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RESEARCH

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A new RP-HPLC approach for estimation of potential impurities of Fosamprenavir - method development and validation

Ramreddy Godela^{1†}, Vinod Kumar Nelson^{2,10*†} , Mohana Vamsi Nuli³, Pavan Kumar Jaini⁴, Shilpi Pathak⁵, Krishnaphanisri Ponnekanti⁶, Punna Rao Suryadevara⁷, Gowri Sankararao Burle⁸, Vinyas Mayasa¹ and Kavindra Kumar Kesari⁹

Abstract

The current work aims to develop a reliable and robust RP-HPLC method for analyzing Fosamprenavir and its potential impurities, including isomer, amino, propyl, nitro, and Amprenavir. The method used a Zobrax C18 column with a mobile phase of 0.1% V/V orthophosphoric acid in water and acetonitrile in gradient elution at a flow rate of 1 mL/min to accomplish efficient separation with detection at 264 nm and column temperature of $30 \pm 2^\circ\text{C}$. A diluent with a 1:1 water-to-acetonitrile ratio was used to prepare standard and sample solutions. The developed approach was validated as per ICH Q2(R1) guidelines. Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurities were eluted at retention time (RT) of 5.3 min, 2.3 min, 4.3 min, 4.7 min, 8.1 min and 8.6 min correspondingly with good resolution within a 10-minute run time. Method validation confirmed system suitability, linearity ($R^2 = 0.999$), good sensitivity (LOD/LOQ), specificity, precision (% RSD: 0.5–1.7), accuracy (% recovery: 90.9–104.3%), and robustness. The optimized approach excelled existing methods in lower retention time, run time, sensitivity, and linearity for all potential impurities, making it a novel and trustworthy method for monitoring Fosamprenavir drug quality and assessing stated impurities. The established method allows precise measurement of Fosamprenavir and related substances, supporting drug safety and regulatory compliance.

Keywords Fosamprenavir, Potential impurities, Gradient elution, Sensitivity, Linearity

Introduction

Fosamprenavir, a derivative of amprenavir, is categorized within the protease inhibitor class of pharmaceuticals, pivotal in highly active antiretroviral therapy (HAART) regimens for HIV/AIDS management [1–3]. Its inception in 2003 stemmed from the imperative to surmount amprenavir's bioavailability and dosing intricacies [2]. Fosamprenavir operates akin to amprenavir by impeding the functionality of the HIV protease enzyme, pivotal for viral replication [2–4]. Through this inhibition, Fosamprenavir disrupts the processing of viral polyproteins, impeding the formation of mature, infectious

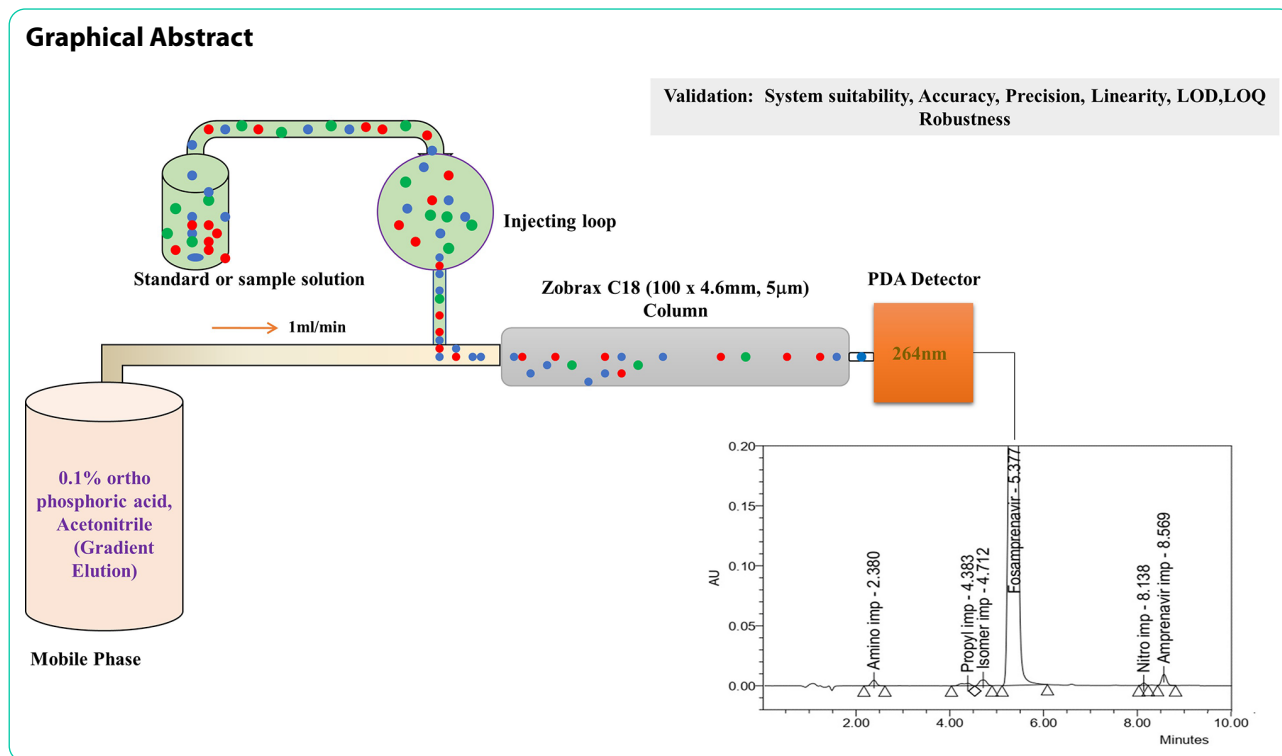
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HIV particles [2–4]. Consequently, viral replication is curtailed, mitigating disease advancement by sustaining low viral levels [4–6]. Fosamprenavir is sparingly soluble in water but freely soluble in Acetonitrile, DMF, DMSO, ethanol, and methanol [7, 8]. Chemically, Fosamprenavir is [(3 S)-oxolan-3-yl] N-[(2 S,3R)-4-[(4-aminophenyl)sulfonyl-(2-methylpropyl)amino]-1-phenyl-3-phosphonooxybutan-2-yl]carbamate with molecular formula of $C_{25}H_{36}N_3O_9PS$ [7, 8].

