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Advanced forced degradation technique for simultaneous estimation of azelnidipine and telmisartan implementing AQbD approach in its tablet dosage form

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***Abstract*---**For simultaneous estimation of Azelnidipine and Telmisartan in pharmaceutical dosage form, a simple, rapid, precise and reproducible RP-HPLC method was developed. Separation was achieved on a Phenomanax Luna C_{18}; 5 µm, 150 mm × 4.6 mm i.d. column using water and methanol 50: 50 (v/v) as mobile phase and detected at 256 nm using PDA detector. Azelnidipine and Telmisartan were exposed to thermal, photolytic, hydrolytic and oxidative stress conditions and stressed samples were analyzed by the proposed method. Linearity, precision, accuracy, specificity and robustness were studied as reported in the International Council for Harmonization guidelines. Linearity of the proposed method was in the range of 4-12 µg mL^{-1} (r^2 = 0.998) for Azelnidipine and 20-60 µg mL^{-1} (r^2 = 0.997) for Telmisartan. Limits of Detection were 1.041 µg mL^{-1} and 0.208 µg mL^{-1}, while Limits of Quantitation were 3.155 µg mL^{-1} and 0.631 µg mL^{-1} for Azelnidipine and Telmisartan respectively. Degradation products produced as a result of stress studies did not interfere with the detection. The proposed stability studies method for simultaneous estimation was found to be specific, accurate and economical that could be applied for routine analysis of drugs in bulk and multi component formulations in quality control laboratories.

***Keywords*---**method development, azelnidipine, telmisartan, RP-HPLC, stability studies.

Introduction

Cardiovascular impairments such as coronary heart disease, heart attack, heart stroke, atrial fibrillation, pulmonary artery disease, and myocardial infarction, as well as progressive renal illness and cognitive decline, are all caused by hypertension. [1] Azelnidipine (AZEL; structure shown in Figure 1) is a modern dihydropyridine calcium passage antagonist that is specific for the L-type calcium passages and has been approved by the FDA for the treatment of hypertension patients.[2] The antihypertensive effects of AZEL could be comparable to those of another drug, amlodipine.[3] AZEL was found more lipid-soluble and has greater selectivity for the vascular surface than older generational calcium passage antagonists, and blood flow to the brain was significantly increased in animal experiments treated with AZEL.[4]

Telmisartan (TELM; structure shown in Figure 2) is an angiotensin II receptor blocker used to treat mild to severe hypertension.[5-7] TELM has a high affinity for type 1 angiotensin II receptors. TELM is more lipophilic angiotensin (II) receptor blocker than most other angiotensin (II) receptor inhibitors, which improves oral absorption and tissue and cell permeation.[8] TELM also has an effect on the nuclear hormone receptor superfamily ligand triggered transcription elements peroxisome proliferator triggered receptors. TELM, a drug that treats both diabetes and hypertension, could be an option for alternative therapy.[9, 10]

The combination of AZEL and TELM is recommended for the patients of hypertension. In the patients, the combination lowers blood pressure, allows the heart to function more effectively, allows blood to flow more effectively to many tissues, and reducing heart-related chest pain by increasing oxygen flow throughout the body.

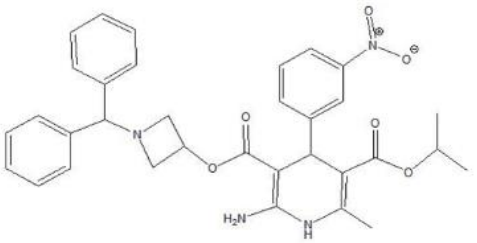

Figure 1 Structure of AZEL

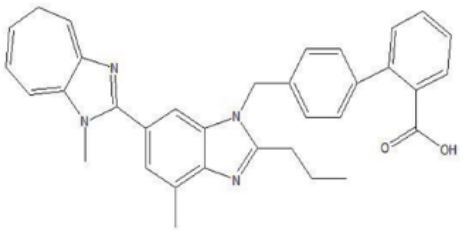

Figure 2 Structure of TELM

The combination of AZEL and TELM, as a tablet formulation, is used to manage increased blood pressure (hypertension). In this combination, AZEL relaxes the blood vessels and makes the heart very effective in pumping blood all through the body while TELM suppresses the β_2-adrenoreceptor activity. RP-HPLC is one of the fastest growing analytical techniques for analysis of drugs. Its simplicity, high specificity and high sensitivity makes it ideal for analysis of both drugs in many dosage forms.[7]

Literature studies revealed few analytical methods for the estimation of AZEL and TELM as a single component or combine with other drug formulation. These methods were: spectrophotometric,[11] High Performance Liquid Chromatography (HPLC),[12-18] liquid chromatography– mass spectrometry (LC–MS),[19,20] high-performance liquid chromatography mass analysis capabilities of mass spectrometry (HPLC-MS-MS).[21] So far only two HPLC method have been reported for their simultaneous estimation in their combined dosage form.[22,23] Also, the reported method did not use any methodical approach like DoE. Further, the reported methodologies had used high amount of phosphate buffer and acetonitrilne in mobile phase for separation of AZEL and TELM. So, there is a need to develop HPLC method (cost effective and rapid) using DoE approach along with study of various factors during forced degradation of AZEL and TELM. The developed method was then validated as per ICH guidelines.[24]

