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Advances in Bioresearch

ORIGINAL ARTICLE

Method Development and Validation for the Simultaneous Determination of Paritaprevir, Ombitasvir and Ritonavir in Formulation by RP-UPLC

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ABSTRACT
A sensitive, rapid and accurate, stability-indicating RP-UPLC method for the simultaneous estimation of OMTR, PRTR and RTNR in formulations was developed and validated as per the ICH guidelines. Retention times for OMTR, PRTR and RTNR were achieved at 0.848 min, 1.464 min, and 0.608 min respectively. Mean percentage recovery of OMTR, PRTR and RTNR were found to be 100.19%, 99.62%, and 99.86% respectively. LOD /LOQ values obtained from regression equations of OMTR, PRTR and RTNR and were found to be 0.34µg/ml /1.03 µg/ml, 0.48µg/ml /1.44 µg/ml and 0.10µg/ml /0.29 µg/ml respectively. Regression equation of OMTR, PRTR and RTNR wer: y = 7495.1x + 947.85, y=13764x + 13436 and y = 6494.1x + 1325.8 respectively. Stability studies of these drugs proven that the percentage degradation of analytes were found in between 0.36% to 13.03%. Retention time and total run times of analytes were decreased. Hence, the developed method was rapid and economical that can be applicable in routine analysis of these drugs in quality control department of pharmaceutical trades.
Keywords: Paritaprevir, Ombitasvir, Ritonavir, Robustness, Accuracy, RP-UPLC.

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INTRODUCTION

Ritonavir, [1] is chemically known as 2,4,7,12-tetra azatridecan-13-oicacid, 10-hydroxy-2-methyl-5-(1-methyl ethyl)-1-[2-(1-methyl ethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolmethyl ester(Fig. 1). It is an antiretroviral drug [2], an inhibitor of HIV-1 (human immunodeficiency virus) protease [3-5] used to treat HIV infection and AIDS (acquired immune deficiency syndrome). As of now once in a while utilized for its own particular antiviral movement [6], yet re-mains generally utilized as a sponsor of other protease inhibitors. This prevents cleavage of the gag-pol polyprotein [7]. All the more particularly, ritonavir is utilized to restrain a specific liver catalyst that ordinarily processes protease inhibitors, CYP3A4 is a member of the cytochrome P450 family of oxidizing enzymes [8]. Ombitasvir is an antiviral medication for the treatment of hepatitis C [9] infection (HCV) due to hepatitis C virus. In the United States, it is affirmed by the Food and Drug Administration for use in the blend with paritaprevir, ritonavir and dasabuvir in Viekira Pak for the treatment of HCV genotype 1 [10] and with paritaprevir and ritonavir in Technivie for the treatment of HCV genotype 4 [11]. Paritaprevir is an acyl sulfonamide inhibitor that shows promising outcomes for the treatment of hepatitis C [12]. At the point when given in mix with ritonavir and ribavirin for 12 w, the rate of supported virological reaction at 24 w after treatment has been evaluated to be 95% for those with hepatitis C virus genotype 1 [13]. Resistance to treatment with paritaprevir is phenomenal, on the grounds that it focuses on the coupling site, however, has been believed to emerge because of transformations at positions 155 and 168 in NS3 [14]. Paritaprevir is available in three fixed-dose products: Viekira Pak (FDA), Technivie (FDA and Health Canada) and Holkira Pak (Health Canada) in Canada and the United States [15]. Different analytical

methods are in like manner itemized in the written work for the estimation of ritonavir, ombitasvir and paritaprevir. As showed by composing study there is one specialized method for the estimation of ritonavir, ombitasvir and paritaprevir by RP-HPLC in tablet estimation [16, 17]. Thus, it has been proposed to make a method for estimation and endorsement of ritonavir, ombitasvir and paritaprevir in the arrangement according to the ICH rules [18].

