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Research Paper

RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF COBICISTAT AND ATAZANAVIR IN BULK AND PHARMACEUTICAL DOSAGE FORM

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A stability indicating RP-HPLC method has been developed and subsequently validated for the simultaneous estimation of cobicistat and atazanavir in API and tablet dosage form. Optimized chromatographic condition were achived by Eclipse XBD-C18(250mm x 4.6mm, 5µ) column, mobile phase as a mixture of buffer (0.02M potassium dihydrogen phosphate, pH-2.5): acetonitril in the ratio of 40:60v/v with a flow rate of 1ml/min., UV detection was performed at 230nm and the sample temperature was maintained ambient which was injected manually. This developed method for simultaneous estimation of cobicistat and atazanavir is linear over a range of 60 – 180 ìg/ml and 120 -360 ìg/ml respectively. The validation parameters as per ICH guide lines show good precision having 0.054 and 0.083 %RSD for cobicistat and atazanavir which shows nice repeatability, limit of detection and limit of quantification for cobicistat and atazanavir was found to be 0.075 and 0.06 and 0.225 and 0.18 ìg/ml respectively. The developed method is easy to perform assay for indicating quality control determinations in bulk and formulated form with rapid, selective and stability indicating.

Keywords: RP-HPLC, Cobicistat, Atazanavir, Validation

INTRODUCTION

Cobicistat

Cobisistat Systematic (IUPAC) name was given as 1,3-Thiazole-5-ylmethy [(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino}-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexane-2-yl]carbamate. Its molecular formula is $C_{40}H_{53}N_7O_5S_2$ and molecular mass is 776.023 g/mol[1]. Cobicistat is adsorbed onto silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow solid with a solubility of 0.1 mg/ml in water

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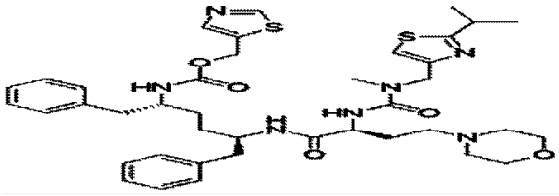
at 20°c. drug shows reduced liability for drug interactions and may have potential improvements in tolerability over ritonavir. In addition it has high aqueous solubility and can be readily co formulated with other agents.

Figure 1: Molecular Structure of Cobicistat

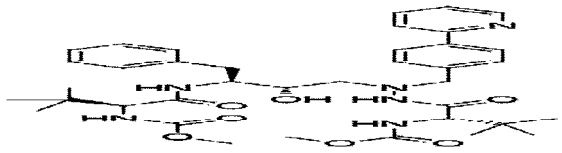


[2]Cobisistat is an anti-retroviral drug from the protease inhibitor class used to treat HIV infection and AIDS. Cobisistat is frequently prescribed with highly active antiretroviral therapy, not for its antiretroviral action, but as it inhibits the same host enzyme that metabolizes other protease inhibitors. This inhibition leads to higher plasma concentrations of these latter drugs, allowing the clinician to lower their dose and frequency and improving their clinical efficacy. It also inhibits intestinal transport proteins, increasing the overall absorption of several HIV medications, including atazanavir, darnavir and tenofovir alafenamide. From the literature survey, it was found that Cobisistat was estimated by analytical methods such as spectrophotometric method, HPLC method and HPTLC method. Ritonavir is very hydrophobic, non-ionizable and retains long in reverse phase chromatography.

Atazanavir

Atazanavir is an antiretroviral drug (protease inhibitor) is chemically methyl N-[(1S)-1-{[(2S,3S)-3-hydroxy-4-[(2S)-2[(methoxy-carbonyl) amino]-3,3-dimethyl-N'-{[4-(pyridine-2-yl) phenyl] ethyl}butane-hydrazido]-1-phenylbutan-2-yl] carbamoyl}-2,2-dimethyl propyl] carbamate-

Figure 2: Molecular Structure of Atazanavir



sulphate. It's molecular weight is 802.9g/mol. And molecular formula is C38H52N6O7.H2SO4. Atazanavir is an azapeptide HIV-1 protease-inhibitor, this compound is selectively inhibits the virus-specific processing of viral gag and gag-pol poly-proteins in HIV-1 infected cells, thus preventing formation of mature virion[3,4&5].

