RESEARCH PAPER

BIOANALYTICAL METHOD DEVELOPMENT, VALIDATION AND STABILITY STUDY OF DRUG IN HUMAN PLASMA USING RP-HPLC

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ABSTRACT

Background: Atazanavir is an HIV-1 protease inhibitor used as part of antiretroviral therapy. Quantitative estimation of antiretroviral drugs in biological matrices is important for pharmacokinetic investigations, therapeutic drug monitoring and bioanalytical research. The complexity of plasma as a biological matrix necessitates efficient sample preparation and reliable chromatographic analysis.

Objective: The present study aimed to develop and evaluate a reversed-phase high-performance liquid chromatographic (RP-HPLC) method for the quantitative estimation of atazanavir in human plasma. The method was developed by optimizing sample preparation and chromatographic conditions and was subsequently evaluated for linearity, precision, recovery, sensitivity, dilution integrity, carry-over, matrix effect and stability.

Methods: Atazanavir was used as the analyte and velpatasvir was selected as the internal standard at a concentration of 5 µg/mL. Plasma samples were processed by protein precipitation using acetonitrile followed by centrifugation, dilution and filtration through a 0.22 µm nylon syringe filter. Chromatographic separation was performed on a Cosmosil C18 column (250 × 4.6 mm, 5 µm) using methanol:water (80:20, v/v) as the mobile phase at a flow rate of 0.8 mL/min. Detection was carried out at 274 nm with an injection volume of 20 µL.

Results: The method demonstrated a linear response over the concentration range of 0.25–10 µg/mL, with a regression equation of $Y = 0.8031x + 0.0107$ and a coefficient of determination (R^2) of 0.9995. Precision expressed as %RSD was 1.688%, 0.550% and 0.624% for LQC, MQC and HQC, respectively. Atazanavir recovery ranged from 53.54% to 58.56%, while internal-standard recovery ranged from 54.59% to 57.71%. The calculated LOD and LOQ were 0.0605 and 0.1835 µg/mL, respectively. Dilution integrity showed a %CV of 0.441%, and no measurable carry-over was observed. Matrix-effect experiments demonstrated reproducible responses with %CV values of 1.848% at LQC and 1.317% at HQC. Stability evaluation indicated comparatively better stability at HQC, whereas LQC samples showed progressive loss of response during long-term storage and repeated freeze–thaw cycles.

Conclusion: The developed RP-HPLC method provided a simple and reproducible approach for estimation of atazanavir in human plasma. The method showed satisfactory linearity, precision, sensitivity, dilution integrity, carry-over performance and reproducible extraction recovery. Further completion of quantitative matrix-factor assessment and numerical accuracy evaluation is recommended before routine regulatory application.

Keywords: Atazanavir, bioanalytical method, human plasma, RP-HPLC, protein precipitation, validation, stability, velpatasvir.

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INTRODUCTION

HIV stands for Human Immunodeficiency Virus, this disease was first identified in 1983, it is a virus that attacks the body's immune system. The untreated HIV progresses into AIDS (acquired immunodeficiency syndrome). At present is no effective cure for AIDS, once a person gets HIV,they have it for life time. However, with proper medical supervision the virus can be controlled [1]. With the support of effective care, diagnosis & treatment, HIV infection has become a manageable chronic malady.

According to UNAIDS- Global Statistics Fact Sheet (2025): An estimated 40.9 million people were living with HIV worldwide in 2025. During the same year, approximately 1.2 million people newly acquired HIV, while 570,000 people died from AIDS related illness. 32.1 million people were accessing antiretroviral therapy (ART) in 2025.

Since the beginning of the HIV epidemic, an estimated 83.5 million people have acquired HIV, and 43.2 million people have died from AIDS related illness. The 2025 UNAIDS statistics demonstrate that, although significant progress has been made in expanding access to ART and reducing AIDS-related deaths over the course of the epidemic, HIV remains a major global public health challenge. With millions of people still living with HIV and over a million new infections occurring annually, sustained international efforts in prevention, early diagnosis, treatment, and community support are essential to further reduce transmission, improve quality of life, and move toward ending the AIDS epidemic as a public health threat. HIV inflicts expenses on both patients and healthcare system. HIV Infection increases the risk of chronic diseases, particularly cardiac and neurological. However, the research development, and widespread availability of dynamic ARTs have helped control the HIV pandemic. Although ART hold up the progression of the disease, the treatment dose not cure the HIV, it causes adverse effects over the patients. HIV transmission is prevented and patient outcomes are improved by using local clinical guidelines. It promotes quality programming to bring about diagnosis, treatment and connections for patient care [2].