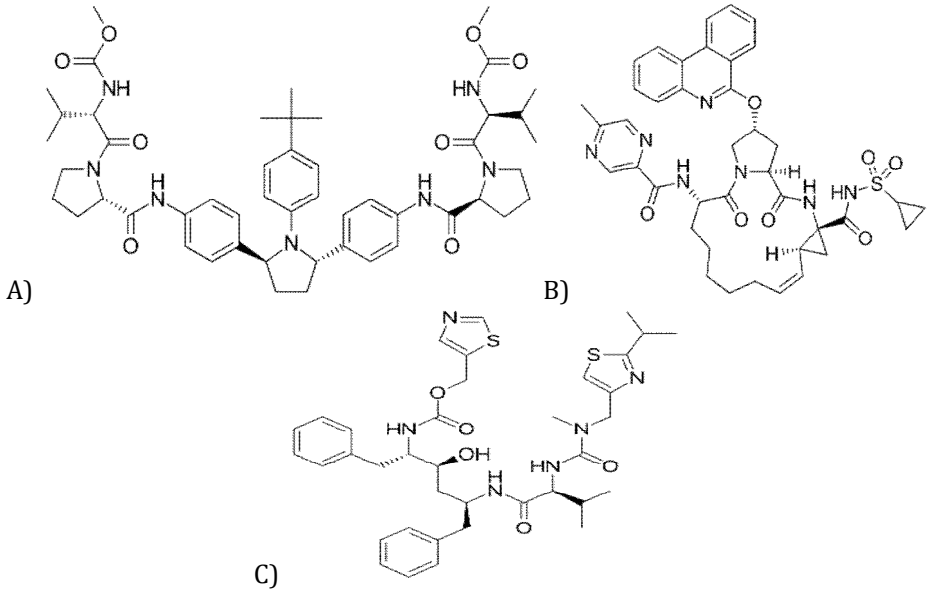

Fig. 1: Structures of A) OMTR, B) Paritaprevir, and C) Ritonavir.

MATERIAL AND METHODS

Chemicals and reagents

The standard components of OMTR, PRTR and RTNR were provided as a gift sample from spectrum Pharma Research Solutions, Hyderabad. Technivie tablets labelled to contain OMTR 12.5mg, PRTR 75 mg and RTNR 50 mg were procured from the local market. HPLC grade methanol was obtained from A.B enterprises, Mumbai, India. Orthophosphoric acid was bought from Ranchem, Mumbai, India. HPLC grade water was processed by utilizing Milli-Q Millipore water purification system used during the method development.

Method development

During the method development various mobile phase compositions consisting of methanol, acetonitrile, water, phosphate buffers and different stationary phases were executed to get fine chromatographic conditions like theoretical plates, resolution, tailing and peak shape. The processed trials were mentioned below:

Optimized Chromatographic Conditions

Chromatographic system of Waters UPLC system furnished with photodiode array detector, auto-sampler, and Zorbax C18 column which have dimensions of 100 x 3 mm, 1.7 µ particle size. The output signal was monitored and integrated utilizing water Empower-2.0 software. The isocratic mobile consisting of 0.01N Potassium dihydrogen ortho phosphate (pH 5.3) and methanol in the proportion of 70:30%v/v, pumped through the Zorbax C18 (100 × 3.0mm, 1.7 µ) column at a fixed flow of 0.3 ml/ min. The injection volume of 0.2 µL was utilized to measure the chromatograms at 252 nm as wavelength maximum in the detection system.

Preparation of buffer

Accurately weighed 1.36gm of Potassium dihydrogen ortho phosphate in a 1000ml of volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water then pH adjusted to 5.3 with dilute orthophosphoric acid solution.

Preparation of standard stock solution

Accurately Weighed and transferred 18.75mg of PRTR, 12.5mg of RTNR and 3.125mg of OMTR working Standards into 25 ml clean dry volumetric flasks, add 10ml of diluent, sonicated for 10 minutes and make up to the final volume with diluent (Water: Methanol (50:50)) to get 750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR.

Preparation of sample solution

20 tablets were weighed and calculated the average weight of tablets and then the weight equivalent to 1 tablet was transferred into a 100 mL volumetric flask containing 50mL of diluent and sonicated for 25.0 min. Further the volume made up with diluent and subjected for filtration by HPLC filters (750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR). From the filtrate 1.0 ml solution was pipetted out into a 10.0 ml volumetric flask and made upto 10.0 ml with diluent to get 75µg/ml of PRTR, 50µg/ml of RTNR and 12.5µg/ml of OMTR.

Analytical method validation

The developed method for OMTR, PRTR and RTNR was subjected for validation for the parameters like limit of detection (LOD), limit of quantification (LOQ), linearity, robustness, precision, system suitability and accuracy as per the guidelines of ICH[18,19].

RESULTS AND DISCUSSION

Method development

With different mobile phase compositions and stationary phases five different trials were executed and sixth trail was optimized. In all the five trials there was no base line separation in trial-1 and trial-2, merged peaks were observed in trail-3, peak shape was poor in the trail-4, and there was poor resolution in the trial -5. Optimized chromatographic peaks were shown in Fig. 2

