SPECTROPHOTOMETRIC METHODS FOR SIMULTANEOUS ESTIMATION OF ESOMEPRAZOLE MAGNESIUM AND NAPROXEN IN A TABLET DOSAGE FORM

NILESH JAIN1*, SNEHA KULKARNI1, DEEPAK KUMAR JAIN2 and SURENDRRA KUMAR JAIN1

1Sagar Institute of Research and Technology-Pharmacy, Bypass Road, Bhopal, M.P-462038 India
2Truba Institute of Pharmacy, Karond Gandhi Nagar Bypass Road, Bhopal, M.P-462038 India

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Esomeprazole (ESO) is a proton pump inhibitor which is used as antiulcer agent. It is official in IP and USP. Chemically it is (Fig-1A) (S)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridine-2-yl) methylsulfinyl]-3H-benzimidazole (1-3). Several methods have been employed for the estimation of esomeprazole such as spectrophotometric method and RP-HPLC method (5-8). Naproxen (NAP); (Fig-1B) (S)-2-(6-methoxynapthalen-2-yl) propionic acid is used as non steroidal anti-inflammatory agent (1, 2, 4). Literature survey reveals that there are some UV and HPLC method for the estimation of naproxen in pharmaceutical formulations (9, 10).

The review of literature revealed that no method was yet reported for the simultaneous estimation of both the drugs in combined dosage forms. This paper describes two simple, rapid, accurate, reproducible and economic methods for the simultaneous estimation of esomeprazole and naproxen in tablet formulations using simultaneous equation and absorbance ratio method.

EXPERIMENTAL

Instrument

The proposed work was carried out on a Shimadzu UV-visible spectrophotometer (Model UV-1700 series), which possesses a double beam, double detector configuration with matched 1 cm quartz cells.

Reagents and standards

Reference standard of ESO was a generous gift from Glenmark Pharma Ltd., Baddi, and NAP was obtained from Aurbindo Pharma Ltd., Hyderabad. Methanol was obtained from Merck Chemical Division, Mumbai. Reverse osmosis water was used throughout the study. Commercial tablets of ESO and NAP, VIMOVO (AstraZeneca Mumbai Ltd.)

Figure 1. Chemical structure of A – esomeprazole and B – naproxen

* Corresponding author: e-mail: nilujain01@yahoo.co.in; mobile: +919425074520

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was procured from the local drug market. Label claim of ESO and NAP in tablet is 20 and 500 mg, respectively.

**Preliminary solubility studies**
Solubility of ESO and NAP was determined at 25±1°C. Accurately weighed 10 mg ESO and NAP was added in different 10 mL volumetric flasks containing different solvents. It was found that both the drugs are having good solubility in methanol 50%.

**Preparation of standard solution**
Standard stock solutions were prepared by dissolving separately 100 mg of ESO and 500 mg of NAP in 50 mL of methanol 50% solution and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to the mark (100 mL) with the same solvent to get a concentration of 1000 µg/mL and 5000 µg/mL for both the drugs respectively. Solutions were diluted with methanol 50% to obtain concentrations in the range 5 – 25 µg/mL for ESO and 50 – 250 µg/mL for NAP, respectively, for direct analysis.

**Preparation of overlay spectra**
Working standard solution from the standard stock solution prepared as stated above of 20 µg/mL of ESO and 200 µg/mL of NAP were scanned in the spectrum mode over the range of 200-400 nm against 50% methanol as blank and the overlaid spectra of the two were recorded. ESO showed an absorbance peak at 301.60 nm whereas NAP shows an absorbance peak at 330.20 nm. The overlaid spectra also showed isosbortive points at 311.50 nm (Fig. 2). Due to difference in absorbance maxima and having no interference with each other, both drugs can be simultaneously estimated by simultaneous equation method (Method-I) and absorbance ratio method (Method-II).