Impurity profiling is the process of identifying and quantifying impurities in a pharmaceutical substance or product. Impurities can come from various reasons, including the manufacturing process, storage conditions, and the drug's degradation over time [9]. The presence of impurities can affect a drug's safety and efficacy. Impurity profiling can be performed using a range of analytical techniques, such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), and nuclear magnetic resonance (NMR) [9–11]. HPLC is a potent method for separating, detecting, and quantifying impurities in pharmaceutical compounds. Its adaptability and capacity to combine with other analytical methods make it an essential tool in impurity profiling to ensure drug safety and quality [10, 11].

The potential impurities of Fosamprenavir during synthesis or storage include isomer, amino, propyl, nitro, and Amprenavir impurities [12, 13]. An in-depth exploration of the literature regarding analytical methods for Fosamprenavir ensures that few UV and HPLC methods

are used to estimate Fosamprenavir in drug substances and products [14–19]. Along with the HPLC method, few LC-MS methods are reported for the estimation of Fosamprenavir in biological samples and the characterization of metabolites and forced degradants [20, 21]. Only one HPLC method was reported for concurrently identifying and estimating Fosamprenavir and its isomer, amino, and Amprenavir impurities [13]. Along with the prior method, one more liquid chromatographic method is reported for the estimation of potential impurities of Fosamprenavir [22]. Propyl and Nitro impurities of Fosamprenavir are also potential impurities stated in the previous method. A competent, accurate, specific, and sensitive HPLC method is essential for identifying and estimating all potential process impurities in trace levels. Hence, an attempt was made to make a good and proficient RP-HPLC method for simultaneous analysis of Fosamprenavir and its process impurities (Amino, Propyl, Isomer, Nitro impurities, and Amprenavir). The chemical structures of Fosamprenavir and stated impurities are shown in Fig. 1.

Materials and methods

The pure forms of Fosamprenavir (99.98%), Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurities were obtained as gift samples from Icon Laboratories, Andhra Pradesh, India. The potencies of all the impurities ranged from 99.87 to 99.93%. The HPLC-grade methanol and acetonitrile were purchased from a local