Based on genetic characteristics and difference in the viral antigens HIV is classified into Type 1 (HIV 1) & Type 2 (HIV 2), both can lead to AIDS [3] [4]. HIV-1 is the most common type.HIV-2 occurs in a much smaller number of people, mostly in West Africa.

DRUG PROFILE

The physicochemical properties of **Atazanavir [5]**are summarized in Table 1.

Table 1: Drug Profile of Sulfasalazine

Attributes	**Description**
Name	Atazanavir
Category	ARV- Antiretroviral (protease inhibitor), used to treat HIV.
Molecular Formula	$C_{38}H_{52}N_6O_7$
IUPAC Name	methyl N-[(1S)-1-{N'-[(2S,3S)-2-hydroxy-3-[(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanamido]-4-phenylbutyl]-N'-{[4-(pyridin-2 yl) phenyl] methyl} hydrazinecarbonyl}-2,2-dimethylpropyl] carbamate
Molecular Weight	704.8555g/mol
Melting Point	205°C to 210°C
Solubility	Atazanavir is generally recognized as having poor solubility in water (BCS Class II) but shows good solubility in organic solvents like methanol, ethanol, dimethyl sulfoxide (DMSO), and dimethyl formamide (DMF).
Route of Administration	orally in the form of capsules or oral powder
Storage	Do not store above 30°C, it is crucial to keep the medication in a tightly closed container, protected from moisture, light, and excessive heat.

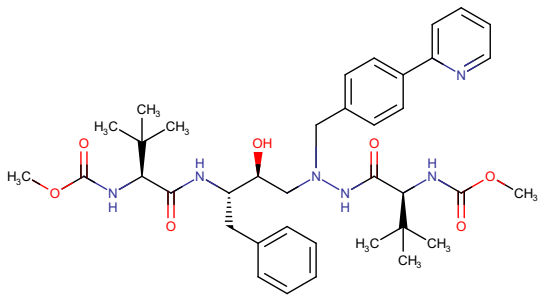


Figure 1: Chemical Structure of Sulfasalazine[8]

MATERIALS AND METHODS

A Bioanalytical Method was developed for quantitative estimation of drug- Atazanavir in Human Plasma using reversed-phase high-performance liquid chromatography (RP-HPLC). Velpatasvir was selected as the internal standard (IS). The method development involved optimization of standard solution preparation, plasma sample preparation and chromatographic conditions to obtain satisfactory separation of the analyte and internal standard with appropriate peak shape, retention and reproducibility.

Chemical and Reagents:

The drug sample (API), Internal standard (IS), acetonitrile, methanol and water were used. All the chemicals / solvents used were of HPLC Grade and were purchased from the local vendor. Human plasma was used as the biological matrix.**Instruments**:

The analysis was carried out using an RP-HPLC system equipped with a specific detector. Other instruments included a centrifuge and vortex mixer.

Chromatographic Condition:

Chromatographic separation was achieved using a C18 column. The mobile phase composition, flow rate, and detection wavelength were optimized to obtain sharp and well-resolved peaks.

Optimized Chromatographic Conditions:

Various mobile phase compositions, flow rates, and column types were tested. After several trials, optimized chromatographic conditions were achieved, which are presented in the following table 2.

Table 2: Optimized Chromatographic conditions

Sr. No.	Parameter	Optimized Condition
1.	HPLC System	Shimadzu Prominence
2.	Detector	SPD-20A
3.	Pump	LC-20AD UFLC
4.	Column	Cosmosil C18
5.	Column Dimension	250 mm x 4.6 mm
6.	Particle Size	5 µm
7.	Mobile Phase	Methanol: Water (80:20, v/v)
8.	Flow Rate	0.8 mL/min
9.	Detection Wavelength	274 nm
10	Injection Volume	20 µL
11	Data System	LC Solution
12	Total Run Time	15.73 min
13	Pressure	11-12 MPa

Preparation of Solutions:

Diluent: HPLC-grade methanol was used as the diluent for preparation of standard and working solutions.

Atazanavir standard stock solution: Accurately 10 mg of Atazanavir was weighed, transferred to a 10 mL volumetric flask, dissolved in methanol, and diluted to volume with the same solvent to obtain a 1000 µg/mL (1000 ppm) stock solution.

