A Stability Indicating RP-HPLC Method Validation for Simultaneous Estimation of Azelnidipine and Telmisartan in a Fixed-dose Combination

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ABSTRACT

The present investigation deals with the reverse phase high performance liquid chromatography (RP-HPLC) method validation for simultaneous estimating Azelnidipine and Telmisartan in a fixed-dose combination (FDC). The method was developed using RP-HPLC, Inertsil C-18 Column with 150×4.6 mm×5 µm at column oven temperature 40°C, flow rate 1.5 mL/min, volume 10 µL and run time 12.0 minutes at 254 nm using Acetonitrile and buffer as mobile phase in gradient mode. The developed protocol was most accurate, repeatable, and detectable towards Azelnidipine and Telmisartan in combination without any unwanted interference. When evaluated on various parameters like system suitability, precision, accuracy, linearity, robustness, force degradation study, the method is efficient in separating the API from its degradants and can be utilized for analyzing the samples of Azelnidipine and Telmisartan.

INTRODUCTION

Hypertension (HTN) is still the leading cause of death worldwide, and robust randomized trial studies consistently suggest that lowering blood pressure decreases cardiovascular morbidity and mortality. Due to the difficulty of controlling blood pressure (BP) with one anti-hypertensive drug where most patients can only achieve adequate blood pressure control using two or more anti-hypertensive medications, the target has been set to develop an alternative treatment for treating hypertension (HTN) disorder using a combination of the rational drug. The intention for developing the FDC is that by simultaneously administering two comparable drugs in fewer amounts to give lesser side effects, potential benefits attributable to synergistic pharmacological and physiological effects can be obtained. Combining Rennin Angiotensin Aldosterone drugs, including angiotensin-converting enzyme (ACE) inhibitors or diuretics, can be a good way to lower blood pressure. The combination of angiotensin II receptor blocker (ARB) telmisartan (TEL), and calcium channel blocker (CCB) Azelnidipine is one such example (AZE). The FDC of Azelnidipine and Telmisartan contains 8 mg of Azelnidipine and 40 mg of Telmisartan. Generally, in people, especially those suffering mild to severe hypertension and high-risk patients, this has shown considerably greater blood pressure decreases relative to the use of each immunotherapy portion. Given the widespread use and importance of FDCs in clinical medicine, the development of new analytical approaches for the simultaneous assessment of mixed substances is both a requirement and a challenge for analysts.

AZE, a dihydro-pyridine calcium channel antagonist (Fig. 1) is recently launched in the market. Its therapeutic

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Stability Indicating RP-HPLC method for Azelnidipine and Telmisartan Tablets

The activity is attributed towards inhibition of transmembrane Ca^{2+} influx via vascular smooth muscle voltage-dependent channels.\cite{8} The drug promises a decreased blood pressure which is equal in efficacy to that of dihydropyridines (e.g. amloidipine) but does not produce the disadvantages produced by the same.\cite{8,9} The dose of AZE is about 16 mg/day. After reviewing the literature, it can be said that for AZE, very limited techniques are available to estimate the concentration of AZE, including high-performance liquid chromatography,\cite{10-13} liquid chromatography–mass spectrometry (LC–MS),\cite{14,15} high-performance liquid chromatography mass analysis capabilities of mass spectrometry (HPLC-MS-MS),\cite{16} UV spectroscopy.\cite{17} The literature survey reported that the concentration of TEL can be estimated from the sample by using different methods like HPLC,\cite{19} sweep linear polarography,\cite{20} hydrogen wave method.\cite{21}