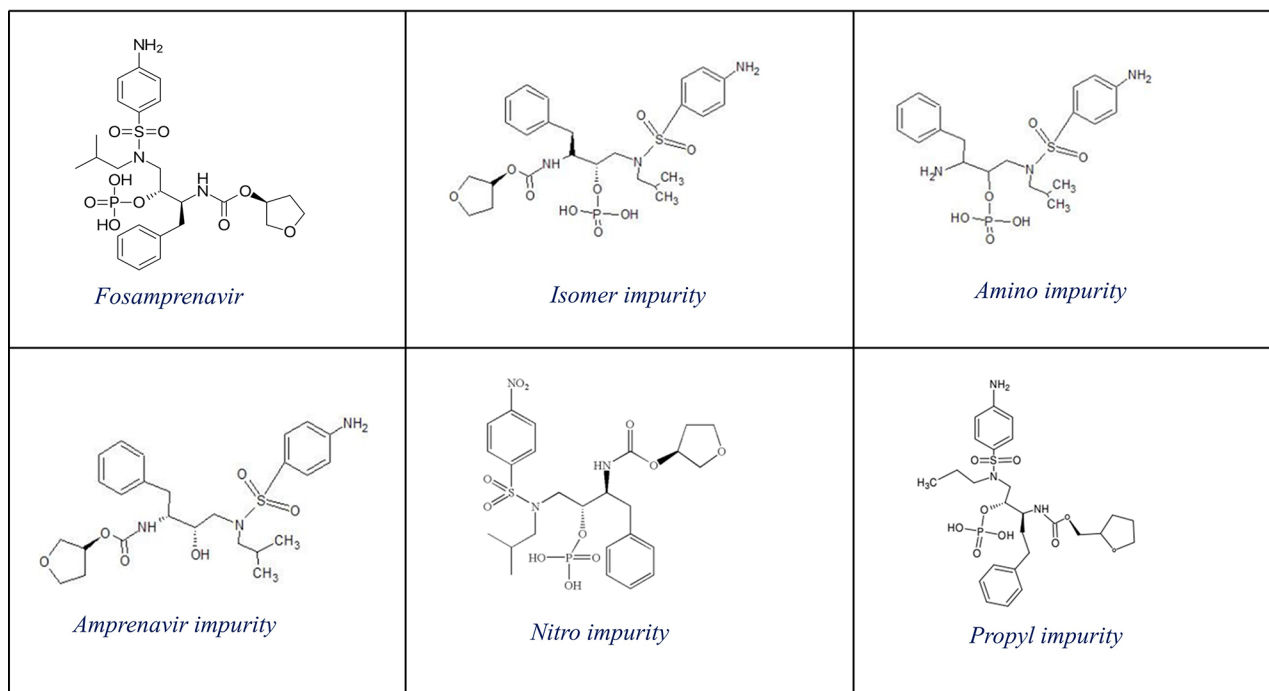


Fig. 1 Chemical structures of Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurity

Table 1 Gradient elution program of the mobile phase of the optimized method

Time (Min)	Flow (ml/min)	Buffer (0.1% OPA) (ml)	Acetonitrile (ml)
1.0	1.0	75	25
2.0	1.0	75	25
10.0	1.0	30	70
12.0	1.0	30	70
13.0	1.0	70	30
18.0	1.0	75	25

distributor of Finar Chemical Limited, India. The executive of the present method development and validation, WATERS HPLC with PDA detector integrated with Empower-2 software, was used.

Method development

The current method was developed by using WATERS HPLC equipped with a binary pump and PDA detector. Initially, method development started with an isocratic mobile phase of various ratios of 0.1% orthophosphoric acid (OPA) and acetonitrile in 50:50, 60:40, and 70:30. During those conditions, good resolution between Fosamprenavir, Isomer and Propylimpurities were too low. Amino and Nitro impurities were not eluted with the isocratic elution. Finally, the Zobrax C18 column (100×4.6 mm, 5 μm) was used in conjunction with a mobile phase of 0.1% v/v OPA in water and acetonitrile in gradient elution mode opted to attain good resolution

among analytes (Fosamprenavir and impurities) (Table 1). The mobile phase was fed to the column at a flow rate of 1 ml/min, and eluted chemicals were detected at a wavelength of 264 nm. The sample input and column temperature were kept at 30 ± 2°C. A diluent with a 1:1 water-to-acetonitrile ratio was used to prepare standard and sample solutions.

Preparation of standard solution

The standard solution was prepared by transferring 1 mg of each Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurity into 100 ml of a volumetric flask. 50 ml of diluent (1:1 ratio of acetonitrile and water) was added and sonicated for 5 min; the remaining volume was adjusted with the same diluent to get a solution of 10 ppm. 0.1 ml of the above-stated solution was further diluted with the same diluent to attain a solution of 1ppm.

Preparation of sample solution

Tablet powder equivalent to 1 mg of each Fosamprenavir 100 ml of volumetric flask. 50 ml of diluent (1:1 ratio of acetonitrile and water) was added and sonicated for 5 min; the remaining volume was adjusted with the same diluent to get a solution of 10 ppm. 0.1 ml of the above-stated solution was further diluted with the same diluent to attain a solution of 1ppm.

Method validation

The present method was validated as per ICH Q2(R1) provisions [23–26].

System suitability

The system suitability of the current RP- HPLC method was confirmed by injecting six subsequent injections of a standard solution consisting of 1 ppm of Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurity each injected into the HPLC system. The chromatograms were interpreted to assess the theoretical plate count, USP resolution, tailing factor, and %RSD of the peak areas for obtained peaks.

