Analytical Method Development and Validation for Simultaneous Determination of Ebastine and Phenylephrine Hydrochloride in Combined Pharmaceutical Dosage Form

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Abstract: Two simple, accurate and sensitive analytical methods have been developed and validated for the simultaneous determination of Ebastine and Phenylephrine Hydrochloride in combined pharmaceutical dosage form. The first method involves UV-spectrophotometric determination of both drugs in combination, using first order derivative method and second method involves RP-HPLC method. For Spectrophotometric methods, The amplitudes at 300 nm (ZCP of PHE) and 250 nm (ZCP of EBS) in the first order derivative spectra were selected to determine Ebastine (EBS) Phenylephrine Hydrochloride (PHE) respectively. In RP-HPLC method both drug were analysed by reverse phase LC column (Hiber-C18, 250 mm × 4.6 mm, 5 μm) with mobile phase containing of Methanol : Phosphate buffer 0.05 M, pH-4 (50:50). The flow rate was set 1.0 ml/min and analysis was performed at wavelength 248 nm using Photo Diode Array (PDA) detector at ambient temperature. Both methods obey Beer's law is obeyed in the concentration range of 5-25μg/ml and 5-25 μg/ml for Ebastine (EBS) and Phenylephrine Hydrochloride (PHE) respectively. For first order derivative method Assay results of the marketed formulation were shown that %label claim of Ebastine and Phenylephrine hydrochloride was found to be 101% and 99% respectively. % recoveries of Ebastine and Phenylephrine Hydrochloride were obtained in the range of 98.88%-99.45% and 99.07%-99.81% respectively. For RP-HPLC method Assay results of the marketed formulation were shown that %label claim of Ebastine and Phenylephrine was found to be 99.98% and 98.84% respectively. % recoveries of Ebastine and Phenylephrine were obtained in the range of 99.18%-99.95% and 98.63%-99.8% respectively. Both of these developed methods were found to be simple, precise and accurate and can be utilize as a quality control tool for the simultaneous estimation of both drugs from their pharmaceutical dosage form.

Keywords: Ebastine, Phenylephrine Hydrochloride, RP-HPLC, first order derivative spectroscopy.
INTRODUCTION

Ebastine (EBS) Chemically is 1-[4-(1,1-Dimethylethyl)phenyl]-4-[4-(diphenylmethoxy)piperidin-1-yl]butan-1-one. It is an Anti-Allergic, Histamine H₁ receptor antagonist; antihistamine. Phenylephrine Hydrochloride (PHE) chemically 3-[(1R)-1-hydroxy-2-(methylamino)ethyl]phenol. It is an Alpha-adrenoreceptor agonist. EBS is official in BP-2009 pharmacopoeia. PHE is official in IP-2007, BP2009, and USPNF-2008 pharmacopoeia. Literature survey revealed that a number of methods have been reported for estimation of EBS and PHE individually or in combination with other drugs. For this combination UV Spectroscopy method has been reported but there is no method has been reported by RP-HPLC. Objective of this study is to develop a Simple, fast and precise method for simultaneous estimation of Ebastine and Phenylephrine Hydrochloride by RP-HPLC and UV spectroscopy method.

MATERIALS AND METHODS

Instrumentation:

For UV-spectrophotometric method Double beam UV-visible spectrophotometer (Shimadzu, model 1800) having two matched quartz cells with 1 cm light path was used. For RP-HPLC method Young Lin, YL 9100 HPLC systems, YL9110 Quaternary solvent delivery Pump, YL9160 Photodiode array (PDA) detector, Hiber C18 Column (5μm) with Young Lin software for data processing was used.

Chemicals & Reagents:
Standard gift sample of EBS was received from Tonira Pharma Limited, Vadodara, Gujarat, India. PHE as gift sample as from West Coast Pharmaceutical Works Ltd., Ahmedabad, Gujarat, India. Combined dose tablet formulation, Ebast-dc containing EBS (100 mg), PHE (10 mg) was purchased from a local pharmacy store. Methanol used for UV-spectrophotometric method was of AR grade. TEA (Merck Chemicals, India), Water (Rankem Ltd. Ahmedabad, India) used in RP-HPLC were of HPLC grade.