Stability studies are important for determining storage conditions and reanalysis periods for newly developed pharmaceutical formulations as well as formulations that are already on the market. Stability studies must be carried out in accordance with ICH or other regulatory guidelines. The concept of stability is well defined in ICH quality guidelines and could be applied in all areas of medicine manufacturing and control. Acid hydrolysis, alkaline hydrolysis and degradation reactions such as photolytic, thermal and oxidation are all part of the stability testing process. It was preferable to first develop an analytical method and then validate it in accordance with regulatory ICH Q1A (R2) guidelines.[25] Understanding how the potency and wellbeing of pharmaceuticals is affected by a drug substance's consistency varying with times and the nature of deterioration products generated under different storage circumstances is critical.[26-27] Stability demonstrating methods must be completely validated, as they are a group of analytical methodologies, which demonstrate the sample stability.

According to ICH Q8 (Quality by Design), QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[29-33] AQbD (Analytical QbD) is a science and risk-based paradigm for analytical method development, endeavoring for understanding the predefined objectives to control the Critical Method Variables (CMVs) affecting the Critical Method Attributes (CMAs) to achieve enhanced method performance, high robustness, ruggedness and flexibility for continuous improvement.[34-36] In this article, a new HPLC method is demonstrated to provide sensitive, precise, and accurate quantification of AZEL and TELM in tablet dosage form. This method allows simple and shorter runtime.

Materials and Methods

Instrumentation

The analysis was performed using High-performance liquid chromatography (Waters 2695 model HPLC system, Autosampler) accompanying with photodiode detector (2998 model) in the procedure development and combination analysis of TELM and AZEL. The very fine particles loaded Phenomanax Luna 150 mm length C_{18} column (4.6 mm inner diameter, 5.0 µm particle size) was utilised for TELM and AZEL chromatographic separation. Flow rate of 1 mL/min was utilised for the TELM and AZEL chromatographic separation. The mobile phase components of water and Methanol (50% volume: 50% volume) was used. The complete process was completed at room temperature. To every sample, the specimen (20 µL) was chosen as the injection quantity. The quantitation of TELM and AZEL was done at 256 nm.

Chemicals

Merck (India) supplied analytical mark hydrochloric acid, phosphoric acid, hydrogen peroxide, sodium hydroxide and HPLC mark methanol along with Milli-Q system base prepared Milli-Q water was employed in the combined analysis of TELM and AZEL.

Reference drugs and tablets

Glenmark pharmaceuticals Ltd. (India) had provided AZEL and Torrent Pharmaceutical Ltd, India had provided TELM reference bulk samples. Uniaz T tablet type (Torrent Pharmaceutical Ltd, India) was bought from a local shop drug retailer and claimed to comprise 8 mg of AZEL and 40 mg of TELM.

Selection of wavelength for detection

Standard solution of AZEL (8.0 µg mL^{-1}) and standard solution of TELM (40.0 µg mL^{-1}) were scanned between 200 - 400 nm using UV-visible spectrophotometer. Wavelength was selected from the overlay spectra of above solutions.

Selection of mobile phase

The final optimized conditions were determined by evaluating the effect of two factors X_1 (mobile phase ratio) and X_2 (Flow rate). Based on retention time and resolution, the optimized conditions selected was mobile phase water: methanol (50:50 v/v) and the flow rate of 1.0 mL/min.

Procedure for AZEL and TELM combination solutions

A stock TELM and AZEL combination solution (concentration: 400 µg/mL TELM and 80 µg/mL AZEL) was made by solubilizing 40 mg of TELM and 8 mg of AZEL in 60 mL of mobile phase and then diluting to 100 mL volume with the very similar solvent. A working TELM and AZEL combination solution (concentration: 40 µg/mL TELM and 8 µg/mL AZEL) was made by solubilizing 1 mL of stock

TELM and AZEL combination solution in 6 mL of mobile phase and then diluting up to 10 mL volume with the very similar solvent.

Procedure for evaluating AZEL and TELM combination in bulk

Different aliquots covering 4.0 µg/mL – 12.0 µg/mL of AZEL and 20 µg/mL – 60 µg/mL of TELM were correctly shifted from stock AZEL and TELM combination solution (concentration: 80 µg/mL AZEL and 400 µg/mL TELM) into separate sets of 10 mL volumetric flasks and then diluting to 10 mL volume with the very similar solvent. A 20 µL volume of each solution were infused into 150 mm length C_{18} column (4.6 mm inner diameter, 5.0 µm particle size) and evaluated with 'stability-indicating HPLC methodology' conditions given (see section: Instrumentation and analysing conditions of AZEL and TELM combination). The peak response values of AZEL and TELM at 256 nm were recorded and afterward calibration curves of AZEL and TELM were drawn followed by calculating regression equations of AZEL and TELM. The concentration of AZEL and TELM in nameless specimen solution can be assessed by exploiting the calibration curves of AZEL and TELM or regression equations of AZEL and TELM, respectively.