Linearity

The linearity for Fosamprenavir and its stated relative impurities was performed for a concentration series of 25–150% level of standard solution (0.5, 0.75, 1, 1.25 and 1.5 ppm). Each concentration level was injected three times ($n=3$), and the mean peak area was considered to plot a linear graph between concentration and peak area to compute the R^2 value.

Sensitivity

The signal-to-noise (S/N) ratio method is commonly used to determine the LOD (Limit of detection) and LOQ (Limit of Quantification). The LOD represents the concentration or amount of analyte yielding a signal three times the standard deviation of the background noise (S/N ratio of 3:1), and the LOQ represents the concentration or amount of analyte producing a signal ten times the standard deviation of the background noise. This method entails detecting the background noise level without an analyte and quantifying the signal produced by a known low analyte concentration. The LOD is then computed as a signal's concentration three times the noise's standard deviation. In contrast, the LOQ is calculated similarly for a signal ten times the standard deviation of the noise. The reliability of LOD and LOQ of stated impurities and Fosamprenavir were confirmed by analysing LOD and LOQ concentrations for 5 repetitive injections to assess the %RSD.

Specificity

Specificity in an HPLC (High-Performance Liquid Chromatography) method refers to its ability to accurately determine the analyte desired in the presence of potentially interfering chemical substances. It ensures that the process can identify and measure the target chemical substances without interference from other substances in the sample matrix. In the current method, specificity was performed by injecting successive injections of individual impurity solutions, a solution of all impurities spiked with Fosamprenavir solution and Fosamprenavir sample

solution into the HPLC system. The recorded chromatograms were interpreted to identify interferences among the RT of all impurities, interferences of RT of Fosamprenavir with RT of individual impurities, and interferences with placebo towards Fosamprenavir and impurities.

Precision

The optimized method's system precision was validated by injecting a standard solution consisting of Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurity in 6 repeated injections. The %RSD was statistically computed for the results in peak areas of Fosamprenavir and stated impurities in the replicated injections. The method precision of the optimized method was done by injecting Fosamprenavir sample solution spiked with 0.1% of each impurity (Amino, Propyl, Isomer, Nitro, and Amprenavir impurity). The % RSD for the %recovery of each spiked solution was calculated for six consecutive injections.

Accuracy

To ensure the accuracy of the current HPLC method, a % recovery procedure was chosen, in which Fosamprenavir sample solutions were spiked with all the related substances or impurities at different concentration levels of LOQ, 50, 100, and 150% of each. Three serial injections of each spiked solution were introduced into HPLC, and the % mean recovery of each impurity in the spiked solution was.

Robustness

To confirm the robustness of the HPLC method, slight variations were made in method conditions with intention. Small, deliberate changes were made to parameters including flow rate (± 0.1 ml/min), column temperature (± 2 and maximum wavelength (± 2 nm). The %RSD of the obtained peaks was determined.

Results

Optimized method

After several trials, a method with Zobrax C18 column (100 \times 4.6 mm, 5 μ m), a mobile phase of 0.1% v/v OPA in water and acetonitrile in gradient elution mode, the flow rate of 1 ml/min, and detection wavelength of 264 nm is used. These chromatographic conditions can be used to separate Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurities at retention time (RT) of 5.3 min, 2.3 min, 4.3 min, 4.7 min, 8.1 min and 8.6 min correspondingly with good resolution (Fig. 2).

Method validation

The system suitability of the analytical method was ensured by assessing the % RSD, USP tailing, USP plate count, and resolution. All the parameters' values were