Procedure

Preparation of standard stock solution

Accurately weighed 10 mg EBS and 10 mg PHE was transferred into two separate 10 ml volumetric flasks and dissolved in methanol and dilute upto the mark with methanol to give a stock solution having concentration of 1 mg/ml (1000 µg/ml). Accurately measured 1 ml of above two stock solution was transferred into two separate 10 ml volumetric flasks and diluted to the mark with methanol to obtain a working standard solution (100 µg/ml) of Ebastine and Phenylephrine Hydrochloride respectively.

METHOD 1 First order derivative method

In the UV-spectrophotometric methods, First order derivative method The diluted solutions of Ebastine And Phenylephrine HCl over concentration ranges of 5-25 µg/ml and 5-25 µg/ml were scanned from 400-200 nm respectively. The zero order UV spectra of Ebastine And Phenylephrine HCl over were transformed to first order derivative spectra and Overlaid them. Zero crossing point (ZCP) of Ebastine And Phenylephrine HCl was obtained from their overlain first order derivative spectra. Wavelengths selected for determination of Ebastine And Phenylephrine HCl in the sample solution were 300 nm (ZCP of Phenylephrine HCl) and 250 nm (ZCP of Ebastine). Derivative Spectra which is shown in Figure 1, 2, 3

SPECTROPHOTOMETRIC CONDITION

VALIDATION OF THE METHOD

The proposed methods were validated as per ICH guidelines

LINEARITY RANGE

Linearity is expressed in terms of correlation co-efficient of linear regression analysis. The linearity response was determined by analyzing 5 independent levels of calibration curve in the range of 5-25 µg/ml for EBS and PHE. The calibration curve of absorbance vs concentration was plotted and correlation coefficient and regression line equations for EBS and PHE were determined.
PRECISION

1. Intraday Precision: For Intraday precision, it was carried out by preparing 3 replicates of 3 different concentrations, within the linearity range and measuring the absorbance of each solution on the same day. % RSD (% relative standard deviation) was calculated.

2. Interday Precision: For Interday precision, it was carried out by preparing 3 replicates of 3 different concentrations, within the linearity range and measuring the absorbance of each solution on the 3 different days. % RSD (% relative standard deviation) was calculated.

ACCURACY

To study accuracy of the method, recovery studies were carried out by addition of standard drug in a tablet sample at 80%, 100% and 120%. The percentage of recovery was calculated (table1.3).

LIMIT OF DETECTION (L.O.D.)

The L.O.D. was estimated from the set of 3 calibration curves used to determine method linearity. The L.O.D. may be calculated as \( \text{LOD} = 3.3 \times \left( \frac{\sigma}{S} \right) \)

Where, \( \sigma \) = Standard deviation of the Y-intercepts of the 3 calibration curves.

\( S \) = Mean slope of the 3 calibration curves.

LIMIT OF QUANTIFICATION (L.O.Q.)

The L.O.Q. was estimated from the set of 3 calibration curves used to determine method linearity. The L.O.Q. may be calculated as \( \text{LOQ} = 10 \times \left( \frac{\sigma}{S} \right) \)

Where, \( \sigma \) = Standard deviation of the Y-intercepts of the 3 calibration curves.

\( S \) = the mean slope of the 3 calibration curves.

ASSAY

- It was tested by analysis of commercially available marketed formulation. Twenty tablets were weighed accurately and powdered.

- A quantity of tablet powder equivalent to 10 mg of Ebastine & Phenylephrine HCl was transferred to 100 ml volumetric flask containing 50 ml of methanol, gentle shaking was carried out for 5 min and ultrasonicated for 5 min. The volume was made up to the mark with methanol.
The tablet sample solution was filtered through Whatman filter paper no. 41. 5 ml of filtrate was further diluted to 50 ml of methanol to get 100 μg/ml concentrations.

