. The % R.S.D. values for intra-day and inter-day precision study were <2.0%, confirming that the method was sufficiently precise. The method can be successfully employed for the simultaneous estimation of Betahistine Dihydrochloride and Prochlorperazine maleate in tablet dosage form.

KEYWORDS

Betahistine Dihydrochloride, Prochlorperazine Maleate, Derivative spectrophotometry, First order, Validation

INTRODUCTION

Betahistine (BET) is chemically N-Methyl-2pyridine-ethanamine (Figure 1) well known Anti Vertigo drug.¹ It is official in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), European Pharmacopoeia (EP), and United States Pharmacopoeia (USP). In which USP² and IP³ describe Liquid chromatographic method for estimation. While BP⁴ and EP⁵ describe potentiometric method for estimation.

*Address for Correspondence: Patel Vishvas D Department of Quality Assurance S. K. Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana , India. E-Mail Id: patelvishvas223@gmail.com Literature survey reveals HPLC for estimation Betahistine Dihydrochloride in human serum.⁶ it also shows colorimetric method⁷, HPLC⁸, Voltammetric method⁹ for the estimation of Dihydrochloride Betahistine in tablet. Prochlorperazine maleate (PRO) is 2-chloro-10-[3-(4-methyl piperazinIyl)propyl]phenothiazine dihydrogen maleate.(figure 2) It is official in IP, BP, USP, EP, and Japanese Pharmacopeia (JP). IP^{10} . JP^{11} . USP^{12} describe liquid chromatographic method for estimation while BP¹³ and EP¹⁴ describe potentiometric method for estimation. Literature survey reveals and HPLC¹⁶ colorimetric¹⁵ methods for

determination of PRO in single dosage form. Literature survey also reveals spectrophotometric¹⁷ and HPLC¹⁸ methods for determination of PRO with other drugs in combination. The combination of these two drugs is not official in any pharmacopoeia; hence no official method is available for the simultaneous estimation of BET and PRO in their combined dosage forms. Literature survey does not reveal any simple spectrophotometric method for simultaneous estimation of BET and PRO in synthetic mixture or dosage forms. The present communication describes simple, sensitive, rapid, accurate, precise and cost effective spectrophotometric method based on equations for simultaneous simultaneous estimation of both drugs in their tablet dosage form.

MATERIALS AND METHODS

Apparatus

A shimadzu model 1700 (Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV-Probe 2.0 system software. A Sartorius CP224S analytical balance (Gottingen, Germany), an ultrasonic bath (Frontline FS 4, Mumbai, India) was used in the study.

Reagents and Materials

BET bulk powder was kindly gifted by Astrone Pharmaceuticals Ltd., Ahmedabad, Gujarat, India. PRO bulk powder was kindly gifted by Trios Remedies Ltd., Ahmedabad, Gujarat, 0.1 N HCL as Solvent and Whatman filter paper no. 41 (Millipore, USA) were used in the study.

Preparation of Standard Stock Solutions

An accurately weighed quantity of standard BET (10 mg) and PRO (10 mg) powder were weighed and transferred to 100 ml separate volumetric flasks and dissolved in 0.1 N HCL. The flasks were shaken and volumes were made up to mark with 0.1 N HCL to give a solution containing 100μ g/ml each of BET and PRO.

Preparation of Working Standard Solution

From the stock solution of BET 1 ml was pipette out in to 10 ml volumetric flask and volume was adjusted to the mark with 0.1 N HCL to get $10\mu g/ml$ of BET. Same From the stock solution of PRO 1 ml was pipette out in to 10 ml volumetric flask and volume was adjusted to the mark with 0.1 N HCL to get $10\mu g/ml$ of PRO.

Determination of Wavelength for Measurement

The working standard solutions of BET and PRO were prepared separately in 0.1 N HCL having concentration of 10 µg/ml. They were scanned in the wavelength range of 200-400 nm against 0.1 N HCL as blank. The first order derivative spectra of each solution were obtained. The zero crossing points were found to be 252.9 nm (zero crossing point for PRO) and 260.15 nm (zero crossing point for BET) 3). Wavelengths (figure selected for quantification were 252.9 nm for BET (zero crossing point for PRO) and 260.15 nm for PRO (zero crossing point for BET).

Preparation of Calibration Curve

Calibration Curve for BET

Standard BET solutions of $4-24\mu g/ml$ were prepared by pipetting out 0.4, 0.8, 1.2, 1.6, 2.0, and 2.4ml into series of 10 ml volumetric flasks and the volume was adjusted to the mark with 0.1 N HCL. Absorbance of each solution was measured at 252.9nm using First order derivative spectrophotometry. A calibration curve was prepared by plotting absorbance against respective concentration (Figure 4).

Calibration Curve for PRO

Standard PRO solutions of $3-18\mu$ g/ml were prepared by pipetting out 0.3, 0.6, 0.9, 1.2, 1.5, and 1.8ml into series of 10 ml volumetric flasks and the volume was adjusted to the mark with 0.1 N HCL. Absorbance of each solution was measured at 260.15nm using First order derivative spectrophotometry. A calibration curve was prepared by plotting absorbance against respective concentration (Figure 5).

Development and Validation of Method

Linearity and Range

Aliquots of standard solutions of BET and PRO were taken in 10 ml volumetric flasks and diluted with 0.1 N HCL to get final concentrations in range of $4-24\mu$ g/ml for BET and of $3-18\mu$ g/ml of PRO. This calibration range was prepared six times and Absorbances were measured at respective wavelengths for each drug separately.

Precision

Precision of the method was determined by performing interday variation and intraday variation (%RSD). Intra-day precision (%RSD) was assessed by analyzing standard drug Solutions within the calibration range, three times on the same day. Inter-day precision (%RSD) was assessed by analyzing drug solutions within the calibration range on three Different days over a period of 7 days.