A few spectroscopic and Liquid chromatographic procedureshave been reported for the estimation of Atazanavir and Cobicistat individually, but there is no method for simultaneous estimation by RP-HPLC. Therefore there is a need to develop rapid and reliable method and validated for simultaneous estimation of combined dosage form and API (Active Pharmaceutical Ingredient) [6-11].

EXPERIMENTAL METHODOLOGY

Instrumentation: Waters Alliance 2695 separation module (Waters Corporation, Milford, USA) equipped with 2998 UV detector with Empower-2 software was used for the analysis. The HPLC system was equipped with a column compartment with temperature control and an on-line degasser. Data acquisition, analysis, and reporting were performed by Empower-2 chromatography software. Eclipse XDB-C18 (250 mm x 4.6 mm I.D; 5 µm) was used as stationary phase. Solubility of the compound was enhanced by sonication. All the weights in the experiments were done with Essea model: AJ220 Digital Electronic Balance.

Chemicals and Reagents: The reference samples of cobicistat & atazanavir were obtained from Ltd., Hyderabad. Purified water was prepared by using Milli-Q water purification system. HPLC grade methanol (Merck, Mumbai), which was used for preparing dilutions and mobile phase. Analytical grade potassium di-hydrogen phosphate 0.02M, pH 2.5 was adjusted with dilute orthophosphoric acid (buffer) was obtained from Rankem Fine Chemicals Ltd., New-Delhi. Evotaz, a formulation containing 150 mg of cobicistat and 300 mg atazanavir was purchased from local market.

Preparation of standard solution: The standard solution was prepared by dissolving 150mg of cobicistat and 300mg of atazanavir of working standard into a 100ml volumetric flask, dissolve and dilute to volume with diluent (water : acetonitril in ratio of 30:70). Pipette out 5ml into 50ml volumetric flask with and dissolve with diluents to get the working prepared standard solutions as 150 µg/ml and 300 µg/ml respectively. This prepared standard was injected and chromatogram was recorded at 230nm.

Preparation of sample solution: Twenty tablets were weighed and average weight was determined. Tablet powdered equivalent to cobicistat 150mg and atazanavir 300mg (Avg. wt is 605mg) of Evotaz formulation transferred into a 100 ml standard volumetric flask, dissolve with diluent. Solution was ultra-sonicated for 15min., filtered through Whatman filter paper No.42. Filtrate was diluted upto the mark with diluent to obtain final concentration pipette out 5 ml into 50 ml standard volumetric flask dissolve with diluent, this prepared sample (20 µl) was injected and chromatogram was recorded at 230nm. Content of drugs in sample solution was calculated by comparing mean peak area of sample with that of the standard. The typical chromatogram of cobicistat and atazanavir in tablet dosage form.

METHOD DEVELOPMENT

Binary mixture of potassium di-hydrogen phosphate (0.002M) in water adjust pH 2.5 with dilute ortho phosphoric acid (solvent-A) : acetonitrile (solvent –B) in 40:60 v/v proportions in isocratic mode of elution was used as mobile phase. The resultant solution was thoroughly mixed and filtered (poly-tetra-fluoro ethanol (PTFE) filter of 0.45 µm pore size) using vacuum pump and degassed by sonication to expel the dissolved gases in solvent system. The flow rate of mobile phase was adjusted at 1.0 mL/min and 20 ìL solutions as injection volume were maintained. The eluted compounds were monitored at 230 nm by using UV detector. The column oven temperature was maintained at 30æ%C. Data acquisition, analysis, and reporting was performed by LC solution Software found to be an efficient system for elution of drug with good peak shape as well as retention time 2.977 min. and 5.275 min. for cobicistat and atazanavir respectively with baseline stability.

Table 1: Results of Assay from Tablet Dosage Form

S.No.	Drug	Label claim (mg)	Amount found (mg)	Recovery (%)
1.	Cobicistat	150	149.184	99.456
2.	Atazanavir	300	298.914	99.638

METHOD VALIDATION

As per (ICH) International Conference on Harmonization guidelines, the method validation parameters such as specificity, linearity, precision, accuracy, LOD, LOQ and robustness were optimized[13&14].