Procedure for evaluating AZEL and TELM combination in tablets

A total of 20 tablets (UNIAZ -T tablet, claimed to comprise 8 mg of AZEL and 40 mg of TELM) were collected, with the median weight estimated and mashed to a fine powder. Dose comparable to 8 mg of AZEL and 40 mg of TELM was shifted to a volumetric flask (100 mL), blended with 60 mL of mobile and stirred with ultra sonicator at 27 °C for 30 min, diluted with similar solvent up to 100 mL mark and filtered via a filter membrane (0.45 µm). This tablet stock solution has 80 µg/mL AZEL and 400 µg/mL TELM. A sample tablet TELM and AZEL combination solution (theoretical concentration: 40 µg/mL TELM and 8 µg/mL AZEL) for the analysis was made by solubilizing 1 mL of tablet stock AZEL and TELM combination solution in 6 mL of mobile phase and then diluting to 10 mL volume with the very similar solvent. A 20 µL volume of sample tablet AZEL and TELM combination solution were infused into 150 mm length C_{18} column (4.6 mm inner diameter, 5.0 µm particle size) and evaluated with 'stability-indicating HPLC methodology' conditions specified (see section: Instrumentation and analysing conditions of AZEL and TELM combination). At 256 nm, the peak response values of AZEL and TELM were measured. The amount of AZEL and TELM in the tablet specimen solution can be established by employing AZEL and TELM calibration curves or regression equations, respectively.

Forced degradation

Degradation studies were performed according to ICH guidelines.

Preparation of standard stock solution

Accurately weighed 8.0 mg of AZEL and 40.0 mg of TELM was transferred to 100 mL volumetric flask and volume was made up to the mark with diluents (80 µg mL^{-1} and 400 µg mL^{-1}).

Preparation of sample stock solution

A total of 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 40.0 mg TELM and 8.0 mg AZEL was taken in to a 100 mL volumetric flask and 60 mL methanol was added. The solution was shaken for 15 minutes and sonicated for 10 minutes. The volume was made up to the mark with diluents. These (AZEL 80 µg mL^{-1} and TELM 400 µg mL^{-1}) solutions were then filtered using Whatman filter paper no. 1.

For Acid degradation

(1) Blank: In a 10 mL volumetric flask, 5 mL of 0.1 N HCl was taken and the volume was made up to the mark with mobile phase.
(2) AZEL standard degradation solution: In a 10 mL volumetric flask, 1 mL of AZEL (80 µg mL^{-1}) standard stock solution was taken and 5 mL of 0.1 N HCl was added. It was kept aside for 4 hours and then neutralized with 5 mL of 0.1 N NaOH to stop further degradation. The volume was made up to the mark with mobile phase.
(3) TELM standard degradation solution: In a 10 mL volumetric flask, 1 mL of TELM (400 µg mL^{-1}) standard stock solution was taken and 5 mL of 0.1 N HCl was added. It was kept aside for 4 hours and then neutralized with 5 mL of 0.1 N NaOH to stop further degradation. The volume was made up to the mark with mobile phase.
(4) Formulation degradation: In a 10 mL volumetric flask, 1 mL sample stock solution was taken and 5 mL of 0.1 N HCl was added. It was kept aside for 4 hours and then neutralized with 5 mL of 0.1 N NaOH to stop further degradation. The volume was made up to the mark with mobile phase.

For Base degradation

1. Blank: In a 10 mL volumetric flask, 5 mL of 0.1 N NaOH was taken and the volume was made up to the mark with mobile phase.
2. AZEL standard degradation: In a 10 mL volumetric flask, 1 mL AZEL (80 µg mL^{-1}) standard stock solution was taken and 5 mL of 0.1 N NaOH was added. It was kept aside for 5 hours and then neutralized with 5 mL of 0.1 N HCl to stop further degradation. The volume was made up to the mark with mobile phase.
3. TELM standard degradation: In a 10 mL volumetric flask, 1 mL TELM (400 µg mL^{-1}) standard stock solution was taken and 2 mL of 0.1 N NaOH was added. It was kept aside for 5 hours and then neutralized with 2 mL of 0.1 N HCl to stop further degradation. The volume was made up to the mark with mobile phase.
4. Formulation degradation: In a 10 mL volumetric flask, 1 mL sample stock solution was taken and 5 mL of 0.1 N NaOH was added. It was kept aside for 5 hours and then neutralized with 2 mL of 0.1 N HCl to stop further degradation. The volume was made up to the mark with mobile phase.

For Oxidation degradation

(1) Blank: In a 10 mL volumetric flask, 5 mL of 3% H_2O_2 was taken and the volume was made up to the mark with mobile phase.
(2) AZEL standard degradation: In a 10 mL volumetric flask, 1 mL AZEL (80 µg mL^{-1}) standard stock solution was taken and 5 mL of 3% H_2O_2 was added. It was kept aside for 4 hours and then, the volume was made up to the mark with mobile phase.
(3) TELM standard degradation: In a 10 mL volumetric flask, 1 mL TELM (400 µg mL^{-1}) standard stock solution was taken and 5 mL of 3% H_2O_2 was added. It was kept aside for 4 hours and then, the volume was made up to the mark with mobile phase.
(4) Formulation degradation: In a 10 mL volumetric flask, 1 mL sample stock solution was taken and 5 mL of 3% H_2O_2 was added. It was kept aside for 4 hours and then, the volume was made up to the mark with mobile phase.

