Stability-Indicating HPLC Method for Quantification of Celecoxib and Diacerein Along With Its Impurities in Capsule Dosage Form

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A novel stability-indicating reverse phase high performance liquid chromatography method was developed and validated for the simultaneous determination of Celecoxib (CEL) and Diacerein (DIN) and its impurities in capsule dosage form. The method was developed using L1 column with gradient using the mobile phase consist of Solution A (pH = 2.3 buffer) and Solution B (methanol and acetonitrile; 50 : 50, v/v). The eluted compounds were monitored at 255 nm. CEL and DIN were subjected to oxidative, acid, base, hydrolytic, thermal and photolytic stress conditions. The developed method was validated as per International Conference on Harmonisation guidelines with respect to specificity, linearity, limit of detection, limit of quantitation, accuracy, precision and robustness. The limit of quantitation results were ranged from 0.07 to 0.09 µg/mL for CEL impurities and 0.052 to 0.065 µg/mL for DIN impurities. This method is suitable for the estimation of impurities and assay of CEL and DIN in capsules dosage forms.

Introduction

Celecoxib (CEL) is a non-steroidal anti-inflammatory drug (NSAIDS). It is effectively used in the treatment of pain and inflammation. This new agent may be as effective as traditional NSAIDS, showing anti-inflammatory, analgesic and antipyretic activities, and it is comparable with known traditional NSAIDS that inhibits the enzyme cyclooxygenase (COX) which is involved in the synthesis of prostaglandins. CEL is a COX-2-specific inhibitor, promoting a reduction of the inflammatory process and maintaining normal physiological levels of prostanooids in stomach and kidneys. It appears to have a gastrointestinal safety profile superior to the traditional NSAIDS. It is available in 100 and 200 mg capsules. Diacerein (DIN) (diacetylrhein) is used in the treatment of osteoarthritis. It is a readily obtained in few synthetic steps from naturally occurring glucopyranoside aloe. It is the diacetylated derivative of rhein, and it is available in 50 mg capsules (1–7). CEL and DIN capsules produced significant improvement in pain and physical function (8). Imp-A and Imp-D are of CEL impurities, and Rhein (DIN-A), Aloe-Emodin (DIN-B) and Emodin (DIN-C) are of DIN impurities. The chemical structures of CEL and DIN and their impurities are presented in Figure 1.

The literature survey reveals that high performance liquid chromatography (HPLC) and LC–MS methods for CEL (9–16) and HPLC, high performance thin layer chromatography methods (17–23) for DIN are available. However, no method was reported for the estimation of CEL and DIN and their impurities by HPLC in any of combination dosage forms. The present research work is to develop a stability-indicating HPLC method for the simultaneous determination of CEL and DIN and its related impurities in capsules dosage form.

Chemicals and reagents

The purity of all the chemicals were >96%. CEL and DIN combined capsules (100 mg of CEL and 50 mg of DIN) and standards of CEL (99.7%), DIN (99.9%) and their impurities, namely Imp-A (96.2), Imp-D (99.7%), DIN-A (97.4%), DIN-B (97.9%) and DIN-C (98.4), were supplied by Simpson Pharma Ltd., Mumbai, India. The HPLC grade acetonitrile and analytical grade orthophosphoric acid and triethylamine were purchased from Merck, Darmstadt, Germany. High-purity water was prepared by using a Milli-Q Plus water purification system (Millipore, Milford, MA, USA). Standard and test samples were prepared in N, N-dimethylacetamide, methanol and Milli-Q water in the ratio 50 : 37 : 13 (v/v/v) as diluent.

Experimental

Analysis was performed with an Agilent 1260 HPLC (Waldbonn, Germany). HPLC system equipped with a quaternary solvent manager, sample manager, column-heating compartment and photodiode array detector (PDA). The output signal was monitored and processed using ChemStation software. Cintex digital water bath was used for hydrolysis studies. Thermal stability studies were performed in a dry air oven (Cintex, Mumbai, India). Mobile phase was degassed by ultrasonication (Sonicator, Power sonic 420, Labtech, Kyonggi-do, Korea) and filtered through a 0.45-µm Nylon filter (PALL Life Sciences, NY, USA).