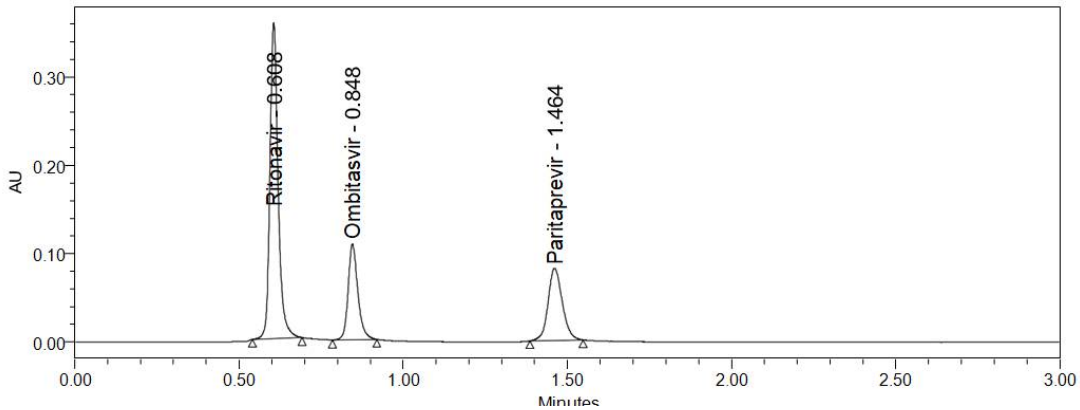

Fig. 2: Optimized chromatogram.

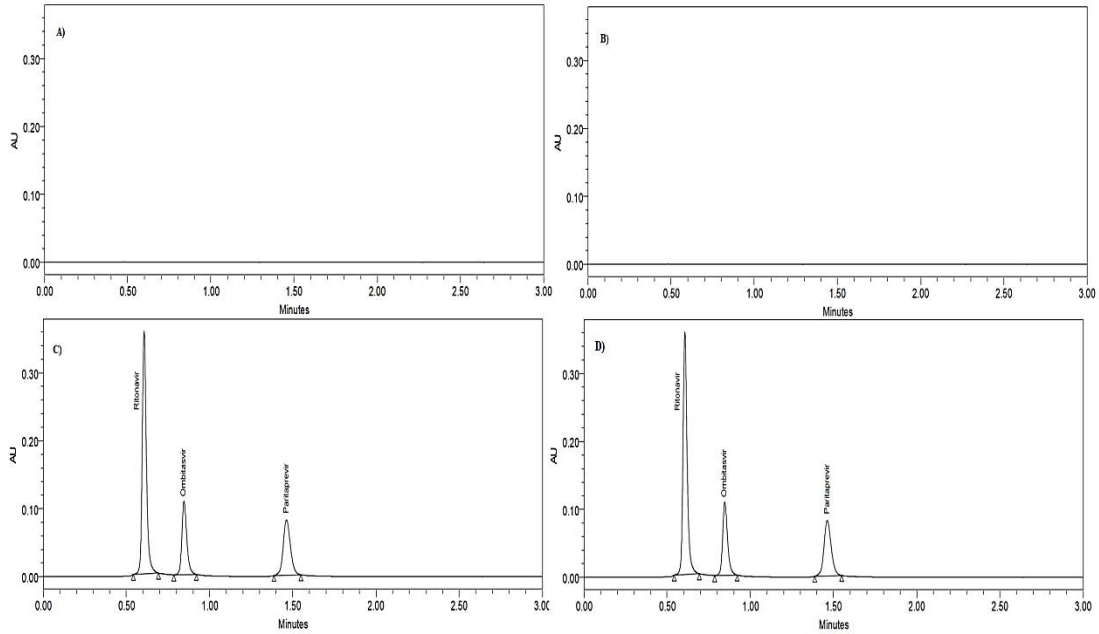

Fig. 3: Chromatograms of A) blank, B) Placebo, C) Standard and D) Formulation.

Method validation

Specificity

It is the ability of a method to unequivocally evaluate the analyte components in presence of other components like impurities, degradants and excipients etc. expected to be present. This parameter was

estimated by injecting and evaluating the blank, placebo, standard and sample solutions and chromatograms respectively [13,14]. Chromatograms of blank, placebo, and sample solution shown no peaks at the retaining time of OMTR, PRTR and RTNR peaks. The chromatograms of OMTR, PRTR and RTNR of standard, blank, formulation, and placebo were represented in Fig. 3.

Linearity

Aliquots of 0.25, 0.50, 0.75, 1.0, 1.25, and 1.50 ml of standard stock solution were pipetted out from the standard stock solution of concentration 750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR and made up to 10.0 ml mark with diluent [10-15]. The resulting solutions were coming into 18.75 to 112.5 µg/ml of PRTR, 12.5 to 75 µg/ml of RTNR and 6.25 to 37.5 µg/ml of OMTR concentration range. The resulting linearity solutions were infused into a chromatographic system and form the chromatograms linearity graph was plotted by taking the peak area on Y-axis and concentration on X-axis. The calibration graphs were shown in Fig. 4-6 and Table 1, and all findings were within the limits.