For Thermal degradation

1. Blank: In a 10 mL volumetric flask, 2 mL mobile phase was taken and the volume was made up to the mark with mobile phase. The solution was kept aside at 80 ^{0}C temperature for 4 hours.
2. AZEL standard degradation: In a 10 mL volumetric flask, 1 mL AZEL (80 µg mL^{-1}) standard stock solution was taken and the volume was made up to the mark with mobile phase. The solution was kept aside at 80 ^{0}C temperature for 4 hours.
3. TELM standard degradation: In a 10 mL volumetric flask, 1 mL TELM (400 µg mL^{-1}) standard stock solution was taken and the volume was made up to the mark with mobile phase. The solution was kept aside at 80 ^{0}C temperature for 4 hours.
4. Formulation degradation: In a 10 mL volumetric flask, 1 mL sample stock solution was taken and the volume was made up to the mark with mobile phase. The solution was kept aside at 80 ^{0}C temperature for 4 hours.

For Photo degradation

(1) Blank: In a 10 mL volumetric flask, 2 mL mobile phase was taken and the volume was made up to the mark with mobile phase. The solution was exposed with sunlight for 12 hours.
(2) AZEL standard degradation: In a 10 mL volumetric flask, 1 mL AZEL (80 µg mL^{-1}) standard stock solution was taken and the volume was made up to the mark with mobile phase. The solution was exposed with sunlight for 12 hours.
(3) TELM standard degradation: In a 10 mL volumetric flask, 1 mL TELM (400 µg mL^{-1}) standard stock solution was taken and the volume was made up to the mark with mobile phase. The solution was kept aside in UV chamber for 3 hours.
(4) Formulation degradation: In a 10 mL volumetric flask, 1 mL sample stock solution was taken and the volume was made up to the mark with mobile phase. The solution was exposed with sunlight for 12 hours.

Method validation

The optimized RP-HPLC method was validated concerning the following parameters. The validation was performed as per the ICH guidelines.

Linearity

Linearity for AZEL and TELM were assessed by analysis of combined standard solution in range of 4-12 µg mL^{-1} and 20-60 µg mL^{-1} respectively, in terms of slope, intercept and correlation coefficient value. The graph of peak area obtained v/s respective concentration was plotted.

Accuracy

The accuracy of the assay method for AZEL and TELM was evaluated in triplicate (n = 3) at concentrations of 8 µg mL^{-1} and 40 µg mL^{-1} respectively for RP-HPLC (80, 100 and 120 % level) of the drug product and the recovery was calculated for each externally spiked concentration.

Precision

The precision includes intra-day and inter-day precision studies; each of three times on the same day for intra-day and different days for inter day precision. The concentrations of 8 µg mL^{-1} of AZEL and 40 µg mL^{-1} of TELM for RP-HPLC were selected and results were represented in the form of % RSD values.

Specificity

In the specificity parameter, the chromatogram of the placebo sample and standard sample were compared. The specificity of developed RP-HPLC method was also studied by determining the interferences of degradation products.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The detection limit and quantification limit were calculated using the standard equation method. The equation for LOD = $3.3 \times \sigma/S$ and LOQ = $10 \times \sigma/S$ where, σ = standard deviation of the response and S = slope of the calibration curve.

Robustness

The robustness was studied by evaluating the effect of small but deliberate variations in the chromatographic conditions. For RP-HPLC, the robustness of the method was studied by deliberately varying parameters like change in mobile phase ratio, pH and flow rate. The robustness of both the developed methods was calculated in terms of % RSD.

Analysis of Marketed formulation (Assay)

Label claim: AZEL - 8 mg and TELM- 40 mg. To prepare sample stock solution, 20 tablets were accurately weighed and powdered. Tablet powder equivalent to 40 mg

TELM and 8 mg AZEL was taken in to a 50 mL volumetric flask and 30 mL methanol was added. It was shaken for 15 minutes and sonicated for 10 minutes and the volume was made up to the mark with diluents. These (AZEL 80 µg mL^{-1} and TELM 400 µg mL^{-1}) solutions were filtered with Whatman filter paper no. 1.

Working sample preparation

In a 10 mL volumetric flask, 1 mL sample stock solution was taken and the volume was made up to the mark with water. The solution formed had a concentration of 8 µg mL^{-1} of AZEL and 40 µg mL^{-1} of TELM. Then, this solution was injected for assay analysis.

Results and Discussion

To record the spectra of the two drugs, 256 nm was selected as suitable wavelength for estimation as shown in the chromatogram of Figure 3.

