Journal of Engineering in Industrial Research

2024, Volume 5, Issue 3

Original Research Article

Specific Stability Indicating RP-UPLC Method for Simultaneous Estimation of Atorvastatin Calcium and Teneligliptin Hydrobromide Hydrate

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Citation A.K.J. Vyas, C. Khandala, C. Jadav, A.I. Patel, A.V. Dudhrejiya, S.R. Shah. Specific Stability Indicating RP-UPLC Method for Simultaneous Estimation of Atorvastatin Calcium and Teneligliptin Hydrobromide Hydrate. *J. Eng. Ind. Res.* **2024**, 5 (3):142-151.

https://doi.org/10.48309/jeires.2024.212596

Article info:
Submitted: 2024-09-03
Revised: 2024-11-25
Accepted: 2024-12-24
ID: JEIRES-2409-1127

Keywords:
Atorvastatin calcium; Teneligliptin hydrobromide hydrate; Stability-indicating RP-UPLC; Quantitative analysis; Synthetic mixture analysis; ICH guideline (Q_2R_2)

ABSTRACT

A stability-indicating RP-UPLC method was developed for the quantitative analysis of atorvastatin calcium (ATV) and teneligliptin hydrobromide hydrate (TEN) in the presence of degradants. The separation was achieved using an Acquity UPLC BEH C18 column with a mobile phase composed of Methanol, Ammonium Acetate Buffer, and Acetonitrile (60:35:5, pH 6.5, adjusted with OPA). The method was optimized with a flow rate of 1.0 mL/min, an injection volume of 2 µL, and UV detection at 245 nm. The retention times (RT) were 2.2 min for ATV and 0.9 min for TEN. The calibration ranges were 10–30 µg/mL for ATV and 5-15 µg/mL for TEN, with correlation coefficients of 0.9999 and 0.9998, respectively. The method demonstrated accuracy ranging from 99.70-100.07% for ATV and 99.60-100.40% for TEN. The limits of detection (LOD) were 1.8543 µg/mL for ATV and 0.6228 µg/mL for TEN, while the limits of quantification (LOQ) were 1.0319 µg/mL for ATV and 3.1271 µg/mL for TEN. The results confirm that the developed method is robust and suitable for the analysis of a synthetic mixture in the presence of generated degradants.

Introduction

ATV is a medication that inhibits HMG-CoA reductase and is prescribed for managing hyperlipidemia. The structure of the ATV is presented as Figure 1 [1].TEN is used to manage type 2 diabetes (T2D). The structure of TEN is shown in Figure 2 [2].

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Combination therapy can help improve lipid and glucose metabolism, as well as reduce the risk of cardiovascular disease in these patients [3]. Forced degradation, more than accelerated conditions [4], influences drug quality over time due to environmental factors [5-6]. Impurities affect both stability and pharmacology [7-12]. Analytical quality by design (AQbD) and central composite design (CCD) are instrumental in developing RP-HPLC methods, conducting stress testing, and ensuring regulatory compliance [13-15].

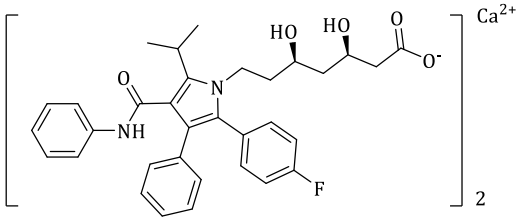

Figure 1: ATV structure

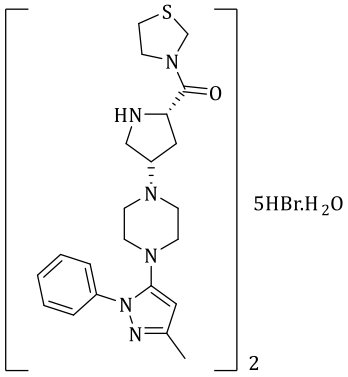

Figure 2: TEN structure

Analytical methods for drug estimation include UV spectrophotometry [16-21], RP-HPLC [22-27], stability-indicating HPLC [28-32], UPLC [33], stability-indicating UPLC [34], and LC-MS/MS [35]. One study on a stability-indicating RP-HPLC method [36] with a 17 min run time for degradation study and a 10 min RT for basic hydrolysis showed inadequate % degradation. RP-UPLC offers shorter run times, reduced solvent use, and cost savings, promoting eco-friendliness. Thus, developing and validating an isocratic RP-UPLC stability-indicating method for routine analysis is valuable.