The TEL (Fig. 2) an oral AT-II specific receptor antagonist with chemical formula 2-{[4-methyl-6-(1-benzodiazol-1-yl)methyl]phenyl} benzoic acid with a longer duration of action and long half-life.\cite{18} The TEL dose is about 16 mg/day. After reviewing the literature, it can be said that for TEL, very limited techniques are available to estimate the concentration of TEL, including high-performance liquid chromatography,\cite{10-13} liquid chromatography–mass spectrometry (LC–MS),\cite{14,15} high-performance liquid chromatography mass analysis capabilities of mass spectrometry (HPLC-MS-MS),\cite{16} UV spectroscopy.\cite{17} The literature survey reported that the concentration of TEL can be estimated from the sample by using different methods like HPLC,\cite{19} sweep linear polarography,\cite{20} hydrogen wave method.\cite{21}

The FDC containing 8 mg of AZE and 40 mg of TEL is available in the market with the brand name of UNIAZ T 40 under the therapeutic class of anti-hypertensive agent, calcium channel blocker. The rationale behind selecting a combination of the drug is the superiority of upfront combination therapy compared to monotherapy of ARB and calcium antagonist in controlling the prevalent condition like hypertension associated mortality and morbidity rate.\cite{22,23} Here, an effective control of blood pressure can significantly lower the consequence. The FDC of AZE and TEL has shown additive anti-hypertensive action with decreased incidences of adverse events and improved adherence to therapy by combining antihypertensive therapy for administration as a single, once-daily tablet.\cite{22} Although this FDC is well tolerated by patients and effectively lowers BP, no practical method for simultaneous detection of AZE and TEL is available.\cite{23,24} In the present investigation, we have developed an analytical procedure that is fast, accurate, and reproducible to perform simultaneous estimation of both drugs.

**MATERIAL AND METHODS**

**Chemicals and Reagents**

The laboratory (working) standards of azelnidipine, Telmisartan were received as gift samples from M/s. Synokem Pharmaceutical Limited, Haridwar, Utrakhand. FDC product of AZE and TEL was prepared with a label claim of 8 mg and 40 mg, respectively. Solvents like Acetonitrile, Methanol were HPLC grade, and reagents Ammonium dihydrogen orthophosphate, Orthophosphoric acid, Hydrochloric acid, Sodium hydroxide, Hydrogen peroxide were analytical grade, and high purity Milli-Q water for buffer was obtained from M/s. Kusum Healthcare Pvt. Ltd., Bhiwadi, and Rajasthan.

**HPLC Method Development**

**Chromatographic Conditions and Instrument**

The performance of chromatographic analysis RP-HPLC instrument equipped with photodiode-array detection (PDA) detector was used (Shimadzu make, model-LC-2010 CHT with empower software). The stationary phase is Inertsil C-18 column with 150×4.6mm×5µm, HPLC column oven temperature 40°C, autosampler temperature 10°C, with the flow of 1.5 mL/min. The injection volume was kept at 10 µL with a run time of 12 minutes, and a wavelength of 254 nm was optimized. The mobile phase in gradient mode is shown in Table 1. The mobile phase in gradient mode is shown in Table 1. Other instruments used in the validation like analytical balance, ultra sonicator, and pH meter were calibrated.

**Preparation of Buffer Solution**

About 2 gm of Ammonium dihydrogen orthophosphate was weighed and transferred to a container of 1000 mL of distilled water mix well to dissolve completely. The pH of the final solution was made up to 3.0 ± 0.05 with diluted orthophosphoric acid, and the solution was filtered using a 0.45 µm millipore membrane filter.

**Preparation of Diluent**

Prepare a degassed mixture of Acetonitrile and buffer in the ratio of 25:75 (v/v) respectively and used as the diluent and blank solution.

**Table 1:** Combinations of different mobile phases at different time intervals.

<table>
<thead>
<tr>
<th>Time</th>
<th>Pump A % (Acetonitrile)</th>
<th>Pump B % (Buffer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>3.00</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>5.00</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>7.00</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>8.00</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>12.00</td>
<td>45</td>
<td>55</td>
</tr>
</tbody>
</table>
**Preparation of 0.1N Sodium Hydroxide Solution**
About 4.0 gm of sodium hydroxide pellets were weighed, poured in a 1000 mL volumetric flask containing water, appropriately dissolved, and diluted with water to make up the final volume.