Software Aided Method Optimization

The final optimized conditions were determined by evaluating the effect of two factors X_1 (mobile phase ratio) and X_2 (Flow rate). The desirability plot for AZEL and TELM was generated by the Design Expert software. Based on retention time and resolution, the optimized conditions selected was mobile phase were water: methanol (50:50 v/v) and the flow rate of 1.0 mL/min. Table 1 shows the system suitability parameters of selected mobile phase.

Stability indicating properties of AZEL and TELM was performed by forced degradation study and was evaluated by HPLC. The standard and sample stability chromatogram is shown in Figure 4 and Figure 5. The standard for stability of AZEL and TELM is shown in Table 2. By using central composite design, 13 runs were performed for AZEL and TELM. The proposed regression equations for various chromatographic responses of both regression equations for various chromatographic responses of both the drugs are given in Table 3. 3D surface plot of effects of interaction of X_1 and X_2 on retention time and resolution of AZEL and TELM is shown in Figure 6.

It was observed that the best-fitted model for both drugs was quadratic and linear model. The optimization, while a positive value represents an effect that favors optimization while a negative value indicates the inverse relationship between factors and response.

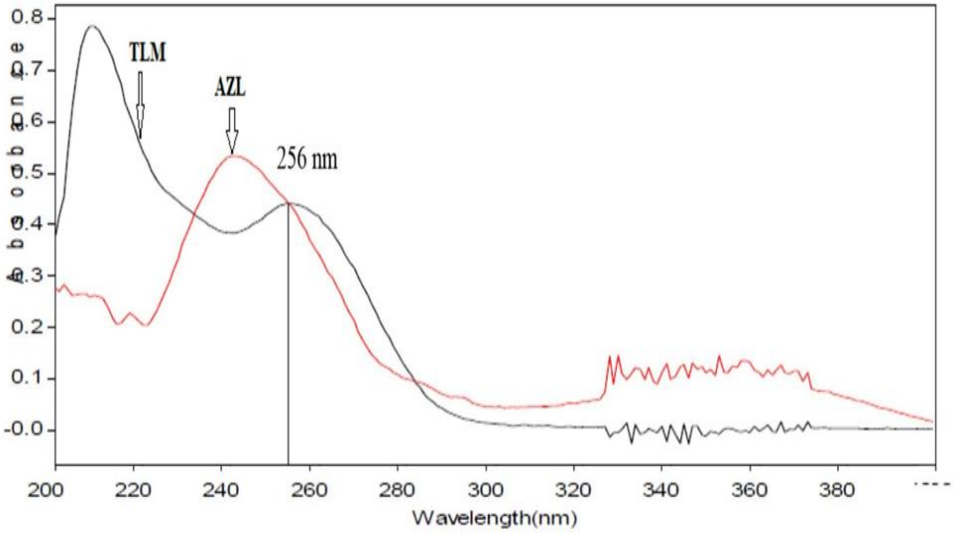

Figure 3 UV spectra: AZEL (8 µg mL^{-1}) and TELM (40 µg mL^{-1}) in Methanol (Best absorbance at 256 nm)

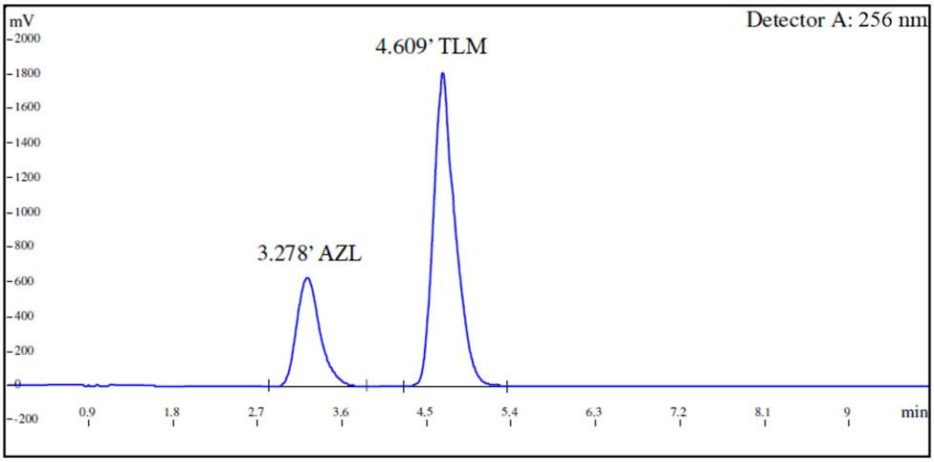

Figure 4 Chromatogram of AZEL (8 µg mL^{-1}) and TELM (50 µg mL^{-1}) in Buffer (pH – 4.0): Methanol (65:35 % v/v), standard for stability

Table 1 System suitability parameters

Parameters	AZEL	TELM
Retention time (min)	3.278	4.609
Theoretical plates	7765	14469
Asymmetry	1.1	1.1
Resolution	4.9	