Related substances and assay standard and sample preparation

Preparation of standard solutions

A stock solution of CEL and DIN (500 µg mL⁻¹ of CEL and 250 µg mL⁻¹ of DIN) was prepared by dissolving appropriate amount of drugs in diluent. Working solutions of 20 µg mL⁻¹ of CEL and 10 µg mL⁻¹ of DIN, and 1 µg mL⁻¹ of CEL and 0.5 µg mL⁻¹ of DIN were prepared from the above stock solution for related substance and assay determination, respectively. A stock solution of individual impurity (mixture of Imp-A, Imp-D, DIN-A, DIN-B and DIN-C) at 100 µg mL⁻¹ was prepared in diluent.

Preparation of sample solution

Capsule powder (100/50 mg tablets) equivalent to 50 mg of DIN (100 mg of CEL) drug was dissolved in diluent with sonication for 20 min to give a solution containing 500 µg mL⁻¹ of CEL and 250 µg mL⁻¹ of DIN. The above solution was centrifuged...
at 4,000 rpm for 5 min in order to eliminate insoluble excipients. The supernatant liquid was used for RS analysis. A solution of 20 mg mL\(^{-1}\) of CEL and 10 mg mL\(^{-1}\) of DIN was prepared by diluting supernatant solution for assay analysis.

**Chromatographic conditions**

The method was developed using Inertsil ODS 3V, 250 × 4.6 mm; 5 μm column (GL Sciences, Inc., Japan) with mobile phase containing a gradient mixture of Solvents A and B. Buffer with 0.1% triethylamine, pH adjusted to 2.3 with phosphoric acid was used as Solvent A and methanol and acetonitrile in the ratio 50 : 50 (v/v) was used as Solvent B. The gradient program (T/ %B) was set as 0/60, 9.5/70, 11/80, 13/90, 17/90, 17.5/60 and 24/60. The flow rate of the mobile phase was 1.0 mL min\(^{-1}\). The column temperature was maintained at 40°C, and the chromatography was monitored at 255 nm. Injection volume was 20 μL.

**Method validation**

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. The method was validated according to International Conference on Harmonization Q2 (R1) guidelines (24) for validation of analytical procedures in order to determine the specificity, linearity, limit of detection (LOD), limit of quantitation (LOQ), accuracy, precision and robustness.

**Solution stability**

The stability of CEL and DIN in solution for assay was determined by leaving test solutions of the sample and reference standards in tightly capped volumetric flasks at room temperature and were assayed at 12 h intervals up to 48 h. The stability of CEL and DIN and their impurities in solution for related substance...
The precision of the method was verified by injecting six individual preparations of dosage form (CEL 100 mg and DIN 50 mg) spiked with 0.2% of its impurities. CEL impurities are spiked at 0.2% with respect to CEL concentration 500 μg mL⁻¹ and DIN impurities are spiked at 0.2% with respect to DIN concentration 250 μg mL⁻¹. % RSD of area for each impurity was calculated. Assay method precision was evaluated by carrying out six independent test preparations of CEL and DIN at 20 μg mL⁻¹ of CEL and 10 μg mL⁻¹ of DIN against qualified reference standard.

The same experiment was repeated on different day with different chromatographic system and different analyst to find variability.

Robustness
To determine the robustness of the method, experimental conditions were deliberately altered and the resolution between CEL and DIN impurities and tailing factors for CEL and DIN and their impurities were recorded. The effect of flow rate was evaluated at 0.8 and 1.2 mL min⁻¹ instead of 1.0 mL min⁻¹. The effect of the column temperature was studied at 35 and 45°C instead of 40°C. The effect of the percent organic strength was studied by varying acetonitrile ± 5%. The effect of pH of mobile-phase buffer was studied by varying pH ± 0.1 units of method pH (2.3) keeping other mobile-phase components constant.