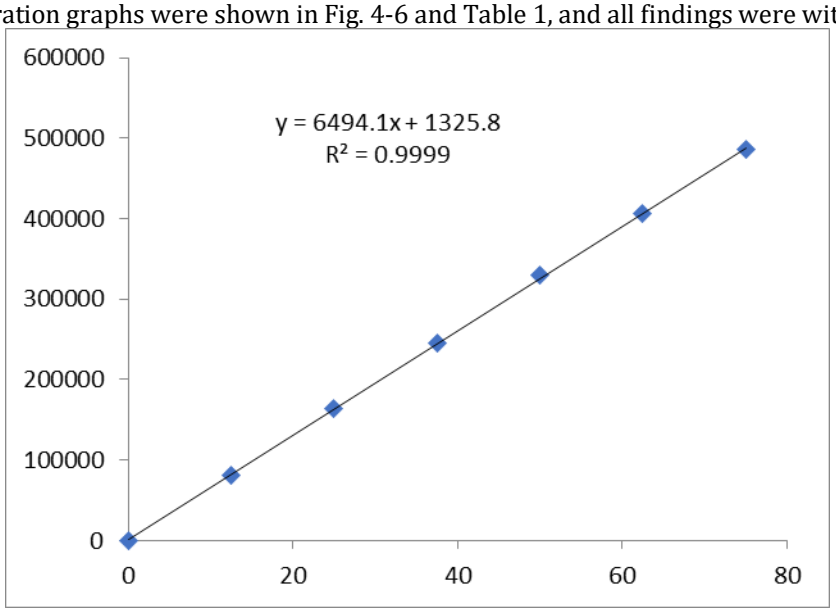

Fig.4: Linearity of RTNR

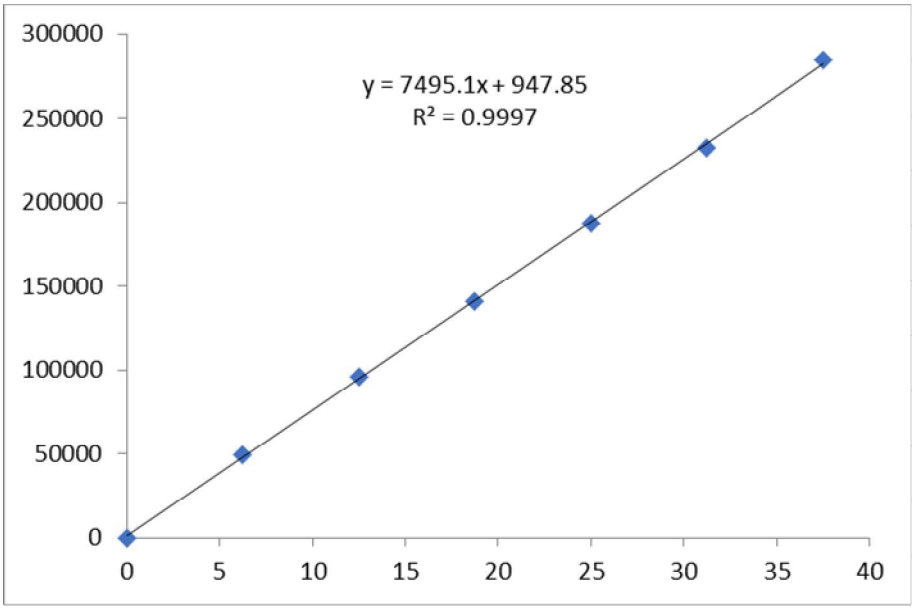

Fig. 5: Linearity of OMTR

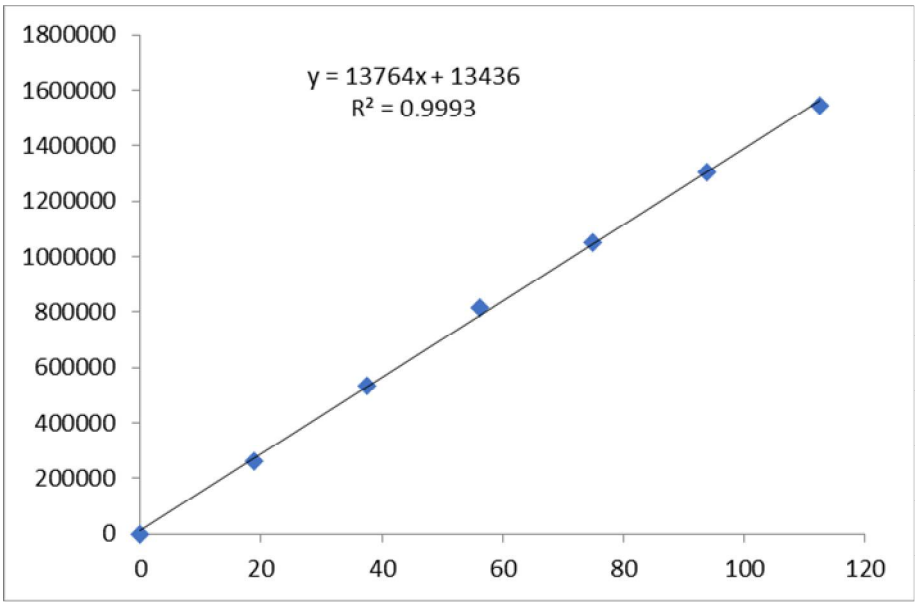

Fig.6: Linearity of PRTR

Table 1: Calibration curve data of OMTR, PRTR and RTNR.