Table 2 AZEL and TELM Standard for stability

Name of Drug	Area
AZEL	4112208
TELM	8830872

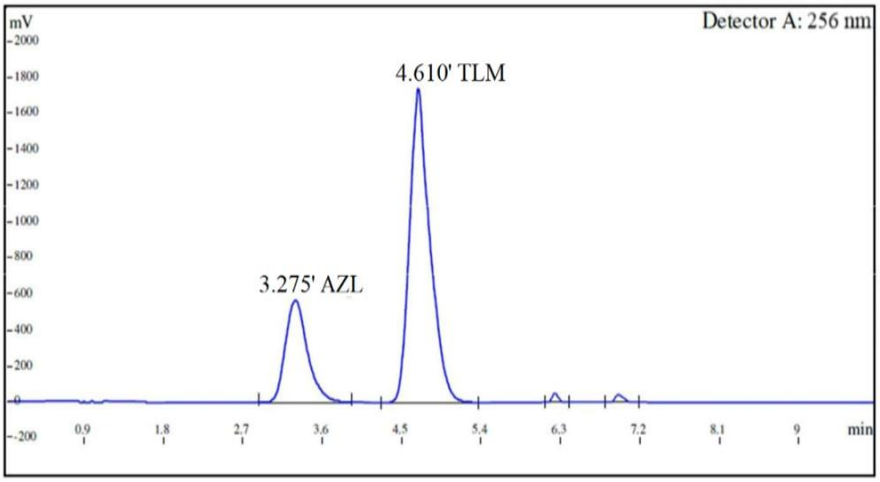

Figure 5 Chromatogram of stability for AZEL and TELM sample solution

Table 3 Regression equations for AZEL and TELM

Drug	Regression equations
AZEL	4.62 + 2.02 X1 - 2.52 X2 + 0.86 X1 X2 + 1.50 X12 +0.73 X22
TELM	3.56 + 2.28 X1 - 1.06 X2 + 1.85 X1X2 + 2.82 X12 + 2.43 X22

The decrease in peak area of AZEL and TELM indicates that the drug was degraded in all selected conditions. Results showed that the drug AZEL was degraded highest in base condition and least in photolytic condition and TELM was degraded highest in thermal condition and least in photolytic condition (Figure 7-11). All the stress condition has been studied and the % degradation is shown in Table 4 and Table 5.

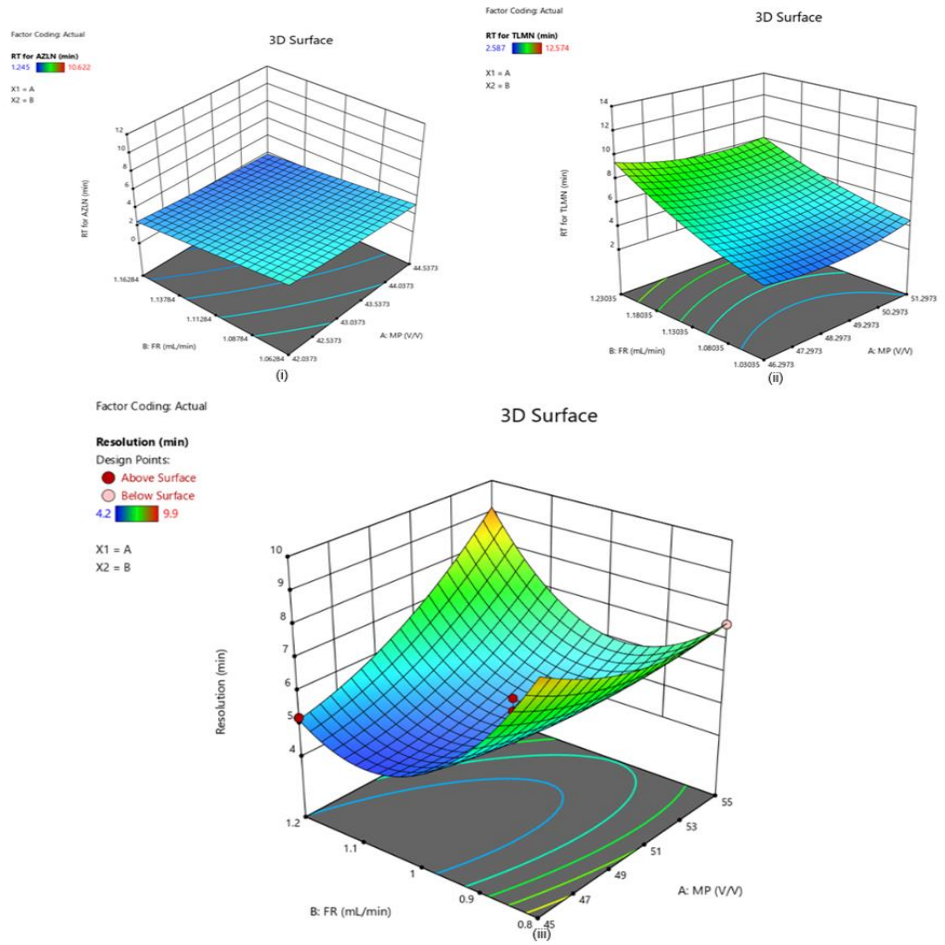

Figure 6 3D surface plot of effect of interaction of X1 and X2 on: (i) retention time of AZEL (ii) retention time of TELM (iii) Resolution of AZEL and TELM