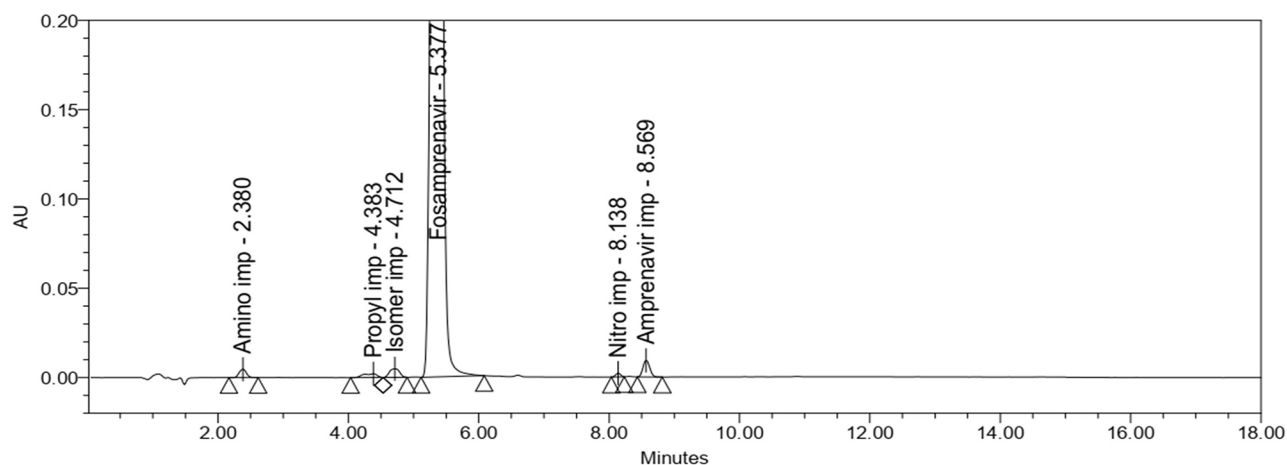


Fig. 2 Optimized method chromatogram

Table 2 System suitability test of Fosamprenavir and its impurities

Parameter (n = 5)	Amino	Propyl	Isomer	Fosamprenavir	Nitro	Amprenavir	Acceptance criteria
Retention Time (RT)	2.389	4.384	4.749	5.372	8.165	8.603	± 10%
USP plates	4959	9751	13,490	21,124	58,525	57,180	> 2000
USP tailing	1.15	1.08	1.10	1.11	1.15	1.10	≤ 2
Resolution between Isomer and Fosamprenavir	3.42						< 2

Table 3 Linearity results from a series of concentrations of Fosamprenavir and its impurities

Concentration (ppm)	Peak area (m AU)					
	Amino	Propyl	Isomer	Fosamprenavir	Nitro	Amprenavir
0.5	10,240	10,041	16,685	6900	3719	19,056
0.75	15,634	15,579	25,589	10,046	6015	31,261
1	21,484	21,038	34,669	13,936	8218	41,900
1.25	27,145	26,887	43,588	17,240	10,295	53,117
1.5	32,874	32,133	52,146	20,709	12,317	63,370
R ²	0.999	0.999	0.999	0.999	0.999	0.999

aligned with Q2 specifications ICH guidelines (Table 2). The R² value for the Fosamprenavir and stated impurities were assessed to be 0.999, corresponding to the stated concentration series (Table 3; Fig. 3). This demonstrates the effectiveness of the suggested methodology in exhibiting notable linearity throughout the designated concentration series. The LOD and LOQ results ascertained by the S/N ratio method for all analytes were in the very low range, demonstrating the remarkable sensitivity of the stated method for Fosamprenavir and its impurities. The sensitivity results, including LOD and LOQ with their S/N ratio and %RSD of peak responses, were stated in Table 4. The chromatogram representing LOQ levels was shown in Fig. 4. There was no interference at the RT Fosamprenavir with blank and stated impurities in the recorded chromatograms (Fig. 5), which disclose the specificity of the current HPLC approach towards the Fosamprenavir and stated impurities of Fosamprenavir.

The %RSD results of system precision (peak responses of all analytes in standard solution) and method precision (% recovery of impurities from spiked solutions) were in the range of 0.5 to 1.7, confirming the precision of the developed approach in accordance with ICH regulations (Table 5). The % mean recovery of each impurity in spiked solutions of Fosamprenavir was computed to be in the range of 90.9–104.3% (Table 6), which powerfully reveals the accuracy of the stated method. The method can maintain consistent results even after making slight intentional alterations to the method's conditions. The robustness of the approach is demonstrated by the %RSD values of peak responses, which were within the permissible limits established by the ICH (Table 7).