PRTR		RTNR		OMTR	
Concentration (µg/ml)	**Peak area**	**Concentration (µg/ml)**	**Peak area**	**Concentration (µg/ml)**	**Peak area**
18.75	264180	12.5	81636	6.25	49632
37.5	535644	25	164776	12.5	95550
56.25	814159	37.5	245348	18.75	140564
75	1052124	50	329483	25	187293
93.75	1304536	62.5	406730	31.25	232810
112.5	1542961	75	486017	37.5	284512
Regression equation					
y = 13764x + 13436		y = 6494.1x + 1325.8		y = 7495.1x + 947.85	
Correlation coefficient (R2)					
0.9993		0.9999		0.9997	

System suitability

Six replicates of the standard reference solution were processed and infused to perform the system suitability parameter and the resulting chromatograms peak area, retention time, resolution, plate count, and tailing were measured. The findings of system suitability parameter were shown in the Table 2 and related chromatograms were given in Fig. 3.

Table 2: OMTR, PRTR and RTNR system suitability results.

S No	Peak name	Peak area	Retention time	Plate count	Resolution	Tailing
1.	RTNR	322068	0.608	3637		1.15
2.	OMTR	196787	0.848	5770	4.9	1.31
3.	PRTR	903096	1.464	7291	4.2	1.32

LOD and LOQ

LOD and LOQ parameters for OMTR, PRTR and RTNR were calculated form the linear regression equation[18]. Linearity values, graph and regression equation were got from the linearity study and the LOD and LOQ values were represented in the Table 3 (Fig 7,8).

Table 3: Limit of detection and limit of quantification results

Parameter	Measured concentration (µg/ml)		
	OMTR	PRTR	RTNR
LOD	0.34	0.48	0.10
LOQ	1.03	1.44	0.29