**Preparation of Stock and Standard Solution**
Stock solution for AZE and TEL was prepared by transferring about 40.33 mg of AZE and 201.50 mg of TEL into a 100 mL calibrated volumetric flask. Accurately measured 70 mL of diluent (Buffer: Acetonitrile 25.75 %v/v) was added, and this solution was sonicated to dissolve all the content, and a final volume of 100 mL was made with the same diluent. This solution is considered a stock solution.

Approximately 5 mL of aliquot was transferred into a 50 mL volumetric flask to make up the final volume with diluent from this stock solution. All the contents were mixed well to get the final concentration of 40.16 µg/mL AZE and 200.81 µg/mL of TEL. The resultant solution was filtered using a 0.45 µm PVDF membrane filter and used as the standard solution.

**Preparation of Placebo Solution**
The placebo equivalent to 80 mg AZE and 400 mg of TEL (excluding active substance, about 2060 mg placebo, the average weight of 1 tablet is 254 mg) was weighed and transferred into a 200 mL volumetric flask. In this solution, approximately 120 mL of diluent was added and allowed for sonication till 20 minutes with intermittent stirring; the final volume was made with diluent after cooling the solution and mixed well. A volume of 10 mL of this solution was transferred to 100 mL volumetric flask, and volumes were made with diluent to mix well. This was filtered using a 0.45 µm PVDF membrane filter.

**Preparation of Sample Solution**
About 20 intact tablets of AZE and TEL were weighed, crushed, and transferred powder weight equivalent to 10 tablets into a 200 mL volumetric flask. To this mixture, around 120 mL of diluent was added and sonicated for 20 minutes. Total volume was made up of diluent. A volume of 10 mL from this was transferred into a 100 mL volumetric flask and made up the volume with diluent. The final volume was passed through a 0.45 µm PVDF filter.

**Method Validation**
The method for validation proposed in this study was validated for various parameters like system suitability, specificity, precision (system, method, intermediate), accuracy, linearity, the limit of detection (LoD), the limit of quantitation (LoQ), robustness, force degradation study and stability in analytical solution (SIAS).

**Criteria for System Suitability**
The % RSD for the respective area, tailing factor, theoretical plate, and retention time were the chromatographic criteria chosen to conduct the test—these parameters employed to confirm the resolution and reproducibility towards the protocol. A fundamental fact that gets underlined here is that whatever equipment, electronics, and test portions constitute nonavoidable systems need to be tested. Around six replicates injection of standard solution were evaluated and a chromatogram was recorded.

**Specificity**
Specificity towards analytical protocol was assessed by giving inputs of a single injection of Blank, placebo, standard, and sample solution. Samples were checked for interference peak at the Rt of the analyte in the chromatogram.

**Precision**
The precision of the analytical method is established by performing three types of precision study. i.e., System precision, method precision and intermediate precision study or ruggedness.

*System Precision:* To assess system precision, the samples of AZE and TEL were injected into the system as six replicate injections of standard solutions as per the methodology mentioned earlier. The relative standard deviation for peak area should be NMT than 2.0%.

*Method precision:* After establishing system suitability as per methodology, the blank solution was injected in single, and six sample solutions that were prepared independently were injected in duplicate. The assay value observed for six sample solutions should meet specifications. The RSD for observed should be NMT 2.0%.

*Intermediate precision (Ruggedness):* It was conducted by employing different (day, HPLC, Analyst, and period). Six sample solutions from the same batch (as used for method precision) were prepared for intermediate precision. After establishing system suitability as per methodology, the blank solution was injected in a single, and six sample solutions that were prepared independently were injected in duplicate. The assay value observed for six sample solutions should meet specifications. The relative standard deviation for observed assay values of six samples should not be more than 2.0%. The overall RSD should be NMT 2.0%.