From the 100 μg/ml of sample stock solution take 1ml of solution and diluted up to the mark in 10 ml volumetric flask. So the final solution was made which contains 10 μg/ml Ebastine and 10μg/ml Phenylephrine HCl both.

The solution was scanned from 400-200 nm. Then the spectrum was transformed to first order derivative.

Measure the absorbance of first order derivative spectrum at 300 nm (ZCP of PHE) and at 250 nm (ZCP of EBS).

Find out the actual concentration of Ebastine and Phenylephrine HCl from the linear regression equation respectively. % label claim of each drug was find out. (Table 1.4)

**METHOD 2  RP-HPLC Method**

**Chromatographic conditions:** Preliminary studies were conducted and trails are made for the method development. Separation and analysis was carried out on Hiber C18 column (4.6 x 250mm), 5µ particle size. The optimized mobile phase consisting of Phosphate buffer(0.05Mm)pH4: Methanol(50:50v/v) adjusted with 1% H₃PO₄ and filtered through 0.45 μm membrane filter using vacuum pump. Flow rate was maintained at 1 ml/min and run time for 10 min, prior to sample injection, column was saturated with mobile phase for 40 min and injection volume was 20 μl injected by auto sampler. The detection response was measured at 248 nm and maintained at ambient temperature.

**Preparation of Phosphate buffer (0.05M) pH4:**

Take 6.8 gm Potassium Dihydrogen Phosphate in to a 1000 ml beaker, Add 800ml water and dissolve it. Then adjust the pH 4.0 with 1 % H₃PO₄ and make up 1000ml with water.

**Preparation of mobile phase:**

Phosphate buffer(0.05Mm)pH4: Methanol(50:50v/v) pH4 adjusted with 1 % H₃PO₄

**Preparation of standard stock solution:** same as UV method
VALIDATION OF THE METHOD

The proposed methods were validated as per ICH guidelines.

LINEARITY RANGE

Linearity was taken for Ebastine and Phenylephrine HCl in the concentration range of 5-15 μg/ml and 5-15 μg/ml respectively. The calibration curve was obtained by plotting absorbance vs. concentrations.

PRECISION

1. **Intraday Precision**: For Intraday precision, it was carried out by preparing 3 replicates of 3 different concentrations, within the linearity range and measuring the absorbance of each solution on the same day. % RSD (% relative standard deviation) was calculated.

2. **Interday Precision**: For Interday precision, it was carried out by preparing 3 replicates of 3 different concentrations, within the linearity range and measuring the absorbance of each solution on the 3 different days. % RSD (% relative standard deviation) was calculated.

ACCURACY

To study accuracy of the method, recovery studies were carried out by addition of standard drug in a tablet sample at 50%, 100% and 150%. The percentage of recovery was calculated. (Table 2.4)

LIMIT OF DETECTION (L.O.D.)

The L.O.D. was estimated from the set of 3 calibration curves used to determine method linearity. The L.O.D. may be calculated as \[ \text{LOD} = 3.3 \times \left( \frac{\sigma}{S} \right) \]

Where, \( \sigma \) = Standard deviation of the Y-intercepts of the 3 calibration curves.

\( S \) = Mean slope of the 3 calibration curves.

LIMIT OF QUANTIFICATION (L.O.Q.)

The L.O.Q. was estimated from the set of 3 calibration curves used to determine method linearity. The L.O.Q. may be calculated as \[ \text{LOQ} = 10 \times \left( \frac{\sigma}{S} \right) \]

Where, \( \sigma \) = Standard deviation of the Y-intercepts of the 3 calibration curve

\( S \) = the mean slope of the 3 calibration curves.

ROBUSTNESS
The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. In chromatography I change flow rate and mobile phase. and observe their effect on system suitability test and assay. (Table 2.6)

**ASSAY**

- It was tested by analysis of commercially available marketed formulation. Twenty tablets were weighed accurately and powdered.