RESULTS
Method development
The main target of the chromatographic method is to get the separation of impurities, namely Imp-A, Imp-D of CEL, DIN-A, DIN-B and DIN-C of DIN and the degradation products generated during stress studies from the analyte peaks along with the actives.

Chromatographic conditions with Inertsil ODS 3V, 250 × 4.6 mm; 5 μm column and the mobile phase consists of Solution A (0.1% triethylamine buffer pH adjusted to 2.3 with orthophosphoric acid) and Solution B (methanol and acetonitrile in the ratio 50:50, v/v), with gradient program: time (t)/% Solution B: 0/60, 9.5/70, 11/80, 13/90, 17/90, 17.5/60 and 24/60 at detection wavelength 255 nm were suitable in separating CEL, DIN and its impurities from one other (Figure 2A and B). Details of relative retention time (RT), relative response factor, resolution and tailing factor values are summarized in Table I.

Method validation
Validation was performed on the developed analytical method for its acceptable performance to ensure suitability of indent purpose. The validation parameters like accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, ruggedness and robustness were executed and established method conditions to meet the requirements to execute the analysis of CEL and DIN combination dosage product. Under the specificity experiment samples were stressed various stress conditions and analyzed along with unstressed samples. CEL was found to be very stable under all degradation conditions but DIN showed significant degradation leading to the formation of two major

Linearity
Linearity test solutions for CEL and DIN and their impurities were prepared by diluting stock solutions to required concentrations. The solutions were prepared at six concentration levels from LOQ to 200% of the specification level 0.2% (LOQ: 0.10, 0.15, 0.20, 0.30 and 0.40%). Linearity test solutions for the assay method were prepared from CEL and DIN stock solutions at six concentration levels from 50 to 200% of assay concentration (10, 15, 20, 25, 30 and 40 μg mL⁻¹ for CEL and 5, 7.5, 10, 12.5, 15 and 20 μg mL⁻¹ for DIN). The peak area versus concentration data were treated by least-squares linear regression analysis.

Limits of detection and quantitation
The LOD and LOQ for CEL and DIN and their impurities were determined at a signal-to-noise ratios of 3:1 and 10:1, respectively, by injecting a series of dilute solutions with known concentrations. Precision study was also carried out at the LOQ level by injecting six individual preparations and calculated % relative standard deviation (RSD) of the area.

Accuracy
The accuracy of the assay method was evaluated in triplicate at five concentration levels 50, 75, 100, 150 and 200% on capsules (100/50 mg capsules). Standards of CEL and DIN were spiked in the dosage form test preparation at different concentration levels namely LOQ: 0.1, 0.2, 0.3 and 0.4% with respect to their test concentration in triplicate and evaluated for accuracy of impurities. The percentages of recoveries for CEL and DIN and their impurities were calculated.

precision
The precision of the method was calculated by leaving spiked sample solution in a tightly capped volumetric flask at room temperature for 48 h and measuring the amounts of the five impurities at every 12 h.

Specificity
Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities. The specificity of the developed LC method for CEL and DIN was carried out in presence of its five impurities. Stress studies were performed at the concentration 500 μg mL⁻¹ of CEL and 250 μg mL⁻¹ of DIN on capsules to show the stability-indicating property of the method. The forced degradation was carried out on individual dosage forms to prove that degradants are not co-eluting with any of the known impurities and active molecule.

