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ORIGINAL ARTICLE

Validated RP-HPLC Assay for Fixed-Dose Combination in Chemotherapy with Forced Degradation Studies

Jhansi Rani Sriramula[1]*, Shivaraj[2]
[1]*Research Scholar, University College of Technology, Osmania University, Hyderabad-500007, Telangana State, India.
[2]Professor and Principal, University College of Science and Bos Chemistry, Osmania University Hyderabad-500007, Telangana State, India.
***Correspondence author email:** ranijansi25@gmail.com

ABSTRACT
A novel, accurate and precise method has been developed for the simultaneous estimation of the Olaparib and Bevacizumab in tablet dosage form by RP-HPLC technique. Chromatographic elution was processed through the mobile phase composition of Acetonitrile and OPA (30:70 v/v,) using Inertsil ODS 150mmx4.6mm, 3.5µ, 1.0 mL/min flow rate with UV detection at 259 nm and a run time of 6 min. An injection volume of 5 µl was infused through an HPLC system to get the better performance. Retention times of Olaparib and Bevacizumab were found to be 2.336 and 4.873 min respectively. The regression equations for Olaparib and Bevacizumab were found to be y=16815.19x+22410.75 and y=14512.58x+2387.04, respectively. The proposed method was found to be linear in the concentration range of 37.50 to 225 µg/ml and 6.25 to 37.50µg/ml for Olaparib and Bevacizumab respectively and the R2 value of both drugs was found to be more than 0.999. Three levels of Accuracy samples were prepared by standard addition method. Triplicate injections were given for each level of accuracy and mean %recovery was obtained as 99.7% and 100.1% for Olaparib and Bevacizumab respectively indicating the proposed method is accurate. The LOD and LOQ values obtained from regression equations of Olaparib and Bevacizumab were found to be 0.9µg/ml, 0.1500µg/ml and 3.00 µg/ml, 0.5000 µg/ml, respectively which indicates the sensitivity of the method. Forced degradation studies have been performed as per ICH Q1A (R2) and Q1B guidelines, and percentage of degradation was found to be within the range of standard values.
KEYWORDS: HPLC, Method development, Validation, Forced degradation studies, Olaparib Bevacizumab, ICH guidelines

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INTRODUCTION

Olaparib is a selective and potent inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP1 and PARP2 [1-3]. PARP inhibitors represent a novel class of anti-cancer therapy and they work by taking advantage of a defect in DNA repair in cancer cells with BRCA mutations and inducing cell death [4]. Olaparib is used to treat a number of BRCA-associated tumours, including ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer [5]. It was first approved by the FDA and EU in December 2014 and by Health Canada in April 2016 [6]. The molecular formula of Olaparib $C_{24}H_{23}FN_4O_3$ and its molecular weight is 434.4628. The chemical Structure of Olaparib is shown in Figure 1 [7].

In 2004, Bevacizumab (Avastin) gained FDA approval for specific types of cancer, and became the first antiangiogenic agent introduced to the market [8,9]. It is a humanized monoclonal IgG antibody, and inhibits angiogenesis by binding and neutralizing VEGF-A [10,11]. Bevacizumab is generally indicated for use in combination with different chemotherapy regimens which are specific to the type, severity, and stage of cancer [12]. Bevacizumab was approved by Health Canada on March 24, 2010 and by the European Commission on April 21, 2021[13,14].

Interestingly, researchers have identified higher VEGF expression in patients with COVID-19, which may contribute to lung pathologies including acute respiratory syndrome (ARDS) and acute lung injury (ALI). As such, Bevacizumab is being investigated for the treatment of lung complications associated with

severe cases of COVID-19 [15]. The Protein Chemical Formula $C_{6538}H_{10034}N_{1716}O_{2033}S_{44}$ and its Protein Average Weight is 149000.0 Daltons. The chemical Structure of Bevacizumab is shown in Figure 2 [16].