- A quantity of tablet powder equivalent to 10 mg of Ebastine & Phenylephrine HCl was transferred to 100 ml volumetric flask containing 50 ml of methanol, gentle shaking was carried out for 5 min and ultrasonicated for 5 min. The volume was made up to the mark with methanol.

- The tablet sample solution was filtered through Whatman filter paper no. 41. 5 ml of filtrate was further diluted to 50 ml of methanol to get 100 μg/ml concentrations.

- From the 100 μg/ml of sample stock solution take 1ml of solution and diluted up to the mark in 10 ml volumetric flask. So the final solution was made which contains 10 μg/ml Ebastine and 10μg/ml Phenylephrine HCl both.

- After setting the chromatographic conditions and stabilizing the instrument to obtain a steady baseline, the tablet sample solution was injected chromatogram was obtained and the peak areas were recorded. The injections were repeated six times and the amount of each drug present in tablet was estimated from their respective calibration curve. (Table 2.5)

**SYSTEM SUITABILITY**

Standard solution was injected six times into system and chromatograms were recorded, % RSD (relative standard deviation) of retention time & peak area, theoretical plates and tailing factor were calculated. (Table 2.1)

**RESULTS AND DISCUSSION**

**First order derivative method**

The methods discussed in the present work provide a convenient and accurate way for simultaneous analysis of EBS and PHE For simultaneous determination method, wavelengths selected for analysis were 300 nm (ZCP of PHE) and at 250 nm (ZCP of EBS ). The optimized
method was applied for marketed formulation and the % label claim for EBS and PHE was found to be 101% and 99% The method is accurate and precise and can be used for routine pharmaceutical analysis. The data for linearity, precision, accuracy, LOD, LOQ is represented in the table 1.1 and 1.2. Recovery studies were carried out by standard addition method to check the accuracy of the developed methods and to study the interference of formulation additives (Table 1.3). The validated method was successfully applied for the determination of tablet mixture of EBS and PHE. The results are given in Table 1.4, indicate that the amount of drug in tablet samples met with requirements.

**RP-HPLC METHOD**

The methods discussed in the present work provide a convenient and accurate way for simultaneous analysis of EBS and PHE For simultaneous determination method, wavelengths selected for analysis were 248. The optimized mobile phase consisting of Phosphate buffer(0.05M)pH4: Methanol(50:50v/v) adjusted with 1% H$_3$PO$_4$ The optimized method was applied for marketed formulation and the % label claim for EBS and PHE was found to be 99.98% and 98.84% The method is accurate and precise and can be used for routine pharmaceutical analysis. The data for linearity, precision, accuracy, LOD, LOQ is represented in the table 2.2 and 2.3. Recovery studies were carried out by standard addition method to check the accuracy of the developed methods and to study the interference of formulation additives (Table 2.4). The validated method was successfully applied for the determination of tablet mixture of EBS and PHE. The results are given in Table 2.5, indicate that the amount of drug in tablet samples met with requirements. Robustness Evaluation of Method for EBS and PHE is given in table 2.6

**CONCLUSION**

The optimized simultaneous determination Both method provides simple, specific, precise, accurate, economical and reproducible quantitative analysis for simultaneous determination of EBS and PHE in combined tablet dosage form. The method was validated as per ICH guidelines in terms of linearity, accuracy, precision, limits of detection (LOD) and quantification (LOQ). The method can be used for routine analysis of EBS and PHE in combined dosage form.