**Robustness**
It was calculated by performing intentional deviations in the protocol example flow rate ± 10%, column temperature ± 5°C, and wavelength ± 5 nm. After establishing system suitability as per methodology, again establish system suitability criteria and inject sample solutions (Sample prepared for method precision) in duplicate as per methods prepared for robustness study.

**Accuracy (Recovery)**
In three sets, test samples were made ready (level of 50, 100, and 150%) as per the label claim denoting AZE 8 mg and TEL 40 mg strength. After establishing system suitability as per methodology, injections of accuracy
samples were given in duplicate. Accuracy was determined against their respective standard solution as per their strength. The individual % Recovery at all recovery levels is within 98.0 to 102%. The % relative standard deviation at all recovery levels should not be more than 2.0%.

**Linearity**
The aliquots from the standard solution were taken for AZE and TEL in a separate volumetric flask, and this sample is diluted to achieve drug concentration 20.14–60.42 µg/mL and 99.91–299.73 µg/mL of AZE and TEL, respectively. The different solutions of concentration in the range 50–150 % were injected in duplicate. The linearity regression coefficient for AZE and TEL obtained from the graph should not be less than 0.995.

**Limit of Detection (LoD)/Limit of Quantitation (LoQ)**
The detection limit was calculated as the minimum concentration, which can be detected by a signal-to-noise ratio of 3:1. The LoQ was estimated as the lowest possible amount, accurately and precisely quantified using a signal-to-noise ratio of 10:1.

**Stability in Analytical Solution**
The stability of the analytical solution was carried out by injecting method precision sample solution initially and at specific time intervals to monitor change in concentration with time.

**Forced Degradation Studies**
To observe the behavior of the sample through forced degradation study, the drug product and placebo (control sample) were kept under acid hydrolysis, base hydrolysis, oxidation, UV light exposure, thermal exposure, and humidity exposure conditions. After completing the degradation study, they were diluted to get a resultant concentration equivalent to 40 µg/mL of AZE and 200 µg/mL of TEL (as stated on the label claim of marketed formulation). Then about 10μL portion of degraded solution were injected into the chromatographic system to perform analysis using pre-stated HPLC condition.

**Acid hydrolysis:** For this analysis, samples of drug products and placebo were treated with 1 mL of 0.1N HCl, kept at 80°C in the water bath for 1 hour and neutralized using 1 mL 0.1N NaOH.

**Base Hydrolysis:** Here the drug product and placebo were treated with 1 mL of 0.1N NaOH, kept at 80°C in the water bath for 1 hr, and neutralize with 1 mL 0.1N HCl.

**Oxidative degradation:** The drug product and placebo were treated with 0.1 mL of 30% H₂O₂ and stored at 80°C for 1 hr.

**Thermal degradation:** The test, as well as placebo, were kept inside the oven for 8 hours at 80°C.

**Humidity exposure:** The sample of the drug product and placebo was exposed for 8 hours above 75% RH.

**Photolytic degradation:** The drug product and placebo samples were placed under ultraviolet at 254 nm (short wavelength) in an ultraviolet region chamber for 8 hours.

**RESULT AND DISCUSSION**

**Method Development**
When analyzed UV spectrophotometrically, the overlain spectra of TEL and AZE showed isoabsorptive point at 254 nm; therefore, 254 nm was fixed as the detection wavelength for both drugs. The retention time for TEL and AZE were found to be 2.68 and 5.1 minutes, respectively, at a flow rate of 1.5 mL/min in gradient mode. The well-resolved peaks with resolution factor was found to be 11.5 (Fig. 3).

**System Suitability**
For the sample to pass the test few criteria were set up according to which the theoretical plate count for TEL and AZE peaks in the first injection of the standard was MT 2000. A tailing factor to TEL and AZE peaks in the first injection of the standard should be NMT than 2.0 and Resolution between two peaks MT 2. (Table 2). The % RSD of peak area should be NMT 2.0% (Fig. 3).