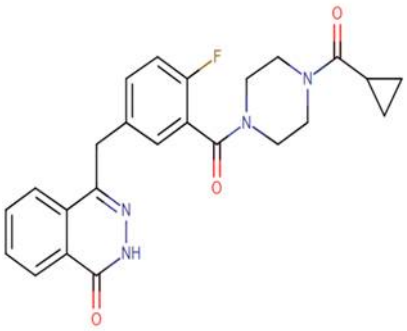


Figure 1: Structure of Olaparib

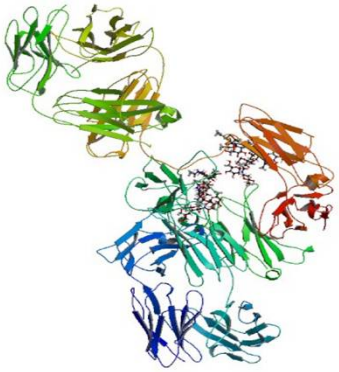


Figure 2: Structure of Bevacizumab

The literature review reveals that different methods have been reported for both drugs individually [17-24]. The present study focuses on the development and validation for the simultaneous estimation of Olaparib and Bevacizumab in Bulk and Pharmaceutical dosage form and its stability studies. Validation of the developed method has been performed following ICH Q2 (R1) guidelines [25]. Stability studies have been performed following ICHQ1A (R2) and Q1B [26].

MATERIALS AND METHODS

Chemicals and reagents

Olaparib and Bevacizumab API samples were procured from Pharma Life Research lab, Hyderabad, Telangana were used in the study. Acetonitrile (ACN), orthophosphoric acid (OPA) (HPLC-grade) (AR-grade) chemicals were acquired from Rankem Chemicals, Haryana, India

Instrumentation

Waters Alliance HPLC with 2695 pump, UV detector, auto-injector and Empower 2 software were used to perform the study. Shimadzu UV–visible spectrophotometer, Ohus Electronic balance, Eutech pH Meter, Phoenix 4.5 L digital ultrasonic cleaner, are used in the study.

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:

Optimization of HPLC method

Trials were performed by varying chromatographic conditions like stationary phase, mobile phase composition and buffer pH. Observations were carefully scrutinized for optimizing the method for low retention time, better resolution, theoretical plates and peak symmetry. The mobile phase composition of Acetonitrile and OPA (30:70 v/v,) was pumped through a column of Inertsil ODS 150mmx4.6mm, 3.5µ at a flow rate of 1.0 mL/min and the detection wavelength was processed at 258 nm. Integration of output signals were monitored and processed by waters Empower software-2.0.

Preparation of Buffer

1 ml of OPA was dissolved in 1lit of HPLC grade water.

Preparation of Mobile Phase

Mixed Acetonitrile and Buffer in the ratio of 30:70v/v and filtered through 0.45µ membrane filter paper.

Olaparib and Bevacizumab Stock solution

Accurately weighed and transferred 150 mg of Olaparib, 25mg of Bevacizumab working standard into a 100 ml clean dry volumetric flask diluent was added and was sonicated to dissolve it completely and volume was made up to the mark with the same solvent. (Stock solution)

Preparation of standard solution

Further pipetted 5 ml of the above stock solutions into a 50 ml volumetric flask and diluted up to the mark with diluent. (150µg/ml of Olaparib, 25µg/ml of Bevacizumab).

Preparation of Olaparib and Bevacizumab Sample Solution

Accurately weighed and transfered 279mg of Olaparib sample and 1ml of Bevacizumab sample into a 100ml clean dry volumetric flask add diluent and was sonicated for 30 mins to dissolve, and centrifuged for 30min to dissolve it completely and volume was made up to the mark with the same solvent. Then it was filtered through a 0.45-micron Injection filter (Stock solution). Further pipetted 5 ml of the above stock solutions into 50 ml volumetric flask and was diluted up to the mark with diluents. (150µg/ml of Olaparib, 25µg/ml of Bevacizumab).

Method Validation

Validation of the proposed method was performed following ICH Q2 (R1) guidelines which includes system suitability, specificity, linearity, precision, accuracy, LOD, LOQ and robustness. Forced degradation studies were performed following ICH Q1A (R2) and Q1B guidelines which include acid hydrolysis, alkali hydrolysis, peroxide degradation, thermal degradation, hydrolytic degradation and photolysis.

RESULTS AND DISCUSSIONS

The chromatographic efficiency parameters are obtained with the mobile phase composition of Acetonitrile and OPA (30:70 v/v,), Inertsil ODS 150mmx4.6mm, 3.5µ, 1.0 mL/min flow rate, UV detection at 258 nm with 5 µL injection volume and 6 min runtime. The results obtained are excellent with better resolution, theoretical plates, tailing factor and retention times 2.336 min and 4.873 min for Olaparib and Bevacizumab, respectively. The optimized chromatogram is shown in Figure 3.and the results are shown in table 1.