The goal of stability and related substance studies is to demonstrate how the quality of a drug or product changes over time due to different environmental factors [37-39]. HPLC, UV spectrophotometric methods, and LC-MS/MS are essential for quality control in pharmaceuticals, where substance stability and integrity are crucial for safety and efficacy [40-46]. The stability and pharmacological effects of active pharmaceutical ingredients (APIs) and drug products are impacted by the presence of contaminants [47-51]. AQbD and CCD help ensure adherence to regulations in the development of stability-indicating techniques, stress testing, and the RP-HPLC method [52]. RP-UPLC offers shorter run times, reduced solvent use, and cost savings, promoting eco-friendliness [53-56].

In this control structure, the central micro grid controller seeks to minimize the operation costs in the island mode and in the grid-connected mode, seeks to optimize the exchange power with the national network in order to reduce the operation costs. In this study, this type of control is used for the energy management system. In decentralized control, each micro grid is controlled by a controller. Decentralized control is a possible solution for many control and energy management

Materials and Methods

Reagents and chemicals

Standards for ATV and TEN were kindly supplied by Piramal Pharma Ltd. in Ahmedabad. HPLC-grade CH_3OH, ACN, and Milli-Q water were used, along with AR-grade ammonium acetate, HCl, NaOH, H_2O_2, and orthophosphoric acid.

Instrumentation

Chromatographic analysis was performed using a PDA detector, an Acquity UPLC-H Class, and Empower 3.6 software for data acquisition.

Chromatographic condition

UPLC was employed, and data processing was performed using Empower software. The column used for chromatographic separation was the UPLC BEH C18. The mobile phase consisted of methanol, ammonium acetate

buffer, and acetonitrile (60:35:5), with an injection volume of 2 µL and a flow rate of 1 mL/min. UV detection was carried out at 245 nm, at room temperature, with the pH adjusted to 6.5 using OPA.

Preparation of mobile phase

CH_3OH, ammonium acetate buffer and ACN were combined in a 65:30:5% v/v ratio, and then the pH was adjusted to 6.5 ± 0.05 using OPA.

Preparation of standard stock solution (200:100 µg/mL)

Approximately 20 mg of ATV and 10 mg of TEN were weighted into 100 mL of volumetric flask, and then 30 mL of diluent and sonicate were added and dilluted with the diluent and mix. The resulting solution will have a concentration of 200 µg/mL of ATV and 100 µg/mL of TEN.

Preparation of working solution of a mixture of ATV and TEN (20:10 µg/mL)

A 50 mL volumetric flask was filled with 5 mL of ATV standard stock and 5 mL of TEN standard stock, and then diluted to the appropriate volume and mix. The resulting solution contained 10 µg/mL of TEN and 20 µg/mL of ATV.

Preparation of test solution

20 mg of ATV and 10 mg of TEN Were weighed and diluted that resulted in concentrations of 20 µg/mL of ATV and 10 µg/mL of TEN.

Forced degradation studies

To evaluate the method's performance in identifying ATV, TEN, and the degradation products generated under different stress conditions, a forced degradation study was conducted.

Suitability of system

Five injections of the standard solution containing ATV and TEN were performed to verify the system's applicability. The adequacy of the system was evaluated by examining parameters such as TF, RT, and TP in the standard chromatogram.

Validation of method

By ICH (Q2R1) guidelines, analytical validation parameters were established for the examination of the suggested method.