Atazanavir working standard solution: 0.1 mL of the 1000 µg/mL Atazanavir stock solution was transferred to a 10 mL volumetric flask and diluted to volume with methanol to obtain a 10 µg/mL working standard solution.

Calibration standards: Calibration standards in the range of 0.25–10 µg/mL were prepared by appropriate dilution of the 10 µg/mL working standard with methanol. The prepared standards were used for construction of the calibration curve.

Atazanavir plasma-spiking solution: A separate 100 µg/mL Atazanavir intermediate solution was prepared by diluting 1 mL of the 1000 µg/mL stock solution to 10 mL with methanol. This solution was used exclusively for preparation of spiked plasma samples and was kept separate from the calibration standards.

QC solutions: LQC, MQC and HQC solutions were prepared at 1, 5 and 10 µg/mL, respectively, by appropriate dilution of the Atazanavir working standard.

Internal standard stock solution: Accurately 10 mg of Velpatasvir was transferred to a 10 mL volumetric flask, dissolved in methanol and diluted to volume to obtain a 1000 µg/mL stock solution.

Internal standard working solution: 0.05 mL of the 1000 µg/mL Velpatasvir stock solution was diluted to 10 mL with methanol to obtain a 5 µg/mL internal standard working solution.

Mobile phase: Methanol and HPLC-grade water were mixed in the ratio of 80:20 (v/v), filtered and degassed before use.

Spiked plasma samples: The required volume of Atazanavir plasma-spiking solution was added to blank human plasma to obtain the desired concentration. The samples were vortex-mixed, followed by addition of acetonitrile for protein precipitation. The samples were vortexed and centrifuged at 3000 rpm for 5 min. The clear supernatant was separated, diluted as required, filtered through a 0.22 µm nylon syringe filter, and transferred to HPLC vials for analysis.

Method Development

Bioanalytical Method Development (BAMD) is the process of designing and optimizing analytical procedures by defining their operating conditions, limitations, and suitability for the intended purpose before validation. Its primary objective is to ensure that the method is reliable, robust, and fit for accurate analysis in biological samples [6]. Bioanalysis plays a vital role throughout drug discovery and development, particularly in toxicological assessments, pharmacokinetic, and pharmacodynamic studies. A typical bioanalytical workflow includes sample collection, sample preparation, analysis, calibration data evaluation, and reporting. Modern bioanalysis relies on efficient sample preparation techniques and advanced hyphenated analytical instruments to achieve accurate and reproducible results [7]. Bioanalysis is an essential component of pharmaceutical research, supporting drug discovery and development through toxicokinetic (TK), pharmacokinetic (PK), and pharmacodynamic (PD) studies. It also has important applications in clinical and preclinical research, forensic toxicology, doping control and biomarker identification for disease diagnosis [8].Since analyte concentrations vary depending on pharmacokinetic, toxicological, metabolic, and absorption studies, establishing an appropriate analytical concentration range is essential. An approximate understanding of the expected analyte levels allows the determination of suitable lower and upper limits of quantification and the construction of a reliable calibration curve, ensuring accurate method validation for both preclinical and clinical studies [9].

Method Validation

The developed RP-HPLC method for the estimation of Atazanavir was validated according to ICH M10 guidelines for Bioanalytical method validation.

RESULTS AND DISCUSSION

Method Validation

The developed bioanalytical method for the estimation of the selected analyte in human plasma

was evaluated for various validation parameters, including linearity, accuracy, precision, recovery, limit of detection (LOD), limit of quantification (LOQ), dilution integrity, carry over, matrix effect and stability. The obtained experimental results are presented and discussed below.

I. Linearity

The calibration curve was represented by the regression equation: Y=0.8031x + 0.0107. With a coefficient of determination: R^2 = 0.9995. The obtained R^2 value close to unity indicates a strong linear relationship between the concertation of the analyte and the corresponding response ratio over the investigated concentration range. The observed linearity demonstrated that the method was capable of producing reproducible analytical responses over the concentration range of 0.25-10 µg/mL.Correlation coefficient (r) typically ≥ 0.99

Table 3: The calibration data and regression parameters

II. Accuracy

Accuracy and precision were evaluated using quality control samples at low, middle and high concentration levels, represented as LQC, MQC and HQC respectively.

Five replicate measurements were performed at each QC level. In the present study, precision was assessed using the standard deviation (SD) and percentage relative Standard deviation (%RSD).