**Simultaneous equation method (Method I)**
From the stock solution of 100 µg/mL, working standard solutions of drugs were prepared by appropriate dilution and were scanned in entire UV range to determine the λmax values. Esomeprazole has λmax of 301.60 nm while naproxen has λmax at 330.20 nm, respectively (Fig. 2). Standard solutions were prepared having concentration 5 – 25 µg/mL for esomeprazole and 50 – 250 µg/mL for naproxen. The absorbances of these standard solutions were measured at 301.60 nm and 330.20 nm and calibration curves were plotted at these wavelengths. Two simultaneous equations (in two variables C1 and C2) were formed using these absorptivity coefficient values.

\[
A_1 = (0.0487) C_1 + (0.0079) C_2 \quad (1)
\]
\[
A_2 = (0.00308) C_1 + (0.0065) C_2 \quad (2)
\]
where, C1 and C2 were the concentrations of ESO and NAP measured in µg/mL, in sample solutions. A1 and A2 were the absorbances of mixture at selected wavelengths 301.60 nm and 330.20 nm, respectively.

By applying the Cramer’s rule to equation 1 and 2, the concentration C_ESO and C_NAP, can be obtained as follows:

\[
C_{ESO} = \frac{A_2 (0.0079) - A_1 (0.0065)}{A_1 (0.0065) - A_2 (0.00308)} \quad (3)
\]
\[
C_{NAP} = \frac{A_1 (0.00308) - A_2 (0.0065)}{0.000293} \quad (4)
\]

**Absorbance ratio method (Method II)**
Q-absorbance method uses the ratio of absorbances at two selected wavelengths, one at isosbortive point and other being the λmax of one of the two compounds. From the stock solutions, working standard solutions of esomeprazole (20 µg/mL) and naproxen (200 µg/mL) were prepared by appropriate dilution and were scanned in the entire UV range to determine the maximum absorbance (λmax) and isosbortive point. Esomeprazole and naproxen have λmax at 301.60 nm and at 330.20 nm, respectively. Both the drugs were found to have the same absorbance at 311.50 nm (isosbortive point). The wavelengths selected for analysis were 311.50 nm and 330.20 nm, respectively (Fig. 2). A series of standard solutions ranging from 5 to 25 µg/mL for esomeprazole and 50–250 µg/mL for naproxen were prepared and the absorbance of the solution were measured at 311.50 and 330.20 nm to plot a calibration curve of concentration versus absorbance. The
Table 1. Results of linearity of esomeprazole (ESO) and naproxen (NAP).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>METHOD I</th>
<th>METHOD II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESO</td>
<td>NAP</td>
</tr>
<tr>
<td>Working λ</td>
<td>301.6 nm</td>
<td>330.2 nm</td>
</tr>
<tr>
<td>Beer’s law limit (µg/mL)</td>
<td>5–25</td>
<td>50–250</td>
</tr>
<tr>
<td>Correlation coefficient (r²)*</td>
<td>0.9994</td>
<td>0.9999</td>
</tr>
<tr>
<td>Slope (m)*</td>
<td>0.0440</td>
<td>0.0068</td>
</tr>
<tr>
<td>Intercept (c)*</td>
<td>0.0015</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

* Average of five determinations. ESO = esomeprazole, NAP = naproxen.

Table 2. Results of recovery studies on marketed formulations.

<table>
<thead>
<tr>
<th>Recovery level %</th>
<th>% Recovery (mean ± SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>METHOD I</td>
</tr>
<tr>
<td></td>
<td>ESO</td>
</tr>
<tr>
<td>80</td>
<td>98.50 ± 0.064</td>
</tr>
<tr>
<td>100</td>
<td>96.70 ± 0.204</td>
</tr>
<tr>
<td>120</td>
<td>99.70 ± 0.055</td>
</tr>
</tbody>
</table>

*Average of 5 determinations. ESO = esomeprazole, NAP = naproxen.

Table 3. Results of validation (mean ± SD).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>METHOD I</th>
<th>METHOD II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESO</td>
<td>NAP</td>
</tr>
<tr>
<td>Repeatability</td>
<td>97.88 ± 0.05</td>
<td>98.22 ± 0.64</td>
</tr>
<tr>
<td>Day to day</td>
<td>98.97 ± 0.06</td>
<td>98.97 ± 0.54</td>
</tr>
<tr>
<td>Analyst to analyst</td>
<td>96.82 ± 0.12</td>
<td>96.82 ± 0.44</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>99.28 ± 0.04</td>
<td>99.10 ± 0.51</td>
</tr>
</tbody>
</table>

*Average of 5 determinations. ESO = esomeprazole, NAP = naproxen.