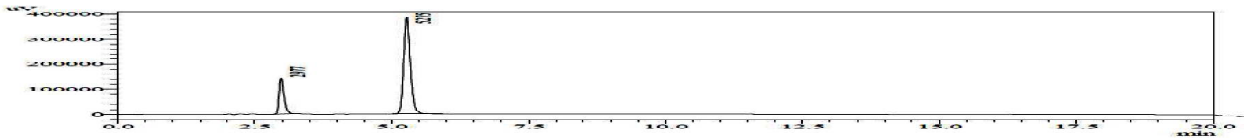
a) Specificity: Specificity is the extension to which the procedure applies to analyte of interest and is checked by examining the formulation sample for any interfering peaks. The specificity of the method was evaluated with regard to interference due to presence of excipients. The excipients used in the formulation did not interfere with the drug peak and thus the method is specific. The HPLC chromatogram recorded for the drug matrix (mixture of the drug and excipients) showed almost no interfering peaks within retention time ranges. Figures 2 and 3 showed the representative chromatograms for standard and the dosage form. The figure describes that the selected drug was clearly separated and the proposed HPLC method is selective.

b) Linearity: To establish linearity, the stock solutions were prepared as 1000 µg/ml using mobile phase, from the stock solution further dilutions were prepared in the concentration range of 600 - 100 µg/ml, elution's are made on HPLC by injecting 20 µg/ml of each concentration repeats it for two times. The coefficient of determination and regression coefficient (R^2) was obtained and shown in the Tables 2 and 3 and Figures 5 and 6.

Acceptance criteria: Correlation coefficient (r^2) should be not less than 0.999.

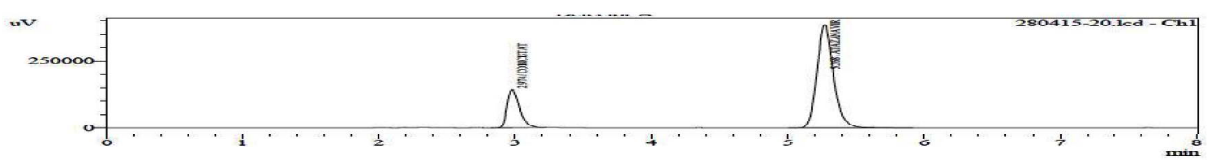
c) Precision: The intraday and inter-day precision was determined by analyzing cobicistat (150 µg/ml) and atazanavir (300 µg/ml) for six times on same day (intra-day) and repeated on the second day (inter-day) studies were given the Table 4 and 5 for Cobicistat and 6 and 7 for Atazanavir.

Figure 3: Chromatogram of Standard Solution of Cobicistat and Atazanavir



Peak	Rt (min.)	Name	Area	% Area	Theoretical Plate	Tailing Factor	Resolution
1	2.977	Cobicistat	897956	21.655	4510.212	1.558	0.000
2	5.275	Atazanavir	3248649	78.345	8615.727	1.228	11.358
Total			**4146605**	**100.00**			

Figure 4: Chromatogram of Evotaz Tablet Formulation Solution



Peak	Rt (min.)	Name	Area	% Area	Theoretical Plate	Tailing Factor	Resolution
1	2.974	Cobicistat	898104	21.658	4510.212	1.825	0.000
2	5.267	Atazanavir	3251274	78.408	8615.727	1.526	11.365
Total			**4149378**	**100.00**			

Table 2: Linearity Results for Cobicistat

Concentration of Drug (µg/mL)	Retention Time (min.)	Peak Area
60	2.997	389085
90	2.994	561590
120	2.989	730943
150	2.985	936818
180	2.979	1136957

Figure 5: Calibration Curve of Cobicistat

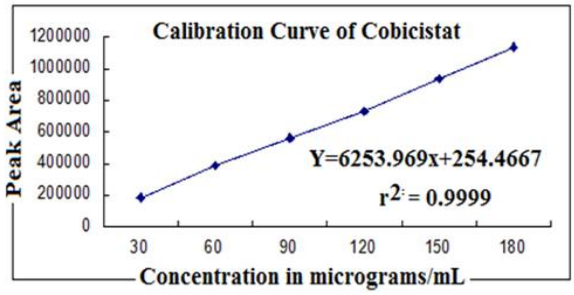


Table 3: Linearity Results for Atazanavir

Concentration of Drug (µg/mL)	Retention Time (min.)	Peak Area
120	5.297	1479296
180	5.302	2061916
240	5.304	2705765
300	5.308	3394149
360	5.310	4117020