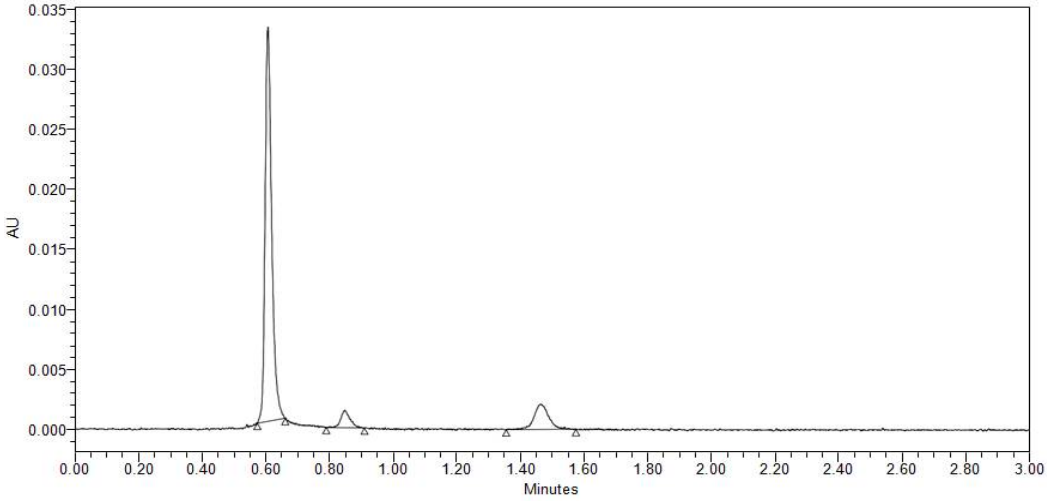

Fig. 7: Chromatogram for LOD

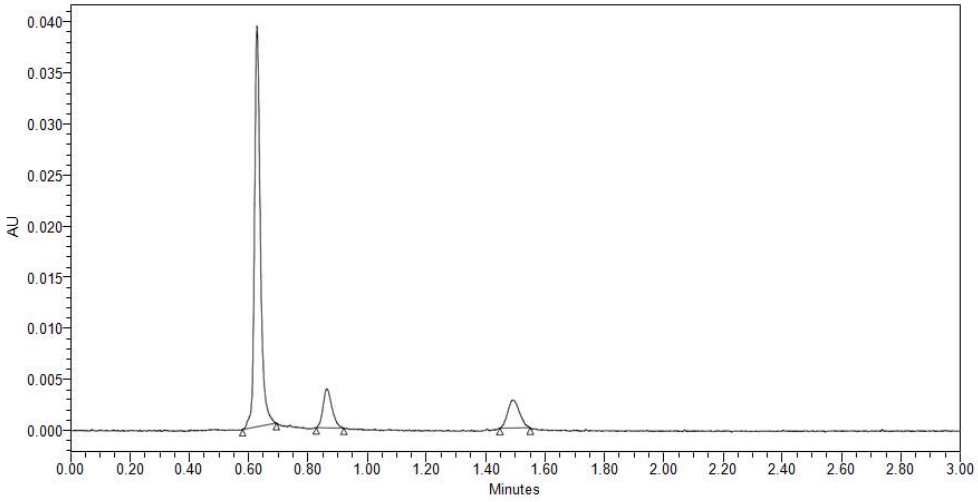

Fig. 8: Chromatogram for LOQ

Precision

Analytical method precision is defined as closeness of agreement between the replicate measurements of the analyte. It is expressed as the percentage coefficient of correlation or relative standard deviation (RSD) of the replicate measurements.

System precision

Working standard preparation of 0.2 µl solution was infused six times into the chromatographic system and chromatograms were obtained. %RSD of the peak area was calculated. The findings of system precision were shown in Table 4.

Table 4: System precision data

S. No.	Peak area response of analytes		
	OMTR	PRTR	RTNR
1	195011	900762	326623
2	196240	908579	323604
3.	198455	908664	322068
4	196312	903595	323068
5	199634	903033	320916
6	196787	903096	325455
Average	197073	904622	323022
STDV	1677.8	3249.7	2117.1
% RSD	0.9	0.4	0.7

Method precision

Working sample solutions of 0.2 µl was infused 6 times into the chromatographic system and chromatograms were obtained[15]. The %RSD of the assay result of six preparations was determined. The findings achieved for assay were represented in Table 5.

Table 5: Method precision results

S. No.	Peak area response of drugs		
	OMTR	PRTR	RTNR
1	198386	905817	328929
2	196022	905698	320925
3.	195669	913631	325056
4	196916	907149	323527
5	197400	900497	324498
6	197831	901256	324874
Average	197037	905675	324635
STDV	1048.6	4729.3	2595.5
% RSD	0.5	0.5	0.8

Intermediate precision

Working standard preparation of 0.2 µl was infused six times test preparations into the chromatographic system and chromatograms were obtained. The %RSD was evaluated for peak areas. The findings of intermediate precision study were represented in Table 6.

Table 6: Intermediate precision results

S. No.	Peak area response of drugs		
	OMTR	PRTR	RTNR
1	180926	862024	306500
2	184329	872445	309802
3	181999	865006	300803
4	180541	871249	307626
5	184666	864840	304839
6	181777	884123	302310
Average	182373	869948	305313
STDV	1733.7	8027.0	3361.3
% RSD	1.0	0.9	1.1

Accuracy

A known amount of OMTR, PRTR and RTNR at each three concentration levels of 50%, 100%, and 150% was added to a pre-analyzed sample solution and injected in triplicate at each level into the chromatographic system[16-20]. The mean percentage recovery of OMTR, PRTR and RTNR at each level was estimated. The findings were represented in Tables 7.

Table 7: Percentage recovery results

	OMTR				PRTR				RTNR			
Spiked level	Spiked (µg/ml)	Recovery (µg/ml)	% recovery	Mean % recovery	Spiked (µg/ml)	Recovery (µg/ml)	% recovery	Mean % recovery	Spiked (µg/ml)	Recovery (µg/ml)	% recovery	Mean % recovery
50%	12.5	12.48	99.80	100.19	37.5	37.25	99.33	99.62	25	25.32	101.27	99.86
	12.5	12.56	100.47		37.5	37.37	99.64		25	25.17	100.69	
	12.5	12.41	99.27		37.5	37.38	99.65		25	25.11	100.43	
100%	25	24.87	99.48		75	75.33	100.44		50	50.01	100.02	
	25	24.97	99.87		75	74.61	99.48		50	49.56	99.12	
	25	25.11	100.45		75	74.51	99.35		50	49.76	99.52	
150%	37.5	38.07	101.53		112.5	111.95	99.51		75	74.048	98.73	
	37.5	37.72	100.60		112.5	112.11	99.65		75	74.65	99.54	
	37.5	37.59	100.24		112.5	111.95	99.51		75	74.58	99.44	

Robustness

Working standard solution prepared as per test method was infused into the chromatographic system at variable conditions such as flow rate at ±0.1 ml/min, mobile organic phase composition by ±10%, and column temperature by ±5°C. The results of robustness study parameter like peak area, retention time, plate count and tailing factor were within the limits.