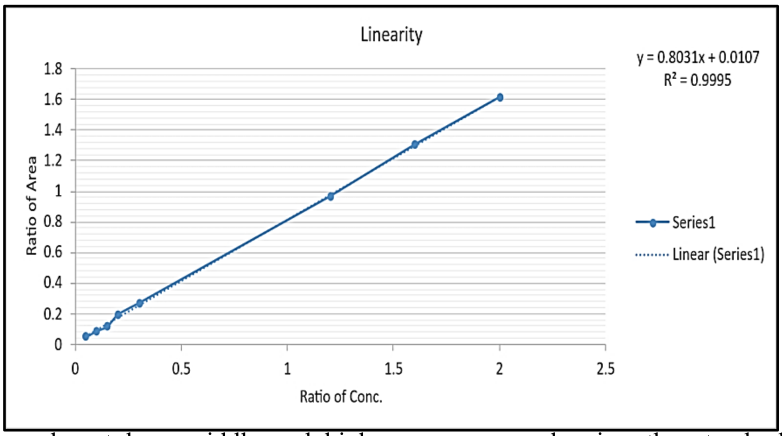


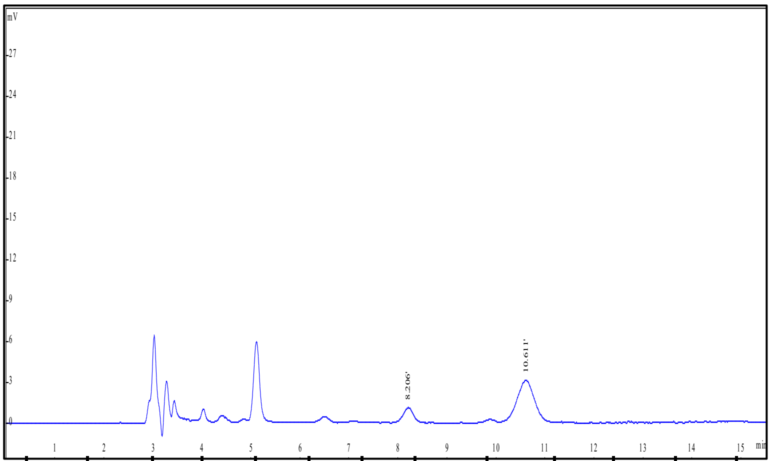
Table 4: Accuracy and Precision for each replicate of each QC samples

Conc. Name	Area of STD	Area of IS	Ratio of Conc.	Ratio of Area
LLOQ	3324	73838	0.05	0.045017471
Std A	6317	76528	0.1	0.082544951
Std B	8304	73834	0.15	0.11246851
Std C	13801	71338	0.2	0.193459306
Std D	20736	77723	0.3	0.266793613
Std E	75988	78797	1.2	0.964351435
Std F	98555	75470	1.6	1.305883132
ULOQ	127592	79147	2	1.612088898

						Standard Deviation		Accuracy	Precision (%RSD)
Conc.	Conc.	Area 1	Area 2	Area 3	Average	Mean	SD		
	LQC1	14004	13827	13927	13919.33333				
1	LQC2	13526	13789	13823	13712.66667				
	LQC3	13630	13648	13726	13668	13661.3333	230.6359	1.6882	
	LQC4	13619	13249	12993	13287				

	LQC5	13981	13984	13194	13719.66667				

	HQC3	128138	125487	124656	126093.6667	125731	784.9753	0.6243	



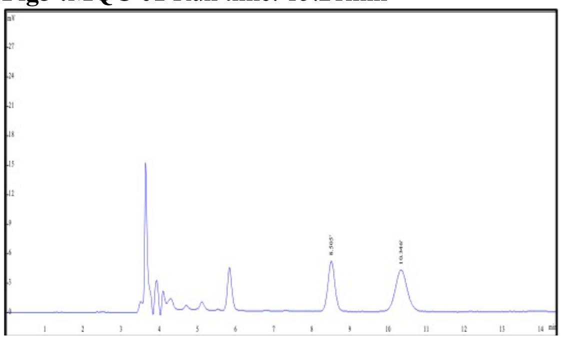
2	MQC1	64003	63487	64378	63956				
	MQC2	64594	63878	63877	64116.33333				
	MQC3	63981	64265	63198	63814.66667	63788.4666	350.8166	0.5499	0.6368
	MQC4	63678	63812	64088	63859.33333				
	MQC5	63040	63113	63435	63196				
3	HQC1	125799	123437	124387	124541				
	HQC2	126787	127688	125476	126650.3333				