Method validation parameters:
Linearity
Specificity
LOD and LOQ
Accuracy
Precision
Robustness
Assay of synthetic mixture

Result and Discussion

Optimized condition

Extensive experimentation was conducted involving variations in mobile phase composition, column types, pH, and flow rates. The most favorable outcome was achieved using a chromatographic condition is presented in Figure 3 and Table 1.

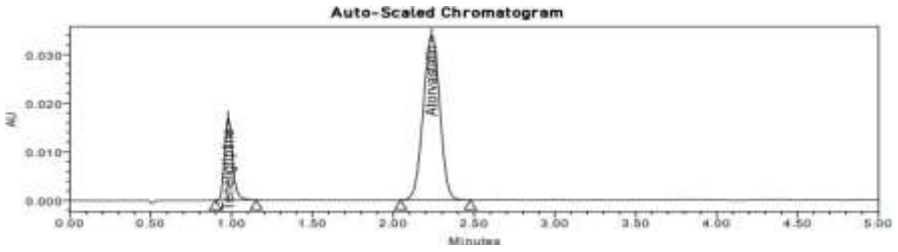

Figure 3: Chromatogram of optimized condition

Table 1: Chromatographic Condition

Sr. No.	Chromatographic parameter	Optimize condition
1	FR	1 mL/min
2	Detection λ	245 nm
3	MP composition	Methanol: Ammonium Acetate Buffer: ACN (60:35:5) (pH 6.5 Adjusted with OPA)
4	Column	Acquity UPLC BEH C18 (50 mm×2.1 mm, 1.7 µm)
5	Injection volume	2 µL
6	Column temperature	Ambient
7	RT	5 min

Linearity

The calibration curve was generated for ATV and TEN within the respective ranges of 10–30 µg/mL and 5-15 µg/mL, as depicted in Figures 4 and 5 as well as Table 2.