Figure 6: Calibration Curve of Atazanavir

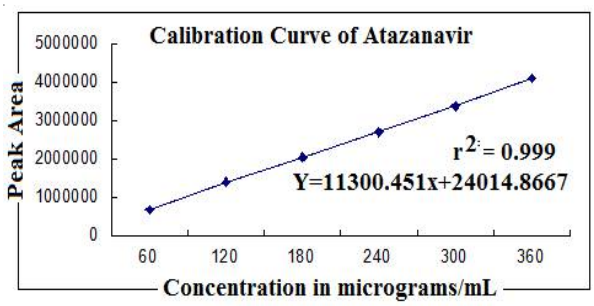


Table 4: Inter-day Precision for Cobicistat

Inj	Retention Time (min)	Peak Area
1	2.974	898188
2	2.975	898781
3	2.973	897805
4	2.972	898801
5	2.979	898461
6	2.978	899152
Mean	2.975	898531
Std.Dev	0.003	484
%RSD	0.091	0.054

Table 5: Intra-day Precision for Cobicistat

Inj	Retention Time (min)	Peak Area
1	2.975	899033
2	2.973	899889
3	2.976	899500
4	2.974	900022
5	2.973	899873
6	2.974	899682
Mean	2.974	899667
Std.Dev	0.001	360
%RSD	0.035	0.040

Table 6: Inter-day Precision for Atazanavir

Inj	Retention Time (min)	Peak Area
1	5.272	3252192
2	5.271	3252169
3	5.268	3249071
4	5.270	3254178
5	5.282	3254079
6	5.284	3257191
Mean	5.275	3253147
Std.Dev	0.007	2712
%RSD	0.126	0.083

Table 7: Intra-day Precision for Atazanavir

Inj	Retention Time (min)	Peak Area
1	5.275	3253683
2	5.271	3252899
3	5.272	3256265
4	5.269	3258247
5	5.268	3258752
6	5.270	3259628
Mean	5.271	3256579
Std.Dev	0.002	2787
%RSD	0.047	0.086

d) Accuracy: The accuracy of the method shall be demonstrated through determination on samples in three concentrations from 120% (600 µg/ml), 100% (500 µg/ml) and 80% (400 µg/ml), three replicates of each of the theoretical concentrations employed as per the usual procedure and the results are summarized in Tables 8 and 9.

Acceptance Criteria: The mean % recovery at each level should be NLT 98.0% & NMT 102.0%.

e) Limit of detection (LOD) and limit of quantification (LOQ): A series of 11 replicate concentrations were analyzed and quantified. Set up the described chromatographic conditions and allow the system to equilibrate. Starting with concentration 20%, 10%, 5%, 2%, 1%, 0.5%, 0.2%, 0.1%, 0.05%, 0.02% and 0.01% peak area values were given in the Table 10 for Cobicistat and atazanavir.

Table 8: Accuracy Results for Cobicistat

S.No.	Recovery at 120 µg/ml (80%) Dilution Level Peak Areas		Recovery at 150 µg/ml (100%) Dilution Level Peak Areas		Recovery at 180 µg/ml (120%) Dilution Level Peak Areas	
	Standard	Spiked (10%)	Standard	Spiked (10%)	Standard	Spiked (10%)
1.	720637	815699	898085	1014219	1117108	1243647
2.	720662	815193	898523	1014874	1117584	1244014
3.	719847	815337	897813	1014923	1117999	1243934
Mean	**720382**	**815410**	**898140**	**1014672**	**1117564**	**1243865**
Std.Dev	463.49	260.71	358	393.07	445.85	192.98
%RSD	0.064	0.032	0.040	0.039	0.040	0.016
% Recovery	**98.4**		**100.29**		**99.38**	
Average % Recovery -99.35						

Table 9: Accuracy Results for Atazanavir

S.No.	Recovery at 80% Dilution Level Peak areas		Recovery at 100% Dilution Level Peak areas		Recovery at 120% Dilution Level Peak areas	
	Standard	Spiked (10%)	Standard	Spiked (10%)	Standard	Spiked (10%)
1.	2623880	2956831	3250637	3703600	4033111	4498039
2.	2624796	2954184	3252870	3704584	4043957	4499580
3.	2623111	2955778	3250314	3706166	4045027	4501188
Mean	**2623929**	**2955598**	**3251274**	**3704783**	**4040698**	**4499602**
Std. Dev	844	1332.68	1392	1294.56	6592.57	1574.62
%RSD	0.032	0.045	0.043	0.035	0.163	0.035
% Recovery	**98.4**		**100.29**		**99.38**	
Average % Recovery -99.35						