**Table 2: System suitability parameters**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters</th>
<th>TEL</th>
<th>AZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Retention time</td>
<td>2.683</td>
<td>5.100</td>
</tr>
<tr>
<td>2</td>
<td>Resolution</td>
<td>-</td>
<td>11.448</td>
</tr>
<tr>
<td>3</td>
<td>Theoretical plate</td>
<td>3298</td>
<td>7518</td>
</tr>
<tr>
<td>4</td>
<td>Tailing factor</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Fig. 3:** The chromatogram of (A) Blank, (B) Placebo, (C) standard solution and (D) sample solution under optimized chromatographic conditions.
Specificity
There should be no interference from blank and placebo at the Rt of AZE and TEL peak (Fig. 3). Retention time of the main peak from sample preparation should be similar to that of standard preparation. The purity angle of AZE and TEL peak is less than the purity threshold in the chromatogram of standard solution and the sample solution.

Precision
System precision was carried out by injecting six replicate injections of standard solution and relative standard deviation (% RSD), which was calculated by 0.2 and 0.1% for TEL and AZE. Method precision was carried out using injecting 6 independently prepared solutions in duplicate and the mean area of two injections utilized to calculate % of label claim. The %RSD of six sample solutions was 0.2 and 0.2% for TEL and AZE, respectively. The % RSD of six intermediate precision sample solutions was 0.6 and 0.8% for TEL and AZE, respectively. The overall relative standard deviation of twelve assay values; six method precision samples, and six of Intermediate precision samples was 0.4 and 0.6% for TEL and AZE. All the parameters and outcomes of the precision study can be observed in (Table 3 and 4).

Accuracy (Recovery)
The extraction recovery or accuracy of the assay method was calculated at three levels i.e., 50, 100, and 150% of sample concentration, and the obtained result was in the range of 98.7–100.9% and 98.1–101.7% for AZE and TEL, respectively (Table 4). The standard error for recovery samples was found at 0.04.

Robustness
The robustness of the method was established by varying the flow rate, wavelength, and column oven temperature. Analysis of standard solution and sample was performed in each varied condition.

The % RSD for Area and Rt of AZE and TEL peak obtained from six replicate standard injections should not be more than 2.0. Tailing Factor & Resolution Factor should not be more than 2.0 and Theoretical Plates should not be less than 2000. The robustness results were shown in (Table 4).

Assay
The results for both drugs showed 100.5% (TEL) and 100.4% (AZE) assays (Table 4).

Linearity
The calibration curve for TEL and AZE was linear over 99.91–299.73 µg/mL and 20.14–60.42 µg/mL, respectively (Fig. 4 A and B). The regression coefficient (R²) value was found to be 0.99814 and 0.99729 for TEL and AZE respectively as shown in (Table 4).

LoD/LoQ
The LOD was 11.21 and 2.75 µg/mL for TEL and AZE respectively, while LOQ was 33.96 µg/mL in TEL and 8.35 µg/mL for AZE observed in (Table 4).