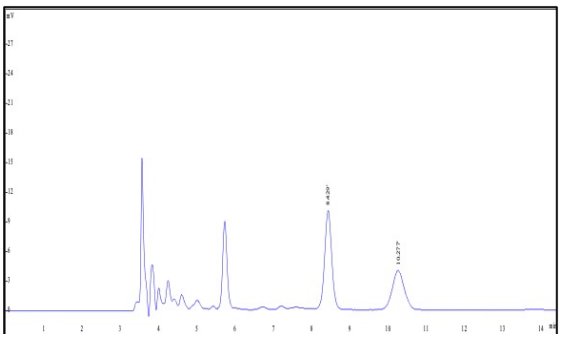
	HQC4	127727	124546	125334	125869				
	HQC5	126531	125436	124536	125501				

Acceptance Criteria: ±15% of nominal value

Fig3: LQC 01 Run time: 16.39min**Fig 4:HQC 01** Run time: 15.15min

Fig5 :MQC 01 Run time: 15.21min





Time Area Resolut. T.PlateNum Asymmetry

8.206 14004 4.61 7212 0.98

10.611 74976 0.00 7402 0.95

III.% Recovery

Recovery was evaluated by comparing the response obtained from extracted plasma samples with the response obtained from the corresponding standard preparation. The recovery experiment was performed at different analyte concentration levels.

For the analyte, recovery values of 58.56%, 53.54% and 55.31% were obtained at 0.5, 1.5 and 10 µg/mL, respectively.For the internal standard, recovery values of 54.59% and 57.71% were reported at 2 and 5 µg/mL, respectively. The results indicate that the extraction procedure produced reproducible recovery of the analyte and internal standard. The observed recovery values can therefore be considered during assessment of the overall suitability of the sample preparation procedure.

Table 5: Recovery of API and API + IS

Sr. No.	API % Composition	Area of Standard	Area of Extracted Sample	% Recovery
1	**0.5ppm**	5862	3433	58.563630 16
2	**1.5ppm**	38446	20583	53.537429 12
3	**10ppm**	232904	128812	55.306907 57
	IS- API			
1	**2ppm**			
2	**5ppm**			

Time Area Resolut. T.PlateNum Asymmetry

8.505 64003 3.99 10541 1.02

10.346 73859 0.00 8152 1.02

IV.Limit of Detection: LOD

In the present study, the LOD was calculated using the standard deviation and slope obtained from the calibration response. The standard deviation used for calculation was 230.636, while the slope of the calibration response was 12,572. nThe calibration relationship used for this evaluation was:

$y = 12572.4476\ x + 323.5585$; with an R^2 value of 0.9992. The calculated LOD was: 0.0605 µg/mL. It indicates that the developed analytical procedure was capable of detecting the analyte at concentrations lower than the established lower limit of quantification. The low LOD value demonstrates the sensitivity of the analytical response for detection of the analyte.

Table 6: LOD

V. Limit of Quantification: LOQ

The LOQ was calculated using the standard deviation and slope obtained from the calibration response. The standard deviation was 230.636 and the slope was 12,572. The calculated LOQ was: 0.1835 µg/mL.the obtained LOQ was lower than the experimentally selected LLOQ concentration of 0.25 µg/mL, indicating that the analytical system theoretically had sufficient sensitivity to detect and quantify concentrations below the lowest calibration standard used in the method. The result indicates adequate sensitivity of the method over the investigated concentration range.

Table 7: LOQ

Sr. No	Conc.	Post extraction spiked sample	Mean	SD	%CV
1	HQC1	125405			
2	HQC2	128064	126159.6667	1660.984748	1.316573507
3	HQC3	125010			
1	LQC1	13468			
2	LQC2	13975	13726.66667	253.6579061	1.847920637
3	LQC3	13737			

Table 9: Matrix Effect

Sr. No	Conc.	Standard Area	Area (Response in Blank Solvent)	% Sample found
1	LLOQ	10000	0	0
2	IS	10000	0	0

Sr. No.	SD	Slope	LOD (ug/ml)
1	230.6359565	12572	0.060539187

Sr. No.	SD	Slope	LOQ (ug/ml)
1	230.6359565	12572	0.183452081

VI. Carry Over

Carry-over was evaluated by injecting blank samples following the highest concentration sample and assessing the response at the retention position of the analyte and internal standard. In the present study, the blank response following the relevant injection sequence was reported as zero for both the analyte and internal standard. The results obtained were: LLOQ: Standard area = 10,000; blank response = 0; Internal Standard: Standard area = 10,000; blank response = 0. The absence of detectable response in the blank sample indicates that there was no observable carry-over of analyte

or internal standard under the experimental conditions employed. Thus, the chromatographic system demonstrated no measurable carry-over in the experiment performed. Thus, the chromatographic system demonstrated no measurable carry-over in the experiment performed.Table 8: Carry over