Table 10: LOD and LOQ Values for Evotaz

S.No.	% Concentration	Concentration(µg/ml)		Peak Area	
		Cobicistat	Atazanavir	Cobicistat	Atazanavir
1	20	30	60	186134	684512
2	10	15	30	96891	347460
3	05	7.5	15	46095	172612
4	02	3.0	06	18608	69375
5	01	1.5	03	10245	39054
6	0.5	0.75	1.5	5218	19033
7	0.2	0.3	0.6	2282	8298
8	0.1	0.15	0.3	1559	6119
9	0.05	0.075	0.15	810	4203
10	0.02	0.03	0.06	ND*	863
11	0.01	0.015	0.03	ND*	ND*
Limit of Detection (LOD):				0.05%	0.02%
Limit of Quantification (LOQ):				**0.15%**	**0.06%**
Note: ND* - Not Detected.					

A series of 11 replicate concentrations were analyzed and quantified. Set up the described chromatographic conditions and allow the system to equilibrate. Starting with concentration 20%,

10%, 5%, 2%, 1%, 0.5%, 0.2%, 0.1%, 0.05%, 0.02% and 0.01% peak area values were given in the Table 10. For Cobicistat and atazanavir.

f) Robustness: The robustness of the method was determined as per USP guidelines, under different conditions including change in flow rate, different column, pH of buffer, and buffer concentration. The results obtained by deliberately variation in method parameters and data are summarized in Table 11.

Acceptance Criteria: There should be no significant effect on the result by doing small deliberate changes in the system as well as in method parameters.

g) System suitability: For system suitability, six replicates of the working standard samples were injected and the parameters like – plate number (N), retention time (Rt), and peak asymmetry of samples were calculated for Evotaz and given in Table 12.

Acceptance criteria: The % RSD for the retention times of principal peak from 5 replicate injections of each standard solution should be not more than 2.0%.

Table 11a: Robustness Results for Cobicistat

Parameter	Peak Areas for Flow Rate		Peak Areas for Variable Column		Peak Areas for pH Change	
	Flow Rate 1.2 ml	Flow Rate 0.8 ml	Zobrax Eclipse XBD-C18	Inertsil ODS - C18	pH – 2.6	pH – 2.4
Injection-1	824041	1002086	905148	898059	818363	1002966
Injection-2	820458	1003006	897996	908743	837366	1002385
Injection-3	823118	1001006	899001	899045	818367	1002975
Mean	**822539**	**1002033**	**900715**	**901949**	**824699**	**1002775**
Std. dev	1860.35	1001.07	3871.84	5904.39	10970.23	338.07
% RSD	0.226	0.100	0.430	0.655	1.330	0.034

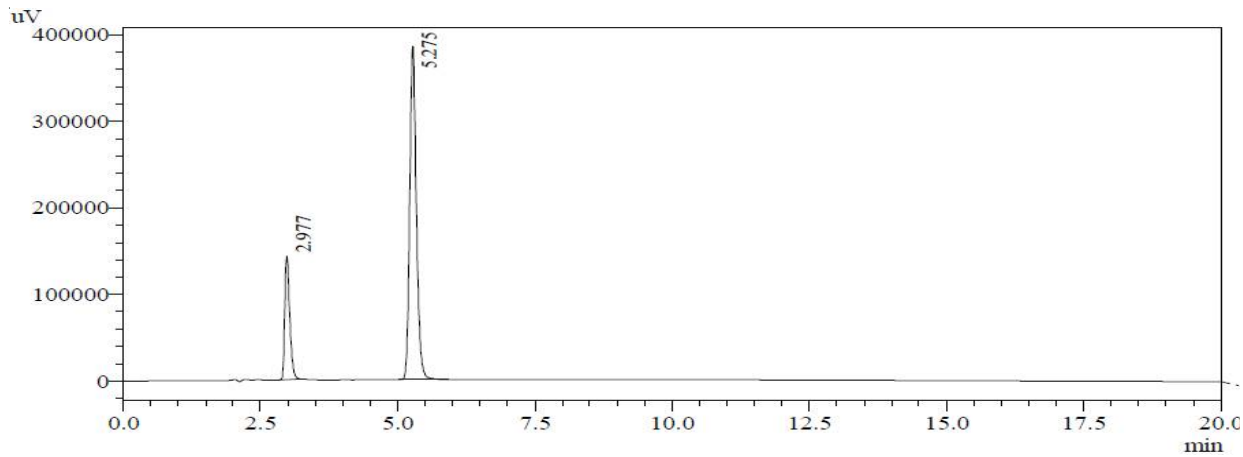
Table 11b: Robustness Results for Atazanavir