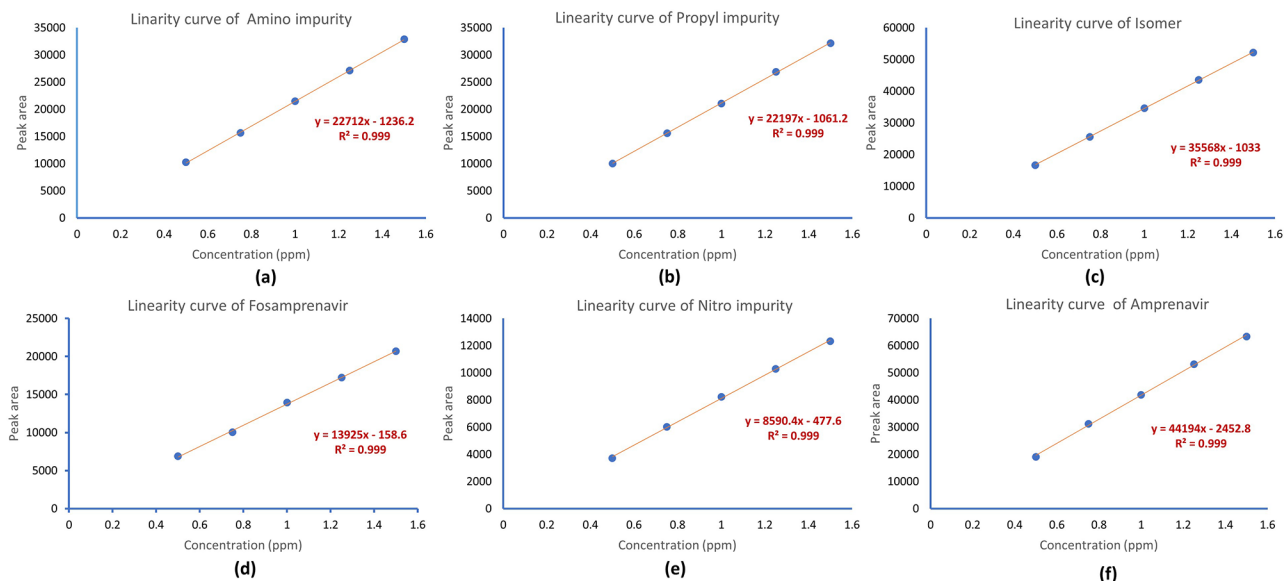


Fig. 3 Linearity plots of Fosamprenavir and its impurities

Table 4 Sensitivity results of Fosamprenavir and its impurities

Name of the analyte	LOD (ppm)	S/N ratio	LOQ (ppm)	S/N ratio	LOQ (Peak area)	
					*Mean ± SD	%RSD
Amino	0.031	2.9	0.095	9	1885 ± 22.62	1.2
Propyl	0.042	2.9	0.130	10.1	2465 ± 21.93	0.89
Isomer	0.024	3.5	0.074	11.5	2051 ± 19.89	0.97
Fosamprenavir	0.055	3	0.167	9.2	1660 ± 22.24	1.34
Nitro	0.082	2.7	0.250	10.6	2107 ± 34.76	1.65
Amprenavir	0.017	3.3	0.052	11.2	2205 ± 22.49	1.02

* Mean of six repetitive injections of LOQ solution; SD- Standard deviation

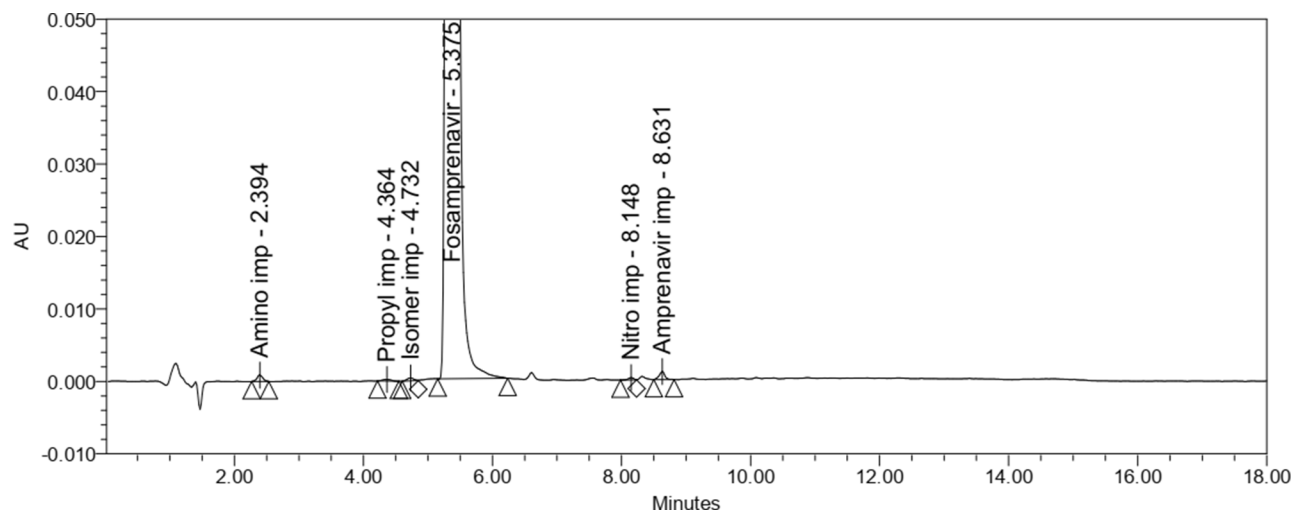
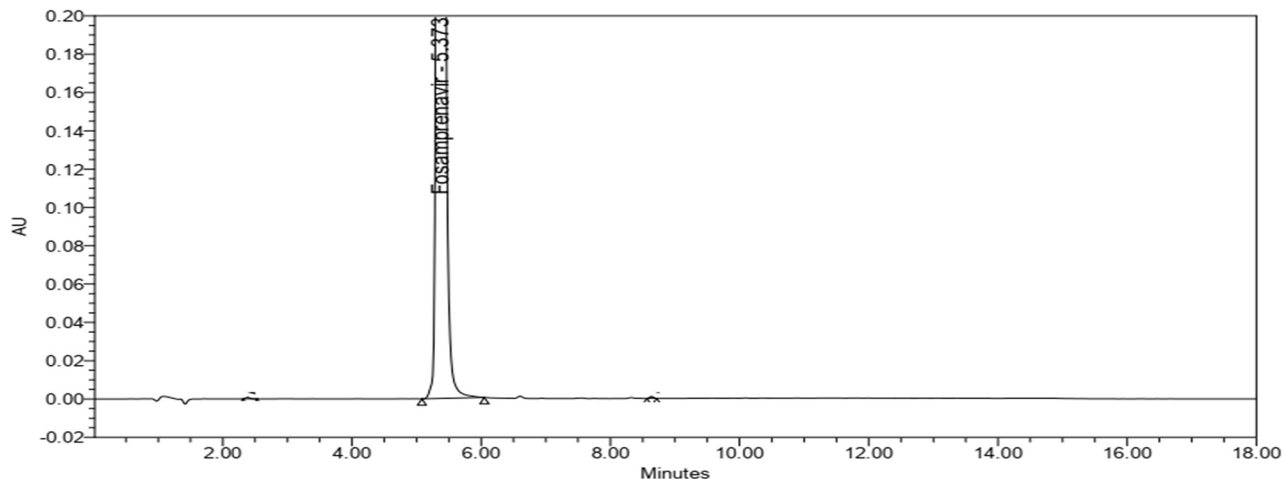