**Tables and Figures**
METHOD 1 FIRST ORDER DERIVATIVE METHOD

Figure 1: Overlain Derivative Spectra of EBS (5-25 μg/ml)

Figure 2: Calibration curve of Ebastine At 300 nm

Zcp of PHE At 300nm
Figure 3: Overlain Derivative Spectra of PHE (5-25 μg/ml)

![Figure 3: Overlain Derivative Spectra of PHE (5-25 μg/ml)](image)

Figure 4: Calibration curve of PHE

![Figure 4: Calibration curve of PHE](image)

Table 1.1: Summary of Validation parameters Derivative Spectroscopy method

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Parameters</th>
<th>Ebastine</th>
<th>Phenylephrine Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Linearity (Range)</td>
<td>5-25μg/ml</td>
<td>5-25μg/ml</td>
</tr>
<tr>
<td>2</td>
<td>Recovery %</td>
<td>98.88%-99.45%</td>
<td>99.07%-99.81%</td>
</tr>
<tr>
<td>3</td>
<td>Precision</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intra-day (n=3)</td>
<td>0.51-0.90</td>
<td>0.46-0.73</td>
</tr>
<tr>
<td></td>
<td>Inter-day (n=3)</td>
<td>0.6-1.02</td>
<td>0.43-1.05</td>
</tr>
<tr>
<td>4</td>
<td>Repeatability</td>
<td>0.40</td>
<td>0.76</td>
</tr>
<tr>
<td>5</td>
<td>LOD(μg/ml)</td>
<td>0.46</td>
<td>0.24</td>
</tr>
</tbody>
</table>
Table 1.2 Linear Regression data of Ebastine and Phenylephrine HCl in Derivative method

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ebastine</th>
<th>Phenylephrine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Wavelength</td>
<td>300nm</td>
<td>250nm</td>
</tr>
<tr>
<td>Range</td>
<td>5-25(μg/ml)</td>
<td>5-25(μg/ml)</td>
</tr>
<tr>
<td>Slope</td>
<td>-0.0009</td>
<td>0.0003</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.0011</td>
<td>0.0002</td>
</tr>
<tr>
<td>Regression Coefficient</td>
<td>0.9997</td>
<td>0.9996</td>
</tr>
</tbody>
</table>

Table- 1.3 : Accuracy (%recovery) data for EBS AND PHE Derivative Spectroscopy method

<table>
<thead>
<tr>
<th>% Level</th>
<th>Amount of Drug Taken (μg/ml)</th>
<th>Amount of Drug Added (μg/ml)</th>
<th>Amount Recovered (μg/ml) ± S.D. (n=3)</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EBS (μg/ml)</td>
<td>PHE (μg/ml)</td>
<td>EBS (μg/ml)</td>
<td>PHE (μg/ml)</td>
</tr>
<tr>
<td>80</td>
<td>10</td>
<td>10</td>
<td>17.88±0.18</td>
<td>17.83±0.21</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>10</td>
<td>19.77±0.17</td>
<td>19.90±0.19</td>
</tr>
<tr>
<td>120</td>
<td>10</td>
<td>10</td>
<td>21.88±0.25</td>
<td>21.96±0.26</td>
</tr>
</tbody>
</table>

Table 1.4 : Assay of Formulation. Derivative Spectroscopy method

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Drug</th>
<th>Labeled claim (mg)</th>
<th>Amount found (mg)± S.D. (n=3)</th>
<th>% label claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebast-DC</td>
<td>Ebastine</td>
<td>10</td>
<td>10.11</td>
<td>101%</td>
</tr>
<tr>
<td></td>
<td>Phenylephrine Hydrochloride</td>
<td>10</td>
<td>9.9</td>
<td>99%</td>
</tr>
</tbody>
</table>

METHOD 2 RP-HPLC
Fig 5: HPLC chromatogram of EBS (10µg/ml) and PHE (10 µg/ml).

Fig 6: HPLC Chromatograph of marketed formulation.