VII. Matrix Effect

The matrix effect study was performed to investigate the influence of plasma matrix components on the analytical response. Post-extraction spiked samples were analyzed at the investigated concentration levels. The relatively low %CV values indicate that the post-extraction responses were reproducible at both LQC and HQC levels. The results obtained demonstrate reproducibility of the post-extraction responses, but a complete matrix-effect assessment should include matrix factor calculations.

Sr. No	Conc.	Area (Spiked and diluted to ULOQ)	Mean	SD	%CV
1	HQC Dilution integrity 1	123874	124502.333	548.5729973	0.440612624
2	HQC Dilution integrity 2	124886			
3	HQC Dilution integrity 3	124747			

VIII. Dilution Integrity

Dilution Integrity was evaluated using HQC samples that were diluted to the ULOQ concentration. Three replicate preparations were analyzed. The obtained responses were 123,874; 124886; and 124,747 with a mean response of 124,502.33 Standard deviation of 548.57 and %CV of 0.441%.

The low %CV indicates that dilution of the high concentration sample did not result in substantial variability among the replicate measurements. This demonstrates good reproducibility of the analytical response following dilution. Table 8: Dilution Integrity

Table 10: Dilution Integrity

IX. Stability Studies

Stability studies were performed at LQC and HQC levels under different storage and handling conditions. The investigated conditions included freeze thaw stability, long-term stability, short-term stability bench-top stability. Stability was assessed by comparing the response of the stability samples with the corresponding standard value and calculating the percentage of degradation.

The result demonstrate that the analytical response remained close to the standard response during the initial 12-hour period but showed a gradual reduction with longer exposure up to 48 hours.

Table 11: Stability studies LQC&HQC

Sr. NO.	Degradation	Actual % degradation LQC	Actual % degradation HQC
1	**Freeze-Thaw**		
	a. Cycle 1	3.215889127	0.369041843
	b. Cycle 2	4.284598868	2.653283598
	c. Cycle 3	7.776205348	3.563957974
2	**Long Term Stability**		
	a. 10 Days	11.83876635	1.090809251
	b. 20 Days	20.63000195	1.781581312
	c. 30 Days	22.71618192	4.915255585
3	**Short Term Stability**		
	a. 12hrs	-0.195198126	1.334595287
	b. 24hrs	4.562756198	1.209725525
	c. 48hrs	6.66357603	1.792716196

Table 12: Bench Top Stability studies

Conc. ppm	Degradation	Area of Standard	Average	SD	%SD
	Bench Top				
0.75	**a. Day 1**	16598	16394.66667	241.315837 3	1.471916704
0.75	**b. Day 2**	16128			
0.75	**c. Day 3**	16458			
5	**a. Day 1**	110797	111198.6667	396.121614 3	0.35622874 5
5	**b. Day 2**	111210			
5	**c. Day 3**	111589			

CONCLUSION

A reversed-phase HPLC method was developed for the quantitative estimation of atazanavir in human plasma using velpatasvir as an internal standard. Protein precipitation with acetonitrile was successfully employed for plasma sample

preparation, followed by chromatographic separation using a Cosmosil C18 column and methanol:water (80:20, v/v) mobile phase. The developed method exhibited good linearity over the concentration range of 0.25–10 µg/mL with an R^2 of 0.9995. Precision was satisfactory, with %RSD values of 1.688%, 0.550% and 0.624% at LQC, MQC and HQC, respectively. Atazanavir recovery ranged from 53.54% to 58.56%, while the internal-standard recovery ranged from 54.59% to 57.71%. The method demonstrated LOD and LOQ values of 0.0605 and 0.1835 µg/mL, respectively. The dilution-integrity experiment showed good reproducibility, with a %CV of 0.441%, and no measurable carry-over was observed. Post-extraction matrix responses were reproducible at both QC levels. Stability studies demonstrated comparatively better stability at HQC, while LQC showed progressive response reduction under repeated freeze–thaw and long-term storage conditions. Thus, the developed RP-HPLC method provides a simple, reproducible and practically applicable analytical procedure for estimation of atazanavir in human plasma within the investigated concentration range. The method may provide a useful foundation for further pharmacokinetic and bioanalytical investigations.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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