Table 1: Results for (Optimized trail)

Name	Retention Time(min)	Area	USP Resolution	USP Tailing	USP Plate Count
Olaparib	2.336	2537472		1.12	5482
Bevacizumab	4.873	362893	10.21	1.04	6615

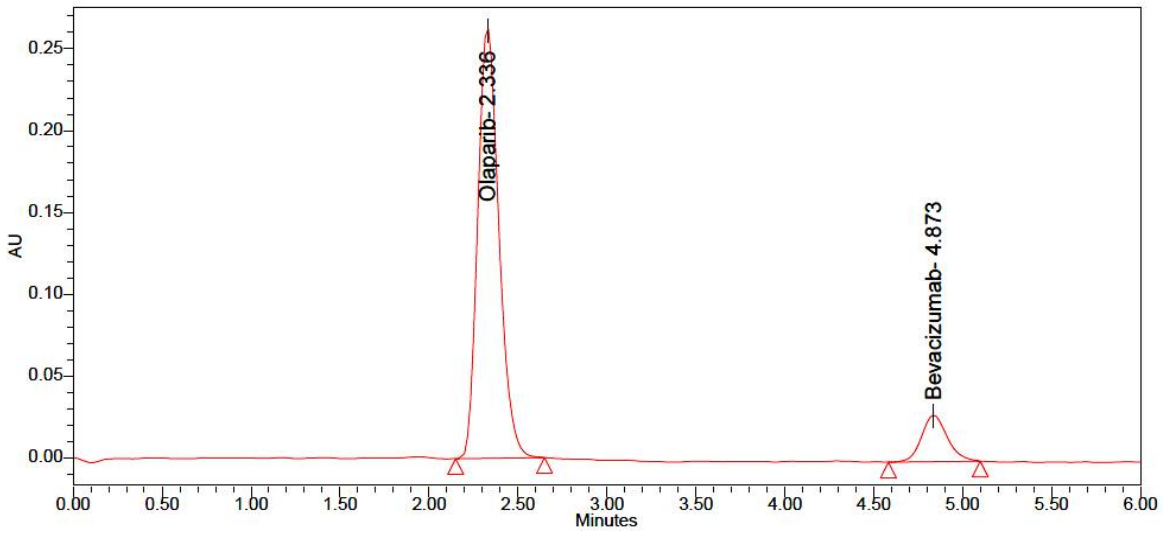


Figure 3: Optimized chromatogram for Olaparib and Bevacizumab

Method validation

Specificity

The proposed method is found to be specific as there are no interfering peaks in the blank, placebo and the sample at the retention times of Olaparib and Bevacizumab. The chromatograms of blank, placebo, standard and sample are shown in Figure 4-7.