Forced degradation studies

Acid Degradation Studies

To 1 ml of stock s solution OMTR, PRTR and RTNR, 1ml of 2N Hydrochloric acid was added and refluxed for 30mins at 60°[19-20]. The resultant solution was diluted to obtain 750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR solution and 0.2 µl solution was injected into the chromatographic system and the chromatograms were recorded to assess the stability of the sample (Fig. 9 and Table 8).

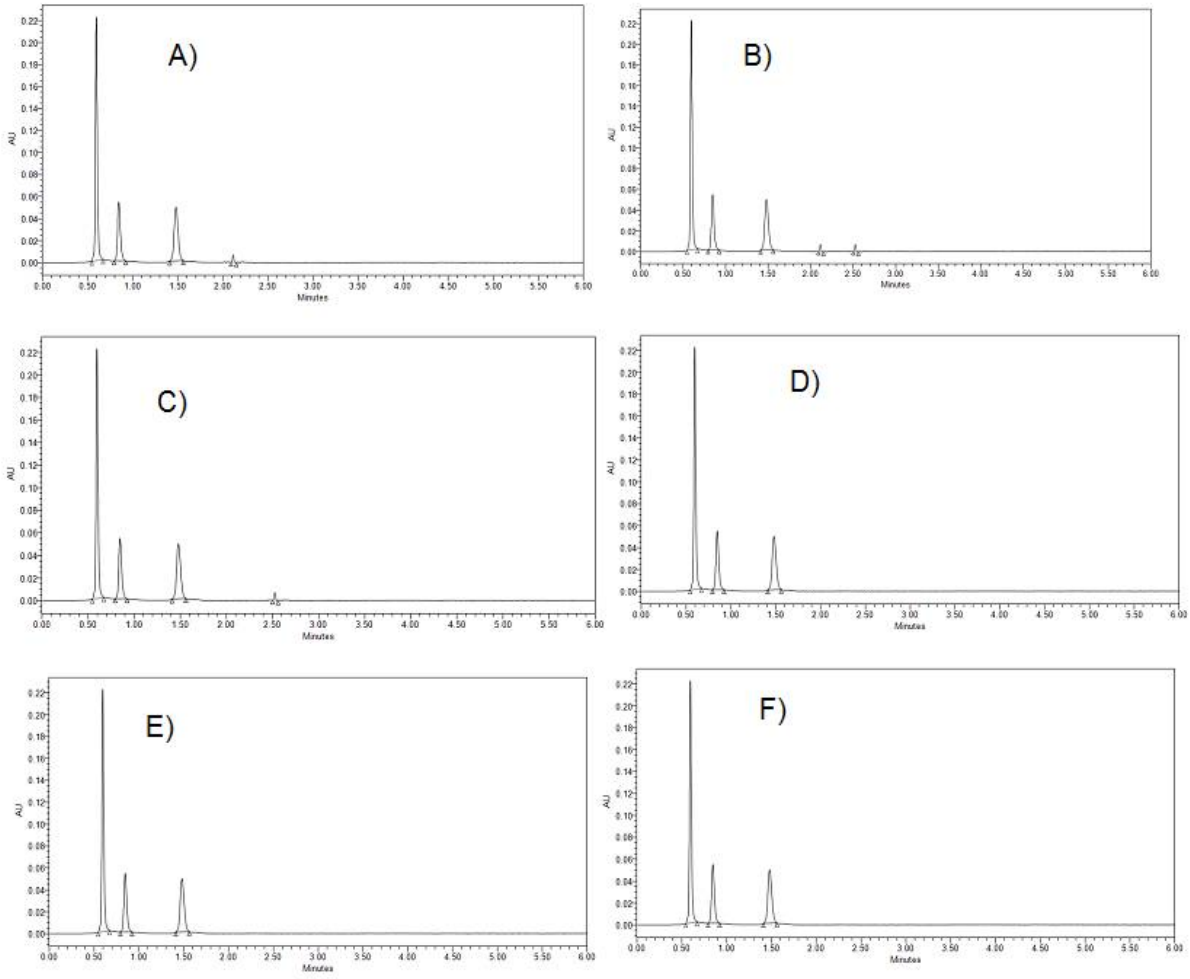

Fig.9: Chromatograms for A) acid B) oxidation C) alkali D) dry heat E) photo F) neutral degradation study.

Table 8: Results of stress degradation study.