Repeatability

For repeatability study, $12\mu g/ml$ of BET and $12\mu g/ml$ concentration of PRO were measured six times.

Recovery Studies

To study the accuracy of the proposed method, recovery studies were carried out by standard addition method at three different levels (50%, 100%, 150%). A known amount of drug was added to pre analyzed sample powder and percentage recoveries were calculated.



Figure 1: Chemical structure of Betahistine



Figure 2: chemical structure of Prochlorperazine



Figure 3: Overlain UV first order derivative absorption spectra of BET and PRO in 0.1 HCL



Figure 4: Calibration curve of BET



Figure 5: Calibration curve of PRO

| Drug | Level | Amount taken (µg/ml) | Amount added (%) | % Mean recovery \pm S.D. (n = 3) |
|------|-------|----------------------|------------------|------------------------------------|
| | Ι | 6 | 50 | 99.22 ± 0.33 |
| BET | II | 6 | 100 | 99.41 ± 0.19 |
| DEI | III | 6 | 150 | 99.53 ± 0.74 |
| | Ι | 6 | 50 | 99.33 ± 0.21 |
| PRO | II | 6 | 100 | 99.08 ± 0.37 |
| | III | 6 | 150 | 98.93 ± 0.64 |

Table 1: Recovery data of proposed method

S. D. is Standard deviation and n is number of replicate, n is number of observation

| Sr. No. | Label claim (mg) | | Amount found (mg) | | % Label claim (mg) (n = 6) | |
|---------|------------------|-----|-------------------|------|----------------------------|-------|
| | BET | PRO | BET | PRO | BET | PRO |
| 1 | 8 | 5 | 7.88 | 4.97 | 98.5 | 99.4 |
| 2 | 8 | 5 | 7.97 | 4.99 | 99.62 | 99.8 |
| 3 | 8 | 5 | 7.95 | 4.92 | 99.37 | 98.4 |
| 4 | 8 | 5 | 8.02 | 5.03 | 100.2 | 100.6 |
| 5 | 8 | 5 | 8.04 | 5.01 | 100.5 | 100.2 |
| 6 | 8 | 5 | 7.93 | 4.97 | 99.12 | 99.4 |
| MEAN | | | 7.965 | 4.98 | 99.56 | 99.63 |
| SD | | | | | 0.736 | 0.763 |

S. D. is Standard deviation and n is number of replicate, n is number of observation

Table 3: Regression analysis data and summary of validation parameters for the proposed method

| PARAMETERS | BET | PRO |
|---|--|--|
| Wavelength (nm) | 252.9 | 260.15 |
| Beer's law limit (µg/ml) | 4 - 24 | 3 - 18 |
| Regression equation (y = mx + c) Slope (m) Intercept (c) | y = 0.0016x + 0.0005 0.0016 0.0005 | y = 0.0038x - 0.0002 0.0038 0.0002 |
| Correlation Coefficient (r ²) | 0.9988 | 0.9991 |
| Accuracy (Recovery \pm S.D.) (n = 3) | 99.38 ± 0.156 | 99.11 ± 0.202 |
| Method precision (Repeatability) (% RSD, n= 6) | 1.03 | 0.50 |
| Interday $(n = 3)$ (% RSD ^a) | 1.02 - 1.48 | 0.67 - 0.82 |
| Intraday($n = 3$) (% RSD) | 0.77 -1.09 | 0.27 - 0.61 |
| LOD (µg/ml) | 0.29 | 0.34 |
| LOQ (µg/ml) | 0.957 | 1.12 |
| Assay \pm S. D. (n = 3) | 99.56 ± 0.73 | 99.63 ± 0.76 |

RESULTS AND DISCUSSION

Validation

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines.¹⁹

Linearity

Calibration plots revealed good linear relationships between absorbance and concentration over the ranges $4-24\mu g/ml$ for BET and $3-18\mu g/ml$ for PRO. The linear equations for the calibration plots were y =0.0016x+0.0005 and y =0.0038x-0.0002 with Regression (r2) being 0.998 and 0.999 for BET and PRO, respectively (Figure 4, 5)

Precision

The low RSD values of interday (1.02-1.48% for BET at 252.9nm and 0.67-0.82% for PRO at 260.15 nm) and intraday (0.77-1.09% for BET at 252.9nm and 0.27-0.61% for PRO at 260.15 nm) variation for BET and PRO, reveal that the proposed method is precise.

Repeatability

The % RSD for absorbance values of BET and PRO were found to be 1.03 and 0.50 respectively.

Accuracy

When the method was used for accuracy and subsequent analysis of both the drugs from the pharmaceutical dosage form, and spiked with 50, 100, and 150% of additional pure drug, the recovery was found to be 99.38 % for BET and 99.11 % for PRO (Table 1).

LOD and LOQ

The LOD and LOQ were calculated by equation. The LOD and LOQ values were 0.29μ g/ml and 0.957μ g/ml for BET and 0.34μ g/ml and 1.12μ g/ml for PRO.

Analysis of BET and PRO in Marketed Formulation

The % purity was found to be 99.56% for BET and 99.63% for PRO. (Table 2)

CONCLUSION

The proposed spectrophotometric method was found to be simple, sensitive, accurate and precise for determination of BET and PRO in tablet dosage form. The method utilizes easily available and cheap solvent for analysis of BET and PRO hence the method was also economic for estimation of BET and PRO in tablet dosage form. The common excipients and other additives are usually present in the tablet dosage form do not interfere in the analysis of BET and PRO in 0.1 N HCL, hence it can be conveniently adopted for routine quality control combined drugs analysis of the in pharmaceutical formulation.

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