Table 4. Results of validation (%RSD).

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>METHOD I</th>
<th>METHOD II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESO</td>
<td>NAP</td>
</tr>
<tr>
<td>Repeatability</td>
<td>0.662</td>
<td>0.643</td>
</tr>
<tr>
<td>Day to day</td>
<td>0.066</td>
<td>0.540</td>
</tr>
<tr>
<td>Analyst to analyst</td>
<td>0.122</td>
<td>0.441</td>
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<tr>
<td>Reproducibility</td>
<td>0.049</td>
<td>0.517</td>
</tr>
<tr>
<td>Robustness*</td>
<td>0.099</td>
<td>0.434</td>
</tr>
</tbody>
</table>

*Average of 5 determinations. ESO = esomeprazole, NAP = naproxen.
calibration curves were found to be linear in the concentration range under study.

The concentration of two drugs in mixture was calculated by using following equations:

\[
C_{Eso} = \frac{Qm - Qy}{Qx - Qy} A1\]

\[
C_{ESO} = \frac{Qm - Qx A2}{Qy - Qx ax1}\]

where, \(A1\) and \(A2\) are the absorbances of mixture at 311.50 nm and 330.20 nm and \(ax1\), \(ax2\), \(ay1\), \(ay2\) are absorptivities \(E (1\%, 1 \text{ cm})\) of esomeprazole and naproxen at 311.50 nm and 330.20 nm and \(Qm = A2/A1\), \(Qy = ay2/ay1\) and \(Qx = ax2/ax1\).

Recovery studies

The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e., 80%, 100% and 120%. The recovery studies were carried out by adding known amount of standard solution of ESO and NAP to preanalyzed tablet solutions. The resulting solutions were then re-analyzed by proposed methods. The whole analysis procedure was repeated to find out the recovery of the added drug sample. This recovery analysis was repeated at 3 replicate of 3 concentrations levels.

Precision studies

To evaluate precision at different parameter like repeatability, intermediate precision, and five dilutions in three replicates were analyzed in same day, in two different days by two analysts for day to day and analyst to analyst variation.

Robustness

As per ICH norms, small but deliberate variations by altering the pH and/or concentration of the solvent were made to check the methods capacity to remain unaccepted. The change was made in the combination of solvent system, containing 50% methanol. Instead the 50 : 50 ratios of methanol and water, 60 : 40 methanol and water were used as solvent.

Analysis of tablet formulation

ESO: An amount of 10 mg was weighed from powdered mass of 20 tablets of VIMOVO (AstraZeneca) with the accuracy up to 0.1 mg. This powder was then transferred to 10 mL volumetric flask. The NAP present in this amount of tablet powder was 250 mg. The weighed amount of powder was poured with 8 mL of methanol 50% and sonicated for 15 min to solubilize the drug and then volume was made up to the mark with the same solvent. After sonication, filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with methanol 50% to get the final concentrations of both drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from both the methods. The procedure was repeated for three times.

RESULTS

For both the two methods linearity was observed in the concentration range of 5–25 µg/mL for esomeprazole and 50–250 µg/mL for naproxen (Table 1). The proposed methods were validated as per ICH guidelines. The accuracy of the method was determined by calculating the mean percentage recovery at 80, 100 and 120% level. The % recovery ranges from 95.98 to 99.70 for esomeprazole and naproxen for both two methods (Table 2). Precision was calculated as repeatability (SD and % RSD is less than 2) and inter and intraday variations (SD and % RSD is less than 2) for both the drugs. The repeatability data and reproducibility data are presented in Tables 3 and 4, respectively. Marketed brand of tablet was analyzed and amount of esomeprazole and naproxen determined by proposed
methods ranges from 98.09 to 99.40 as shown in Table 5.

DISCUSSION AND CONCLUSION

The proposed methods were found to be simple, accurate and rapid for the routine determination of esomeprazole and naproxen in tablet formulation. To study the validity and reproducibility of proposed methods, recovery studies were carried out. The methods were validated in terms of linearity, accuracy, precision, specificity and reproducibility. Both methods can be successfully used for simultaneous estimation of esomeprazole and naproxen in combined dosage form.

REFERENCES


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