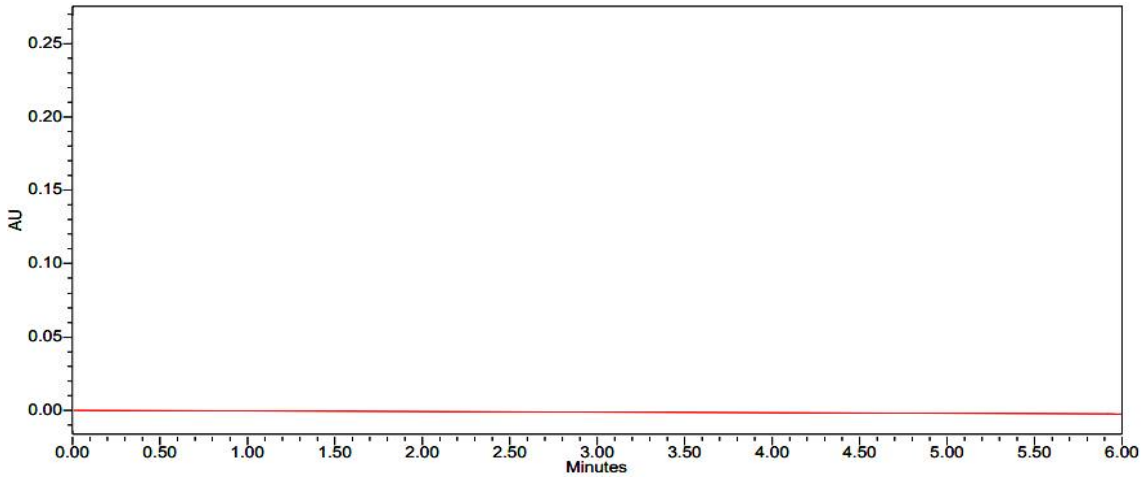


Figure 4: chromatogram of blank

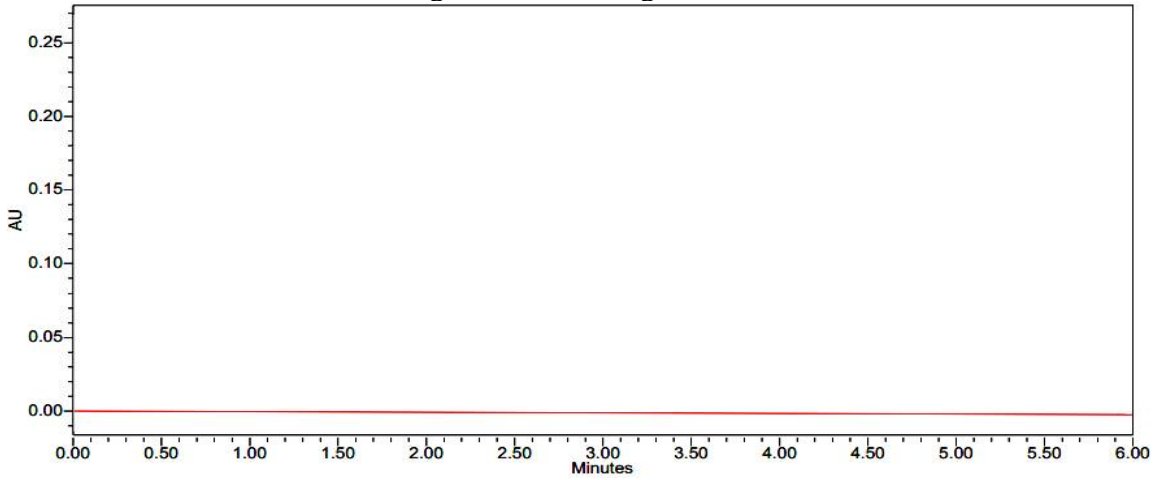


Figure 5: chromatograms of Placebo

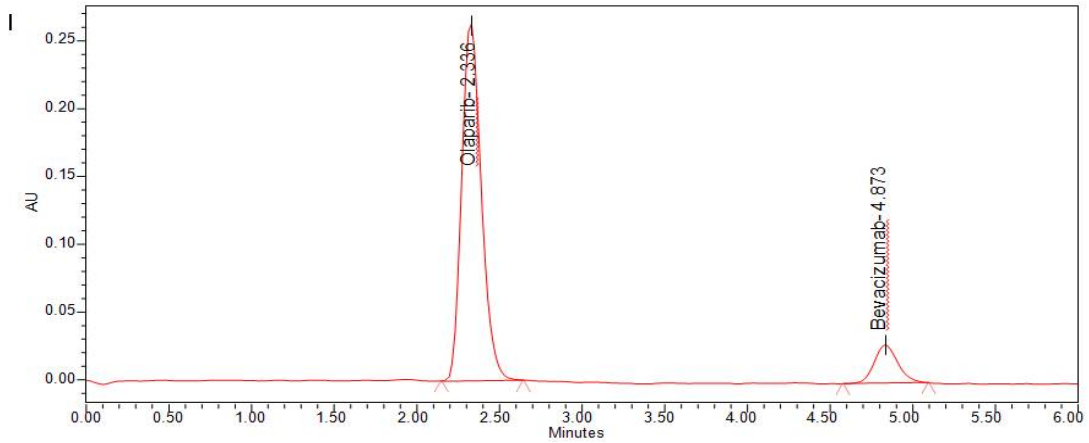


Figure 6: chromatogram of standard

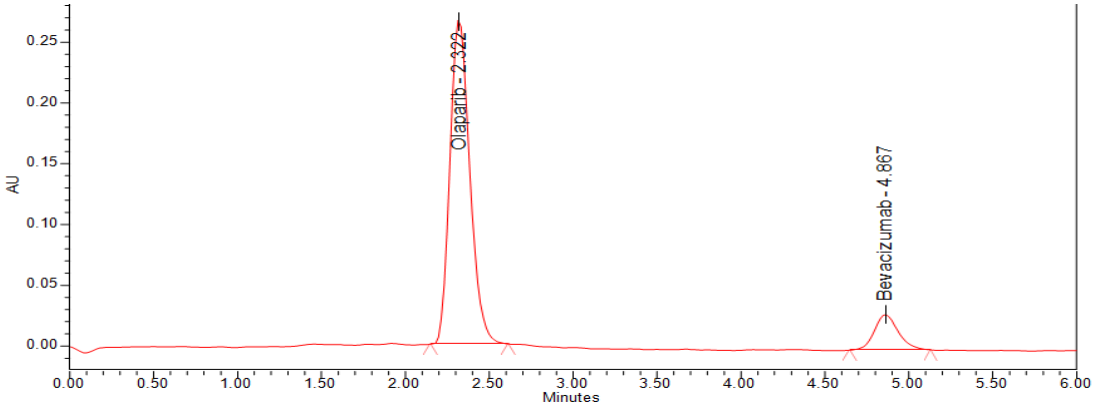


Figure 7: Chromatogram of sample

Linearity

Linearity of the method is determined by preparing aliquots at 37.50, 75.00, 112.50, 150.00, 187.50, 225.00 µg/ml for Olaparib and 6.25, 12.50, 18.75, 25.00, 31.25, 37.50 µg/ml for Bevacizumab. The solutions are analysed in triplicate. The proposed method is found to be linear in the concentration range of 37.50 to 225 µg/ml and 6.25 to 37.50µg/ml for Olaparib and Bevacizumab respectively. The regression equations for Olaparib and Bevacizumab are