### Table 3: Results of method precision

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Average area of sample</th>
<th>Average area of standard</th>
<th>Assay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AZE</td>
<td>TEL</td>
<td>AZE</td>
</tr>
<tr>
<td>1</td>
<td>727397</td>
<td>3438920</td>
<td>728628</td>
</tr>
<tr>
<td>2</td>
<td>729295</td>
<td>3443413</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>729796</td>
<td>3449211</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>728141</td>
<td>3449959</td>
<td>728628</td>
</tr>
<tr>
<td>5</td>
<td>730407</td>
<td>3459519</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>727387</td>
<td>3450405</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%RSD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Summary of validation parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Telmisartan</th>
<th>Azelnidipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>No interference</td>
<td>No interference</td>
</tr>
<tr>
<td>Linearity range (µg/mL)</td>
<td>99.91–299.73</td>
<td>20.14–60.42</td>
</tr>
<tr>
<td>Slope</td>
<td>17462.07</td>
<td>18805.38</td>
</tr>
<tr>
<td>Intercept</td>
<td>-21177.94</td>
<td>-24356.55</td>
</tr>
<tr>
<td>Regression coefficient</td>
<td>0.99814</td>
<td>0.99729</td>
</tr>
<tr>
<td>Limit of detection (µg/mL)</td>
<td>11.21</td>
<td>2.75</td>
</tr>
<tr>
<td>Limit of quantitation (µg/mL)</td>
<td>33.96</td>
<td>8.35</td>
</tr>
<tr>
<td>Precision (%RSD)</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Method precision</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Intermediate precision</td>
<td>0.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Ruggedness (n=6*2)</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Accuracy %</td>
<td>98.1–101.7</td>
<td>98.7–100.9</td>
</tr>
<tr>
<td>Robustness (Mean of % RSD)</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>% Assay</td>
<td>100.5</td>
<td>100.4</td>
</tr>
</tbody>
</table>
Supplemental Immunization Activities (SIAS)
It was assessed by examining the sample at 0 hour (Method Precision first injection of sample1) and approximately 6, 10, and 22 hour time intervals, and percentage changes were monitored in peak area with time. No significant difference was observed in system suitability parameters and area count as compared to the initial result of method precision and result obtained at a different time interval.

Forced Degradation Study
After the records of force degradation study were observed, it has been seen that TEL was susceptible to acid, oxidation, and humidity, whereas AZE were found to undergo only acid, base, oxidation, and humidity exposed degradation conditions (Figs. 5-9). Summary of Force degradation study of Azelnidipine and Telmisartan mentioned in (Table 5).

As per results, a unique, simple, precise, accurate, reproducible, and stability-indicating RP-HPLC method was developed to achieve a simultaneous estimation of Azelnidipine and Telmisartan. The method showed good sensitivity towards estimating Azelnidipine & Telmisartan in FDC with no external interference from degradation products. Assays for drugs were found to be 100.4±0.2% of Azelnidipine and 100.5±0.2% of Telmisartan. We can conclude that as the method could separate the drugs from their degradation products, we may employ it to analyze stability samples of Azelnidipine & Telmisartan.

<table>
<thead>
<tr>
<th>Degradation Condition</th>
<th>% Assay TEL</th>
<th>% Assay AZE</th>
<th>% Degradation TEL</th>
<th>% Degradation AZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidic hydrolysis</td>
<td>98.8</td>
<td>97.4</td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Basic hydrolysis</td>
<td>100.8</td>
<td>99.3</td>
<td>-0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Oxidation</td>
<td>98.3</td>
<td>97.8</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Humidity</td>
<td>99.1</td>
<td>98.6</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Photolytic</td>
<td>101.0</td>
<td>100.4</td>
<td>-0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Thermal</td>
<td>100.3</td>
<td>100.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Fig. 4 (A): Graphical representation of linearity of TEL

Fig. 4 (B): Graphical representation of linearity of AZE

Table 5: Summary of Force degradation study of AZE and TEL

Fig. 5: Acid degradation of the placebo as well as sample in acidic conditions.

Fig. 6: Force degradation of Azelnidipine and Telmisartan in basic environmental conditions.

Fig. 7: Chromatograms of Placebo and sample test solution showing peroxide degradation pattern.

Fig. 8: Chromatogram showing thermal degradation of (A) placebo; (B) sample.
Acknowledgments
The authors are thankful to M/s. Synokem Pharmaceutical Limited, Haridwar, Uttarakhand, M/s. Kusum Healthcare Pvt. Ltd., Bhiwadi, Rajasthan, and School of Medical and Allied Sciences, KR Mangalam University, Gurugram, for their support towards the completion of the present analytical investigation.

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