S.No	Degradation condition	PRTR		RTNR		OMTR	
		% recovery	% Degraded	% recovery	% Degraded	% recovery	% Degraded
1	Acid hydrolysis	93.91	6.09	92.88	7.12	86.97	13.03
2	Base hydrolysis	93.99	6.01	94.70	5.30	95.92	4.08
3	Peroxide	94.94	5.06	89.55	10.45	90.59	9.41
4	Dry heat	97.34	2.66	96.44	3.56	97.32	2.68
5	Photo stability	98.78	1.22	97.43	2.57	98.62	1.38
6	Water sample	99.62	0.38	99.33	0.67	99.64	0.36

Oxidation

To 1 ml of stock solution of VXR, SFR and VLR, 1 ml of 20% hydrogen peroxide (H_2O_2) was added separately. The solutions were kept for 30 min at 60°C. For UPLC study, the resultant solution was diluted to obtain 750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR solutions and 0.2 µl solution was injected into the chromatographic system and the chromatograms were recorded to assess the stability of sample (Fig. 9 and Table 8).

Alkali Degradation Studies

To 1 ml of stock solution OMTR, PRTR and RTNR, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 60°C[38]. The resultant solution was diluted to obtain 750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR and 0.2 µl solution was injected into the chromatographic system and the chromatograms were recorded to assess the stability of sample (Fig. 9 and Table 8).

Dry Heat Degradation Studies

The standard drug solution was placed in oven at 105°C for 6 h to study dry heat degradation. For UPLC study, the resultant solution was diluted to get 750 µg/ml of PRTR, 500 µg/ml of RTNR and 125 µg/ml of OMTR and 0.2 µl solution was injected into the chromatographic system and the chromatograms were recorded to assess the stability of the sample**.** (Fig. 9 and Table 8).

Photo Stability studies

The photochemical stability of the drug was also studied by exposing the (100 µg/ml, 400 µg/ml and 100 µg/ml) solution to UV Light by keeping the beaker in UV Chamber for 3days or 200 Watt hours/m^2 in photo stability chamber[19]. For UPLC study, the resultant solution was diluted to obtain 750µg/ml of PRTR, 500µg/ml of RTNR and 125µg/ml of OMTR and 0.2 µl solution was injected into the chromatographic system and the chromatograms were recorded to assess the stability of sample (Fig. 9 and Table 8).

Neutral Degradation Studies

Stress testing under neutral conditions was studied by refluxing the drug in water for 6 hrs at a temperature of 60 ℃. For UPLC study, the resultant solution was diluted to get 750 µg/ml of PRTR, 500 µg/ml of RTNR and 125 µg/ml of OMTR and 0.2 µl solution was injected into the chromatographic system and the chromatograms were recorded to assess the stability of the sample (Fig. 9 and Table 8).

Assay of marketed formulation

The marketed formulation of Technivie (film coated tablet) was evaluated by infusing 0.2 µl of reference and analyte solutions six times into the chromatographic system and the resulting chromatograms of analytes were documented. The quantity of anaytes existed in the marketed formulation was estimated by equating the peak area of reference and analyte. The % assay of OMTR, PRTR and RTNR were found to be 98.6–101.2%.

In the literature all the methods were reported on the HPLC techniques with more retention time and run times. In the present work we selected UPLC to reduce the total run time. Method development was executed with different columns and mobile phases. Finally, the method was optimized with mobile phase of 0.01N Potassium dihydrogen orthophosphate (pH 5.3) and methanol in the proportion of 70:30%v/v utilizing a Zorbax C18 column which has dimensions of 100 x 3 mm, 1.7µ particle size and the flow rate of 0.3 ml/min. Further, the developed method was subjected for validation and forced degradation studies. Validation was executed as per the ICH Q2R1 guidelines for the parameters specificity, linearity, system suitability, LOD and LOQ, precision, accuracy and robustness. All the parameters were within the limits. Developed method was subjected for forced degradation studies as per the ICH like neutral degradation, photo stability, dry heat degradation, alkali degradation, oxidation and acid degradation. The degradation results also produced in the results section.

CONCLUSION

A sensitive, rapid and accurate, stability-indicating RP-UPLC method for the simultaneous estimation of OMTR, PRTR and RTNR in formulations was developed and validated as per the ICH guidelines. Retention times for OMTR, PRTR and RTNR were achieved at 0.848 min, 1.464 min, and 0.608 min respectively. Mean percentage recovery of OMTR, PRTR and RTNR were found to be 100.19%, 99.62%, and 99.86% respectively. LOD /LOQ values obtained from regression equations of OMTR, PRTR and RTNR and were found to be 0.34µg/ml /1.03 µg/ml, 0.48µg/ml /1.44 µg/ml and 0.10µg/ml /0.29 µg/ml respectively. Regression equation of OMTR, PRTR and RTNR wer: y = 7495.1x + 947.85, y=13764x + 13436 and y = 6494.1x + 1325.8 respectively. Stability studies of these drugs proven that the percentage degradation of analytes were found in between 0.36% to 13.03%. Retention time and total run times of analytes were decreased. Hence, the developed method was rapid and economical that can be applicable in routine analysis of these drugs in quality control department of pharmaceutical trades.

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