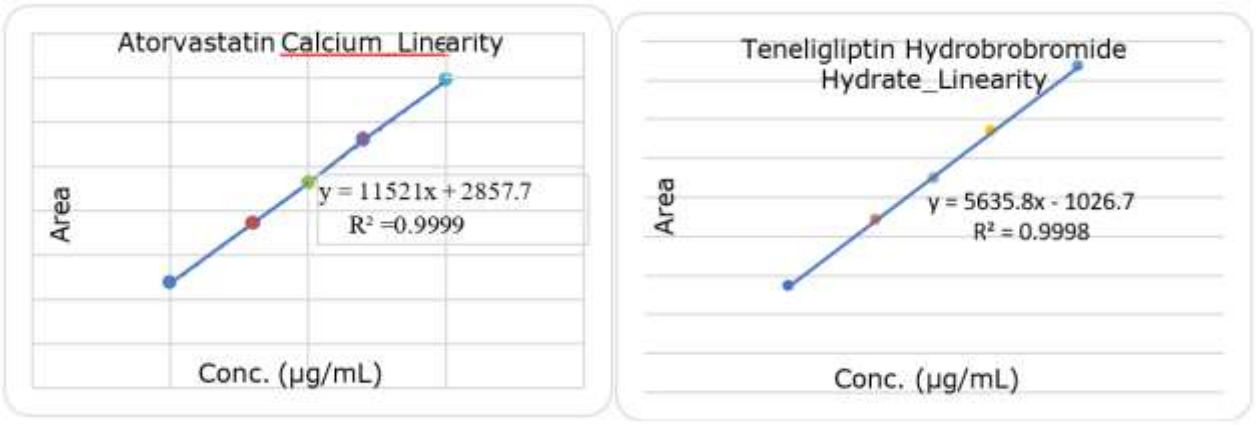

Figure 4: Linearity curve of ATV and TEN

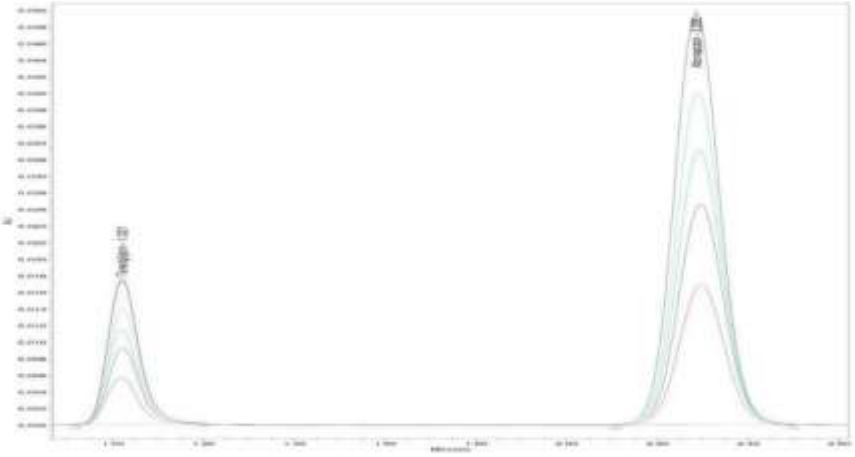

Figure 5: Linearity overlay chromatogram ATV and TEN

Table 2: Repeatability study for ATV and TEN

Drug	Y (Intercept Equation)	R^2
ATV	y = 11521x + 2857.7	0.9999
TEN	y = 5635.8x - 1026.7	0.9998

Specificity

The procedure's specificity was verified when no excipient interference was detected at the 245 nm working wavelength, and the percentage of interference for both drugs was less than 0.5%.

LOD and LOQ

The LOD and LOQ for ATV were found to be 1.0319 µg/mL and 3.1271 µg/mL, respectively, while for TEN, they were 0.6228 µg/mL and 1.8543 µg/mL.

Accuracy

The method demonstrates accuracy, with % recovery falling, as presented in Table 3.

Precision

Repeatability and intermediate precision, expressed as RSD, were both below 2%, signifying the method's precision. Results are presented in Table 3.

Robustness

Intentional variations in temperature, flow rate (FR), and mobile phase (MP) composition were introduced, resulting in RSD values consistently below 2%. This robustness indicates the reliability of the method and is provided in Table 4.

Table 3: Accuracy, intermediate, and repeatability study for ATV and TEN

Drug Name	Level (%) (n = 3)	Interday precision RSD	Intraday precision RSD	Accuracy % drug recovery	Repeatability Concentration (µg/mL) (n=6)	RSD
TEN	50	0.54	0.69	100.10	20	0.21
	100	0.35	0.36	99.87		
	150	0.22	0.28	100.04		
ATV	50	0.23	0.40	99.77	10	0.55
	100	0.14	0.18	99.87		
	150	0.13	0.18	100.04		

Table 4: Robustness study for ATV and TEN

	Flowrate (mL/min)	RSD	Wavelength (nm)	RSD	Mobile phase (MeOH: Buffer: ACN) (pH 6.5)	RSD
ATV	0.9	0.77	244	0.31	64:29:4	0.29
TEN		0.93		0.55		0.56
ATV	1.0	0.31	245	0.35	65:30:5	0.27
TEN		0.82		0.48		0.82
ATV	1.1	0.52	246	0.24	66:31:6	0.31
TEN		0.84		0.38		1.04

Forced degradation study

The optimized stability-indicating approach for ATV and TEN demonstrated good separation of the drug and degradation products. The chromatogram displayed no extra peaks, confirming specificity. Degradants were well separated, with no peak merging. Comprehensive data can be found in Table 5 and Figure 6.

Assay of synthetic mixture

The assay of a synthetic mixture containing ATV and TEN falls within an acceptable range of 98-102%. Detailed data is provided in Table 6.