Intentional degradation was attempted to stress condition of UV light (254 nm), heat (60°C for 30 h), acid (1 N HCl at 60°C for 6 h), base (1 N NaOH at 60°C for 6 h), water (at 60°C for 6 h) and oxidation (3.0% H₂O₂ at 60°C for 6 h) for CEL and acid (0.01 N HCl at 60°C for 4 h), base (0.01 N NaOH at 25°C for 1 h)), water (at 60°C for 4 h) and oxidation (3.0% H₂O₂ at 60°C for 3 h) for DIN to evaluate the ability of the proposed method to separate CEL and DIN from their degradation products. Peak purity test was carried out for CEL and DIN peaks by using PDA detector for stress samples.
Figure 2. (A) Typical chromatograms of CEL and DIN at 255 nm (A, blank; B, impurity mixture; C, RS standard solution). (B) Typical chromatograms of CEL and DIN at 255 nm (A, spiked sample; B, assay standard).
unknowns at RT 9.06 and 10.47 min especially in oxidative and basic conditions (Figure 3A and B). Results of forced degradation studies are reported in Table II. Linearity, limit of quantitation, LOD, precision and precision at LOQ for CEL, DIN and its impurities were established and presented in Table III. The percentage recovery of CEL and DIN in the assay determination and the percentage recovery of impurities in the estimation of impurities are presented in Table IV.

**DISCUSSION**

**Method development**

Experiments were carried out in various combinations using different stationary phases like C8, C18, phenyl, etc., different mobile phases containing buffers-like phosphate, sulfate and acetate at different pH conditions together with acetonitrile and methanol. Among these the experiment with orthophosphoric acid buffer with pH 2.3 and organic solvent (Solvent A is buffer and Solvent B is methanol, acetonitrile in the ratio 50:50, v/v) was found suitable for separation of impurities. However, it is necessary to improve the resolution between impurities and CEL and the peak shapes of CEL and DIN. Buffer solution of mobile phase was replaced with 0.1% triethylamine pH adjusted to 2.3 with orthophosphoric acid had shown better resolution and improved peak shapes. Effect of variations with respect to buffer pH and % of acetonitrile were studied. The tailing of CEL and DIN was high, and resolution was reduced between peaks at higher and lower pH compared with pH 2.3. The resolution of DIN-C from Imp-A was poor when the % of acetonitrile content changes. Based on the experiments with different gradient programs a gradient: 10% during solution stability experiment.

**Method validation**

**Solution stability**

Assay (% of both drugs during solution stability experiments was within ±1%. The variability in the estimation of CEL and DIN impurities was within ±10% during solution stability experiment. The results from solution stability experiments confirmed that standard and sample solutions were stable up to 48 h for both assay and related substances analysis.

**Results of forced degradation studies**

All forced degradation samples were analyzed at an initial concentration 500 μg mL⁻¹ of CEL and 250 μg mL⁻¹ of DIN with LC conditions using PDA detector to ensure the homogeneity and purity of CEL and DIN peaks. During the stress studies, it was observed that CEL was stable, but DIN was degraded significantly. Two major unknowns of DIN at 9.06 and 10.47 min peaks were observed in oxidative (3.0% H₂O₂ at 60°C for 3 h) and base (0.01 N NaOH at 25°C for 1 h) conditions (Figure 3A and B).

The peak purity test result derived from PDA confirmed that CEL and DIN peaks were pure and homogeneous in all the analyzed stress conditions and thus confirms the stability-indicating power of the developed method. Results of forced degradation studies were reported in Table II.

**Identification of major degradation products (at 9.06 and 10.47 RT) formed in base stress**

LC–MS/MS analysis was carried out for the base stress sample of DIN using Waters 2695 Alliance mass spectrometer. The degradation products formed at the RT of 9.06 and 10.47 min had shown the same mass number for both peaks as 326.2 which was 42 less than mass than DIN mass 368.2. The fragmentation pattern shown in Figure 5 indicates that degradants were Monoacetyl Rhein-I and Monoacetyl Rhein-II.

**Linearity**

The linearity calibration plot for the assay method was obtained over the calibration ranges tested and correlation coefficient obtained was >0.999 for both CEL and DIN. Linear calibration plot for impurities was obtained over the calibration ranges tested, i.e., LOQ to 0.40% for impurities. The correlation coefficient obtained was >0.998 (Table III). The above results show that an excellent correlation existed between the peak area and the concentration of all five impurities.