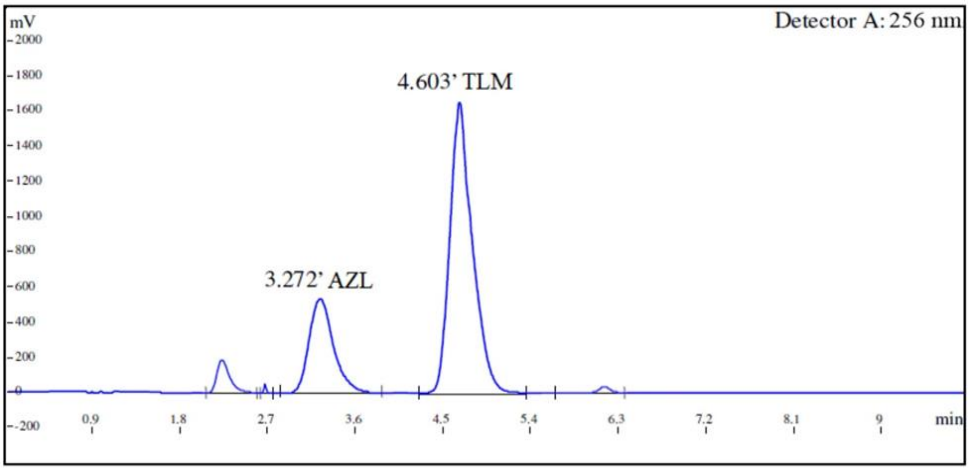

Figure 7 Chromatogram of stability for AZEL and TELM Acid Degradation sample

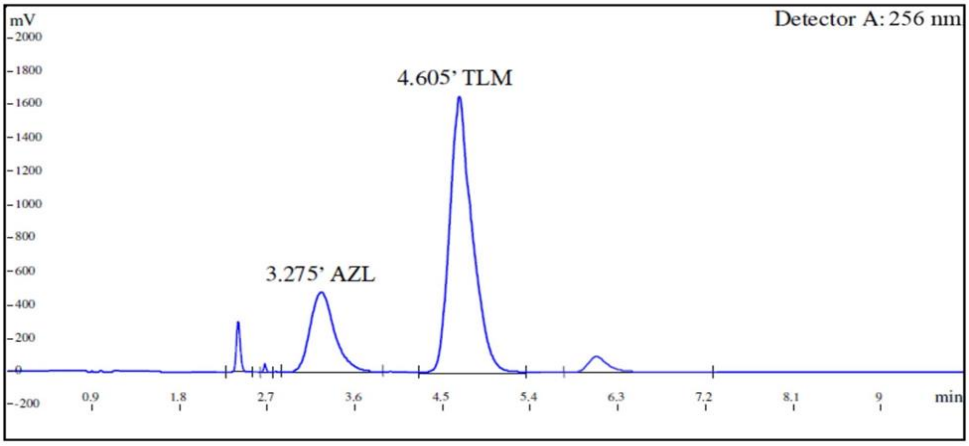

Figure 8 Chromatogram of stability for AZEL and TELM Base Degradation sample

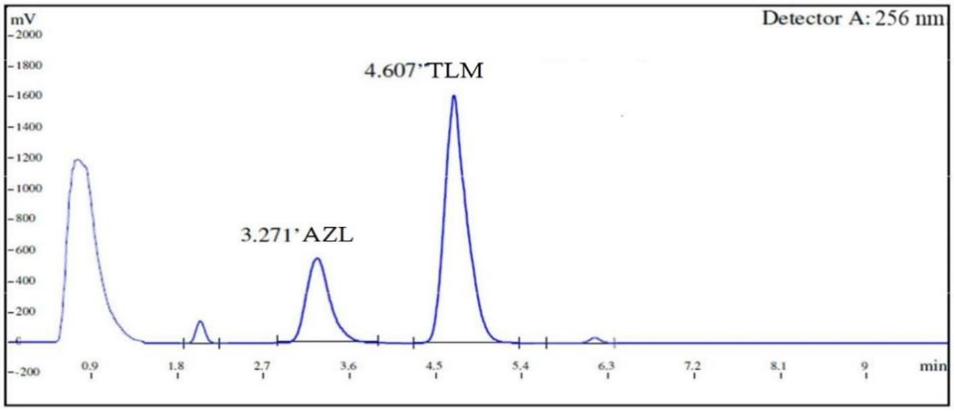

Figure 9 Chromatogram of stability for AZEL and TELM Oxidation Degradation sample