Fig. 4 Typical chromatogram representing the LOQ levels of Fosamprenavir and its impurities

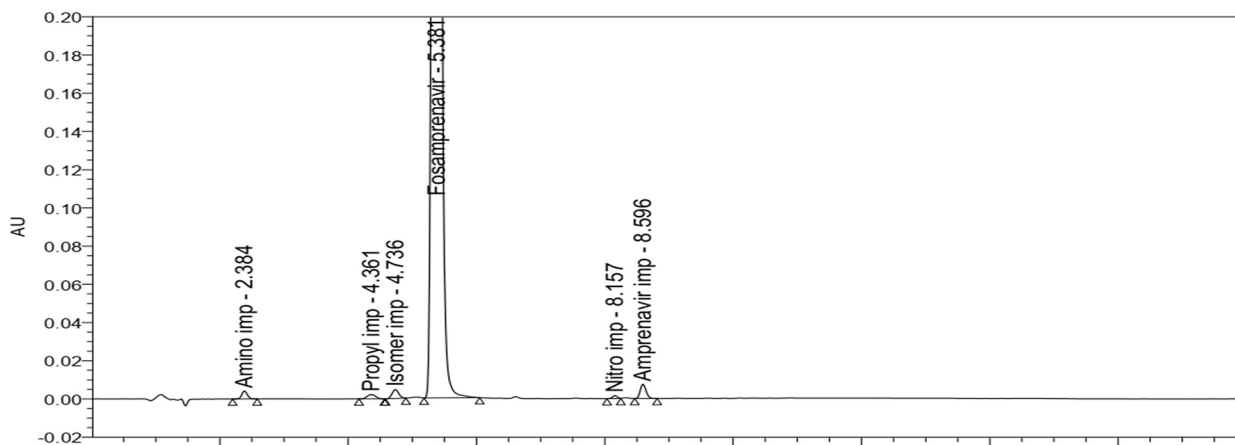
Discussion

Related substances (RS) HPLC procedures have become essential in pharmaceuticals for detecting and quantifying impurities and assuring regulatory compliance,

product safety, stability, and uniformity. The acceptable limits for impurities in Active Pharmaceutical Ingredients (API) as specified by various regulatory agencies are less than 0.1% for each impurity and less than 1% for total



(a) Fosamprenavir sample solution



(b) Fosamprenavir spiked with impurities

Fig. 5 Chromatograms representing the specificity of the method

Table 5 Precision data of the Fosamprenavir and its impurities

Precision		Amino impurity	Propyl impurity	Isomer impurity	Fosamprenavir	Nitro impurity	Amprenavir impurity
System precision	*Mean peak area	21599.8	21,453	34580.4	13403.60	7977.8	41944.20
	SD	107.26	390.75	104.54	108.49	398.46	121.63
	%RSD	0.50	1.13	0.78	1.36	0.95	0.29
Method precision	*Mean % recovery	100	98.2	98.6	100.06	99.68	100.68
	SD	0.80	1.17	1.57	1.01	0.86	1.32
	%RSD	0.80	1.20	1.60	1.01	0.87	1.32