Table 5: An overview of force degradation

Degradation type	% Degradation		Peak purity index	
	ATV	TEN	ATV	TEN
Acid degradation (0.1 M HCl, 8 h)	27.78	24.64	1	1
Base degradation (0.1 M NaOH, 8 h)	25.07	16.86	1	1
Oxidative degradation (3 % H_2O_2, 8 h)	18.93	25.63	1	1
Photolytic degradation (3 h)	7.23	5.15	1	1
Thermal degradation (30 min)	5.50	6.24	1	1

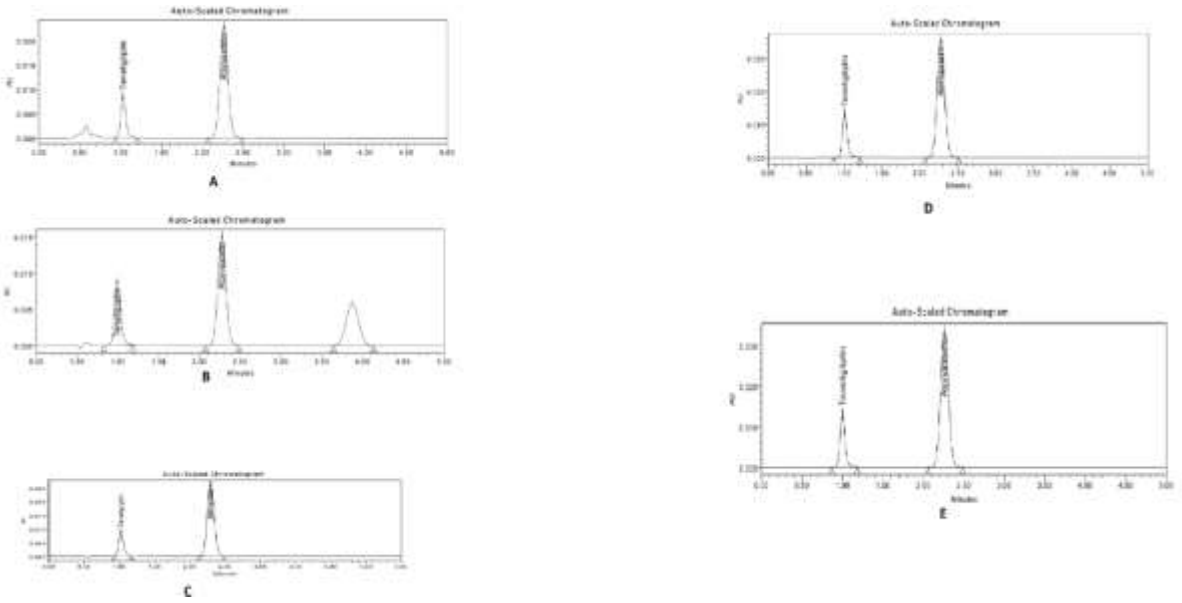

Figure 6: A) Chromatogram of acidic condition, B) chromatogram of basic condition, C) chromatogram of oxidative conditon, D) chromatogram of thermal condition, and E) chromatogram of photolytic condition

Table 6: Result of assay

Conc. (µg/mL: µg/mL) ATV: TEN	Conc. found Mean ± SD	% Drug content

	ATV	TEN	ATV	TEN
(20:10)	19.980±0.0294	9.993±0.032	99.900	99.933

Conclusion

In a synthetic mixture, the levels of TEN and ATV were successfully measured using an RP-UPLC-PDA method that was developed and validated for stability testing. The method effectively distinguishes between the primary drugs and their degradation products. Under various stress-induced degradation conditions, ATV and TEN exhibited superior stability in thermolytic and photolytic environments compared to other stressors. Specifically, ATV demonstrated the highest stability order as thermal > photolytic > oxidation > base > acid, while TEN followed a stability order of photolytic > thermal > base > acid > oxidation. The method's specificity and selectivity were confirmed by assessing RT, resolution, and purity data for all chromatogram peaks using a PDA detector. Comprehensive validation demonstrated satisfactory results across all parameters, making this stability-indicating method suitable for pharmaceutical analysis, enabling the monitoring of drug stability and ensuring quality control.

Acknowledgements

The authors are thankful to Piramal Pharma Ltd, Ahmedabad, Gujarat, India for providing the necessary facilities to carry out the research work.

Conflict of Interest

The authors declare that they have no competing financial interests in this study

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