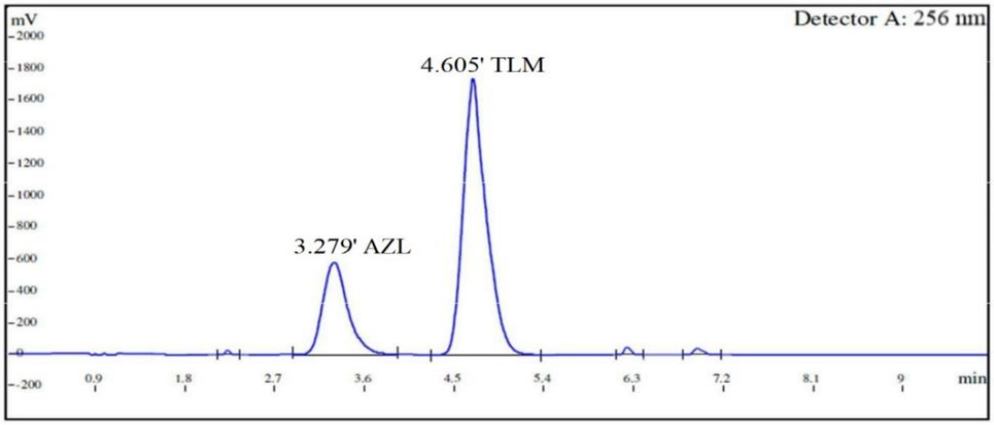

Figure 10 Chromatogram of stability for AZEL and TELM Photo Degradation sample

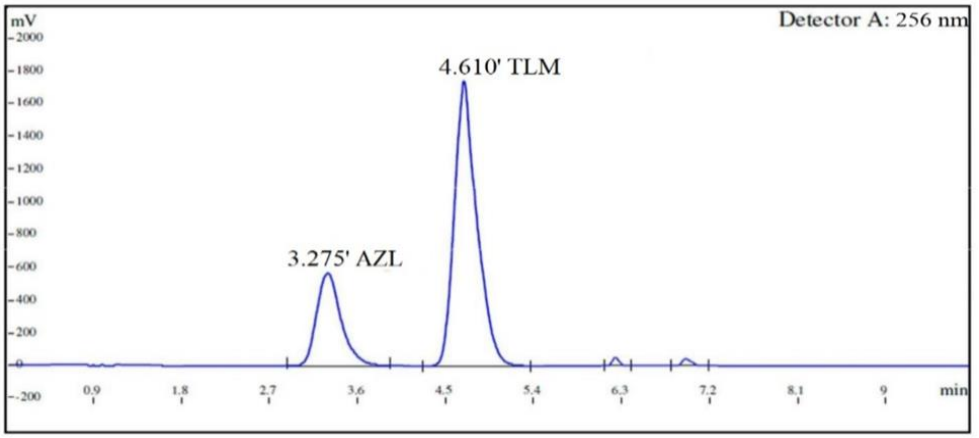

Figure 11 Chromatogram of stability for AZEL and TELM Thermal Degradation sample

Table 4 Magnitude of degradation of AZEL on exposure to various conditions

Parameters	Standard		Sample	
	Area	% Degradation	Area	% Degradation
Acid	3355562	18.4	3326776	19.1
Base	3462479	15.8	3446030	16.2
Thermal	3931270	4.4	3910709	4.9
Oxidation	3799680	8.6	3733885	9.2
Photo	3902485	5.1	3886036	5.5

Table 5 Magnitude of degradation of TELM on exposure to various conditions

Parameters	Standard		Sample	
	Area	% Degradation	Area	% Degradation
Acid	8309850	5.9	8248034	6.6
Base	7921292	10.3	7877138	10.8
Thermal	8512960	3.6	8486468	3.9
Oxidation	8495299	3.8	8459975	4.2
Photo	8468806	4.1	8406990	4.8

The developed stability indicating method was validated as per ICH guidelines. The response of the drug was found to be strictly linear in the investigation concentration range, the % RSD values of intra-day and inter-day precision were <2%, indicating that the method was sufficiently precise. Good recoveries of the drug and the resolution for the drug peak was >2%. The validation parameters are summarized in Table 6.

Table 6 Summary of validation parameters of HPLC method

Sr. No.	Validation Parameters	Results	
		AZEL	TELM
1	Linearity Range	4-12 µg mL^{-1}	20-80 µg mL^{-1}

	Straight line equation	y = 203696.705x + 2424183.739	y = 135389.489x + 3218705.325
	Correlation Coefficient (r^2)	0.998	0.997
2	Precision (%RSD): Intra-day	0.4	0.5
	Precision (%RSD): Inter-day	0.5	0.3
3	Mean % recovery	99.8-100.5	99.3-99.9
4	Specificity	Specific	
5	LOD	1.041 µg mL^{-1}	0.208 µg mL^{-1}
6	LOQ	3.155 µg mL^{-1}	0.631 µg mL^{-1}
7	Robustness: Change in flow rate Robustness: Change in Mobile phase ratio Robustness: Change in mobile phase pH	Complies	

Conclusion

The method was developed and optimized by applying AQbD approach for simultaneous determination of AZEL and TELM. The run time is 13 min for proposed method so rapid determination of analytes is carried out within which the two drugs are well resolved. The AQbD method applied to reduce trails so less time consuming and accurate method. High percentages of the recovery showed that this method is free from interference of excipients present in the formulation. Therefore, this exclusive method may be applied for routine analysis of both drugs in bulk and multi component formulation in quality control laboratories. The method was validated as per ICH guidelines.

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