**Limits of detection and quantitation**

The LOD and LOQ values were established based on the signal-to-noise ratios. Precision at LOQ values for CEL and DIN and its five impurities were established and reported in Table III.

**Accuracy**

The percentage recovery was ranged from 98.4 to 100.5% for CEL and from 98.0 to 100.4% for DIN in the analysis assay. The percentage recovery of impurities varied from 96.2 to 101.8% in

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**Table I**

Summary of Peak Details

<table>
<thead>
<tr>
<th>Peak</th>
<th>RT (min)</th>
<th>RRT *</th>
<th>Relative response factor</th>
<th>Resolution</th>
<th>Tailing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diacerein</td>
<td>7.42</td>
<td>1.0</td>
<td>1.0</td>
<td>–</td>
<td>1.1</td>
</tr>
<tr>
<td>Aloe-Emodin</td>
<td>9.99</td>
<td>1.35</td>
<td>0.74</td>
<td>10.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Rhein</td>
<td>11.68</td>
<td>1.57</td>
<td>0.71</td>
<td>6.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Imp-D</td>
<td>13.29</td>
<td>0.95</td>
<td>0.89</td>
<td>6.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>13.86</td>
<td>1.0</td>
<td>1.0</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Imp-A</td>
<td>14.83</td>
<td>1.05</td>
<td>0.83</td>
<td>4.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Emodin</td>
<td>15.74</td>
<td>2.12</td>
<td>0.57</td>
<td>6.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*R*Relative retention times (RRT) for Imp-D and Imp-C were calculated against the RT of CEL and RRT of Rhein, Aloe-Emodin and Emodin were calculated against the RT of DIN.

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impurities have sufficient absorbance for the measurement. Hence, the 255 nm was selected as suitable wavelength for the estimation of impurities. An overlay UV spectrum with CEL, DIN and their impurities has presented in Figure 4.
Figure 3. (A) Typical chromatograms of CEL and DIN at 255 nm (forced degradation study) (A, DIN acid degradation; B, DIN base degradation; C, DIN peroxide degradation; D, DIN heat degradation). (B) Typical chromatograms of CEL and DIN at 255 nm (forced degradation study) (A, CEL acid degradation; B, CEL base degradation; C, CEL peroxide degradation; D, CEL heat degradation).
Figure 3. Continued

A. Celecoxib acid degradation

B. Celecoxib base degradation

C. Celecoxib peroxide degradation

D. Celecoxib heat degradation
Table II
Specificity

<table>
<thead>
<tr>
<th>Stress condition (degradation)</th>
<th>% of impurities formed (% of area normalization)</th>
<th>Peak purity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imp-D</td>
<td>Imp-A</td>
</tr>
<tr>
<td>As such sample</td>
<td>ND</td>
<td>0.03</td>
</tr>
<tr>
<td>Oxidation</td>
<td>ND</td>
<td>0.04</td>
</tr>
<tr>
<td>Acid</td>
<td>ND</td>
<td>0.03</td>
</tr>
<tr>
<td>Base</td>
<td>ND</td>
<td>0.03</td>
</tr>
<tr>
<td>Thermal</td>
<td>ND</td>
<td>0.03</td>
</tr>
<tr>
<td>Water</td>
<td>ND</td>
<td>0.03</td>
</tr>
<tr>
<td>Photolytic</td>
<td>ND</td>
<td>0.03</td>
</tr>
<tr>
<td>ND, not detected.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ND, not detected.

*Peak purity numbers represented as per Agilent ChemStation software algorithm. Peak is pure only if purity value is >990.