Mean of six replicate injections of standard solution (system precision) and spiked solution method precision

Table 6 Percentage recovery of impurities from spiked sample solution of Fosamprenavir

% Level	Percentage Recovery (%) *Mean ± SD				
	Amino impurity	Propyl impurity	Isomer impurity	Nitro impurity	Amprenavir impurity
LOQ	97.93 ± 1.85	100.10 ± 1.37	100.30 ± 1.00	99.16 ± 1.51	99.63 ± 0.66
50	98.23 ± 1.09	98.86 ± 0.95	98.33 ± 0.55	99.26 ± 1.35	10.46 ± 0.30
100	99.23 ± 0.75	98.70 ± 1.47	98.93 ± 0.66	99.83 ± 1.00	99.26 ± 0.49
150	100.80 ± 0.40	100.93 ± 0.75	98.10 ± 0.81	99.46 ± 0.77	100.53 ± 0.05

* Mean of three repetitive % recoveries

Table 7 Robustness data for Fosamprenavir and its impurities

Variation in Parameter	Peak area	Amino impurity	Propyl impurity	Isomer impurity	Fosamprenavir	Nitro impurity	Amprenavir impurity	
Flow rate (mL/min)	0.9	*Mean	21195.20	20,985	34229.00	13180.00	7770.00	41223.00
		SD	200.69	187.31	165.92	213.40	109.61	413.65
		%RSD	0.94	0.89	0.48	1.61	1.41	1.00
	1.1	*Mean	21,741	21,318	34,969	13539.00	8056.00	42026.00
		SD	267.41	206.78	227.29	151.63	135.34	411.85
		%RSD	1.23	0.97	0.65	1.12	1.68	0.98
Wavelength (nm)	262	*Mean	21526.00	21336.00	34,349	13163.00	7855.00	41891.00
		SD	191.58	204.82	535.84	159.27	142.17	502.69
		%RSD	0.89	0.96	1.56	1.21	1.81	1.2
	264	*Mean	21657.00	21410.00	34491.00	13450.00	8019.00	41922.00
		SD	266.38	147.72	489.77	184.26	87.40	415.02
		%RSD	1.23	0.69	1.42	1.37	1.09	0.99

*Mean of six replicates

impurities [25]. They optimize processes, help evaluate risks, and promote research and development, ensuring the quality and efficacy of pharmaceuticals. The reported potential impurities of Fosamprenavir include isomer, amino, propyl, nitro, and Amprenavir impurities. Only two RS-HPLC methods have been reported for detecting and quantifying Fosamprenavir impurities. Only isomer, amino, and Amprenavir impurities of Fosamprenavir were identified and quantified using one method. In the other method, impurities 2 and 5 of Fosamprenavir were estimated. The present method is superior to the reported methods in terms of sensitivity and linearity range. The LOD and LOQ values of impurities and Fosamprenavir in the current method are higher than in the earlier methods [13, 22]. In the reported method, LOD and LOQ values were found to be isomer (0.06, 0.17 ppm), amino (0.07, 0.2 ppm), and Amprenavir (0.1, 0.3 ppm) impurities [13]. In the reported method, all potential impurities were not estimated concurrently. The current method can estimate all the stated impurities simultaneously with a run time of 10 min and RT of 5.3 min, 2.3 min, 4.3 min, 4.7 min, 8.1 min, and 8.6 min for Fosamprenavir, Amino, Propyl, Isomer, Nitro impurities, and Amprenavir impurity correspondingly with good resolution. The validation parameter results satisfied the ICH Q2 acceptance criteria, ensuring the method's competency.

Conclusion

An easy and efficient RP-HPLC method estimation of Fosamprenavir and its isomer, amino, propyl, nitro, and Amprenavir impurities in bulk and tablet form was developed. Using optimized method conditions, shorter elution time, reproducible precision, and high sensitivity were achieved. The method consists of reproducible specificity to assess Fosamprenavir and its impurities. Hence, the developed method has reasonable application in the pharmaceutical industry.

Abbreviations

OPA	Orthophosphoric acid
LOD	Limit of detection
LOQ	Limit of quantification
RSD	Relative standard deviation
SD	Standard deviation

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Author contributions

All authors contributed to the study's conception and design. RG, MVN, PKJ, VM, KP, SP performed material preparation, data collection, and analysis. RG, PPR, GSB wrote the first draft of the manuscript, VKN, KKK supervised the entire work and edited the manuscript. All authors read and approved the final manuscript.

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Data availability

All data provided within the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

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