Phenylephrine Hydrochloride

\[ y = 32366x + 39992 \]

\[ R^2 = 0.9941 \]
**Figure 7**: Calibration curve of PHE

![Calibration curve of PHE](image)

**Figure 8**: Calibration curve of EBS

**Table 2.1**: System suitability parameters of RP-HPLC method.

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>System suitability Parameter</th>
<th>Observed value</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Retention time (Rt)</td>
<td>5.967</td>
<td>3.250</td>
</tr>
<tr>
<td>2</td>
<td>Resolution (Rs)</td>
<td>9.787</td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td>3</td>
<td>Theoretical plates (N)</td>
<td>3623</td>
<td>6717</td>
</tr>
<tr>
<td>4</td>
<td>Tailing factor (Tf)</td>
<td>1.323</td>
<td>0.952</td>
</tr>
<tr>
<td>5</td>
<td>Asymmetric factor (Af)</td>
<td>1.569</td>
<td>1.381</td>
</tr>
</tbody>
</table>

* Specification

EBS | PHE
---|---
5.967 | 3.250
9.787 | > 1.5
3623 | 6717
1.323 | 0.952
1.569 | 1.381

* mean of five replicates

**Table 2.2**: Summary of System Suitability and validation parameters of RP-HPLC method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ebastine</th>
<th>Phenylephrine Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical plate</td>
<td>3623</td>
<td>6717</td>
</tr>
<tr>
<td>Asymmetric factor</td>
<td>1.569</td>
<td>1.381</td>
</tr>
<tr>
<td>Parameters</td>
<td>Ebastine</td>
<td>Phenylephrine HCl</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Correlation coefficient (R2)</td>
<td>0.9923</td>
<td>0.9941</td>
</tr>
<tr>
<td>Slope (m)</td>
<td>75641</td>
<td>32366</td>
</tr>
<tr>
<td>Intercept (c)</td>
<td>94987</td>
<td>39992</td>
</tr>
</tbody>
</table>

Table 2.3: Linear Regression data of Ebastine and Phenylephrine HCl

| % Assay | 99.98 | 98.84 |

<table>
<thead>
<tr>
<th>% Level</th>
<th>Amount of Drug Taken (µg/ml)</th>
<th>Amount of Drug Added (µg/ml)</th>
<th>Amount Recovered (µg/ml) ± S.D. (n=3)</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>EBS (µg/ml) 10</td>
<td>PHE (µg/ml) 10</td>
<td>17.91±0.061</td>
<td>%EBS 99.53</td>
</tr>
<tr>
<td></td>
<td>EBS (µg/ml) 8</td>
<td>PHE (µg/ml) 8</td>
<td>17.94±0.077</td>
<td>%PHE 99.66</td>
</tr>
</tbody>
</table>
Table 2.4: Recovery data for EBS and PHE from tablet formulation

Table 2.5: Analysis of Marketed Formulation

<table>
<thead>
<tr>
<th>Tablet</th>
<th>Drug</th>
<th>Labeled claim (mg)</th>
<th>Amount found (mg)± S.D. (n=3)</th>
<th>% label claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebast-DC</td>
<td>Ebastine</td>
<td>10</td>
<td>9.98±1.3847</td>
<td>99.98</td>
</tr>
<tr>
<td></td>
<td>Phenylephrine Hydrochloride</td>
<td>10</td>
<td>9.88±1.0257</td>
<td>98.84</td>
</tr>
</tbody>
</table>

Table 2.6: Robustness Evaluation of Method for EBS and PHE

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Variation</th>
<th>% Assay</th>
<th>Ebastine</th>
<th>Phenylephrine HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Assay</td>
<td></td>
<td>99.22</td>
<td>98.96</td>
<td></td>
</tr>
<tr>
<td>Flow rate</td>
<td>+ 0.1 ml</td>
<td>99.84</td>
<td>99.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 0.1 ml</td>
<td>99.80</td>
<td>98.74</td>
<td></td>
</tr>
<tr>
<td>Mobile phase</td>
<td>Phosphate buffer: Methanol (52:48v/v)</td>
<td>99.46</td>
<td>98.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phosphate buffer: Methanol (46:54v/v)</td>
<td>98.25</td>
<td>97.55</td>
<td></td>
</tr>
</tbody>
</table>

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