Table III
Regression and Precision Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Celecoxib</th>
<th>Diacerein</th>
<th>Imp-D</th>
<th>Imp-A</th>
<th>Aloe-Emodin</th>
<th>Rhein</th>
<th>Emodin</th>
<th>LOD (µg/mL)</th>
<th>LOQ (µg/mL)</th>
<th>Correlation coefficient</th>
<th>Bias at 100% response</th>
<th>Precision (%RSD)</th>
<th>Intermediate precision (%RSD)</th>
<th>Precision at LOQ (%RSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOD (µg/mL)</td>
<td>0.020</td>
<td>0.013</td>
<td>0.028</td>
<td>0.021</td>
<td>0.017</td>
<td>0.021</td>
<td>0.016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6%</td>
<td>0.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>LOQ (µg/mL)</td>
<td>0.065</td>
<td>0.0425</td>
<td>0.09</td>
<td>0.07</td>
<td>0.057</td>
<td>0.065</td>
<td>0.0525</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5%</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.9994</td>
<td>0.9992</td>
<td>0.9887</td>
<td>0.9986</td>
<td>0.9986</td>
<td>0.9988</td>
<td>0.9994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bias at 100% response</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precision (%RSD)</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0.9%</td>
<td>0.7%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>1.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate precision (%RSD)</td>
<td>0.8%</td>
<td>0.4%</td>
<td>1.9%</td>
<td>1.5%</td>
<td>1.2%</td>
<td>1.3%</td>
<td>1.6%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precision at LOQ (%RSD)</td>
<td>0.9%</td>
<td>0.8%</td>
<td>2.0%</td>
<td>1.9%</td>
<td>1.7%</td>
<td>1.7%</td>
<td>1.5%</td>
<td></td>
<td></td>
<td></td>
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</table>

Table IV
Evaluation of Accuracy

<table>
<thead>
<tr>
<th>Amount spiked*</th>
<th>% of Recovery*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Diacerein</td>
</tr>
<tr>
<td>LOQ</td>
<td>99.5 ± 0.9</td>
</tr>
<tr>
<td>50%</td>
<td>99.7 ± 0.7</td>
</tr>
<tr>
<td>100%</td>
<td>98.9 ± 0.8</td>
</tr>
<tr>
<td>150%</td>
<td>99.5 ± 0.9</td>
</tr>
<tr>
<td>200%</td>
<td>100.1 ± 0.4</td>
</tr>
</tbody>
</table>

*Amount of five impurities spiked with respect to 0.2% specification level individually to CEL and DIN.

*Mean ± %RSD for three determinations at each level.

Figure 4. Spectra overlay of CEL, DIN and their impurities.
the analysis of impurities. The % recovery values for CEL and DIN and their impurities are presented in Table IV.

**Precision**

The assay results of CEL and DIN during the assay method repeatability study was showed, %RSD of 0.6 and 0.8 for CEL and DIN, respectively. Similarly, the results of all the impurities (Imp-A, Imp-D, DIN-A, DIN-B and DIN-C) in related substance method repeatability study was showed <1.5% RSD for each individual impurity. Data of repeat experiment were showed <0.8% RSD for assay and <2.6% RSD for impurities. These results are conforming good precision of the method. The % RSD values are presented in Table III.

**Robustness**

In all the deliberate varied chromatographic conditions like flow rate (± 0.2 mL min⁻¹ of 1.0 mL min⁻¹), column temperature (± 5°C of 40°C), composition of organic solvent (± 5% of method organic solvent) and pH of mobile-phase buffer (± 0.1 pH 2.3), all analytes were adequately resolved and elution orders remained unchanged. The resolution between all pair compounds was > 2.0 and tailing factor for CEL and DIN and their impurities was < 1.5. The variability in the estimation of CEL and DIN impurities was within ± 10%.

**Conclusion**

The rapid reproducible gradient reverse phase high performance liquid chromatography method developed for quantitative analysis of CEL and DIN and related substances in pharmaceutical dosage form is precise, accurate, linear, robust and specific. Satisfactory results were obtained from validation of the method. The method is stability indicating and can be used for routine analysis of production samples to check the stability (25) of CEL and DIN in combined dosage form.

**References**