Parameter	Peak Areas for Flow Rate		Peak Areas for Variable Column		Peak Areas for pH Change	
	Flow Rate 1.2 ml	Flow Rate 0.8 ml	Zobrax Eclipse XBD-C18	Inertsil ODS - C18	pH – 2.6	pH – 2.4
Injection-1	2972227	3612656	3260274	3277932	2969379	3670412
Injection-2	2968912	3617999	3255359	3300435	3004039	3622048
Injection-3	2969200	3613086	3256417	3262849	2977300	3622202
Mean	**2970113**	**3614580**	**3257350**	**3280405**	**2983573**	**3638221**
Std. dev	1836.43	2968.45	2586.92	18914.67	18161.46	27878.62
% RSD	0.062	0.082	0.079	0.577	0.609	0.766

Table 12: Robustness Results for Cobicistat

Parameter	Results of the Proposed HPLC Method	
	Cobicistat	Atazanavir
Retention time (min)	2.977	5.275
Theoretical plates (n)	4510.212	8615.727
Plates per meter (N)	18040.848	34462.908
HETP (L/n)	0.00005543	0.00002901
Peak asymmetry (Tailing)	1.558	1.228
Linearity range (µg/mL)	60-180	120-360
Regression coefficient (R^2)	0.9999	0.999
Limit of Detection (µg/mL)	0.05	0.02
Limit of Quantification (µg/mL)	0.15	0.06

Figure 7: System Suitability Spectrum with Data for Evotaz



Peak	Retention Time (min)	Name	Peak Area	% Peak Area	Theoretical Plate	Tailing Factor	Resolution
1	2.977	COBICISTAT	897956	21.655	4510.212	1.558	00.000
2	5.275	ATAZANAVIR	3248649	78.345	8615.727	1.228	11.358
Total			4146605	100.00			

RESULTS AND DISCUSSION

The aim of the present study was to develop a simple, sensitive, precise, and accurate RP-HPLC method for the analysis of Cobicistat and Atazanavir in bulk and tablet formulation. To optimize the mobile phase, various combinations of buffer and acetonitrile solvents were studied, on a column Eclipse XBD-C18 (250 mm x 4.6

mm, 5µ). Finally by using mixture of 0.02M potassium di-hydrogen phosphate pH 2.5 (adjusted with ortho phosphoric acid) as buffer and acetonitrile in the ratio of (40:60 v/v) found to be an efficient system for elution of drug with good peak shape as well as retention time 2.977 and 5.275 min., for Cobicistat and Atazanavir respectively, flow rate 1.0 mL/min. at UV wavelength of 230 nm. Quantitative linearity was obeyed in the concentration range of 60 to 180 µg/ml, and 120 to 360 µg/ml the regression equations of concentration over their peak areas were found to be Y= 6253.969.X + 254.4667, r^2=0.9999, and Y=11300.451.X + 24014.8667, r^2=0.999 for cobicistat and atazanavir respectively where Y is the peak area and X is the concentration of drug. The number of theoretical plates obtained was 4510.212 for cobicistat and 8615.727 for atazanavir which indicate the efficient performance of the column. The Limit of detection was 0.05% and 0.02% and limit of quantification was 0.15% and 0.06% for cobicistat and atazanavir, which indicates the sensitivity of the method the high percentage recovery, indicates that the proposed method is highly accurate. No interfering peaks were found in the chromatogram indicating that excipients used in tablet formulation did not interfere with the estimation of the drug by the proposed RP-HPLC method.

CONCLUSION

In conclusion a new isocratic RP-HPLC method was developed and validated for the estimation of Cobicistat & Atazanavir in bulk and combined tablet dosage form. The developed method is simple, precise and accurate and satisfactory results were obtained through the method validation data. The present method can be easily applicable for routine drug analysis in laboratories and pharmaceutical industry.

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