found to be y=16815.19x+22410.75 and y=14512.58x+2387.04, respectively. Table 2 shows the linearity data of Olaparib and Bevacizumab. The method is said to be linear as the R^2 value of both drugs is found to be more than 0.999. The calibration curves of Olaparib and Bevacizumab are shown in Figure 8 and 9.

Table 2: Linearity data for Olaparib and Bevacizumab

Sample	Olaparib		Bevacizumab	
	Conc. (µg/ml)	Peak area	Conc. (µg/ml)	Peak area
1	37.50	639653	6.25	93123
2	75.00	1295299	12.50	189437
3	112.50	1963147	18.75	274437
4	150.00	2541563	25.00	363524
5	187.50	3188539	31.25	451032
6	225.00	3770639	37.50	549932
Slope	16815.19		14512.58	
Intercept	22410.75		2387.04	
R^2	0.9997		0.9998	

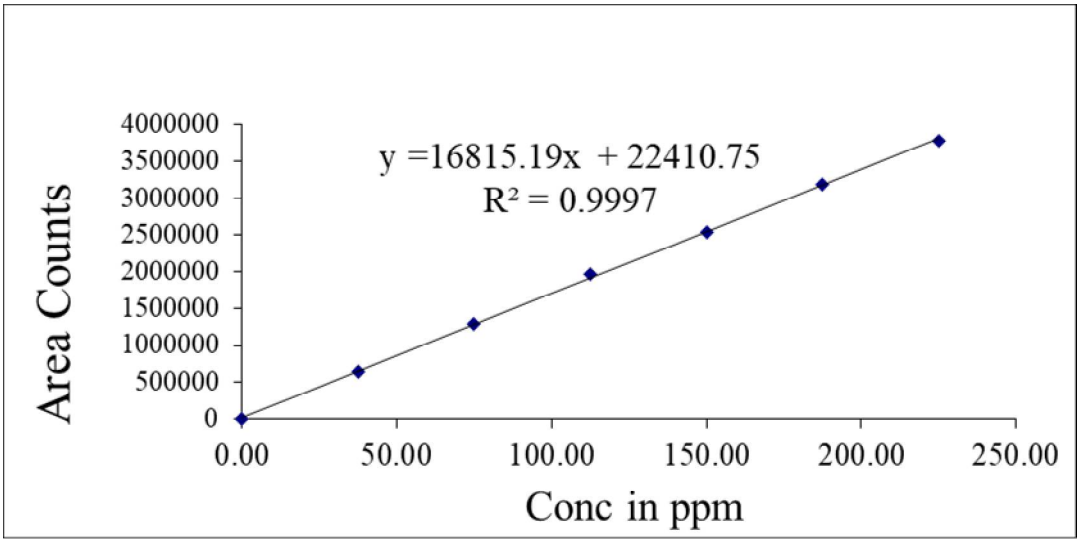


Figure 8: Calibration curve of Olaparib

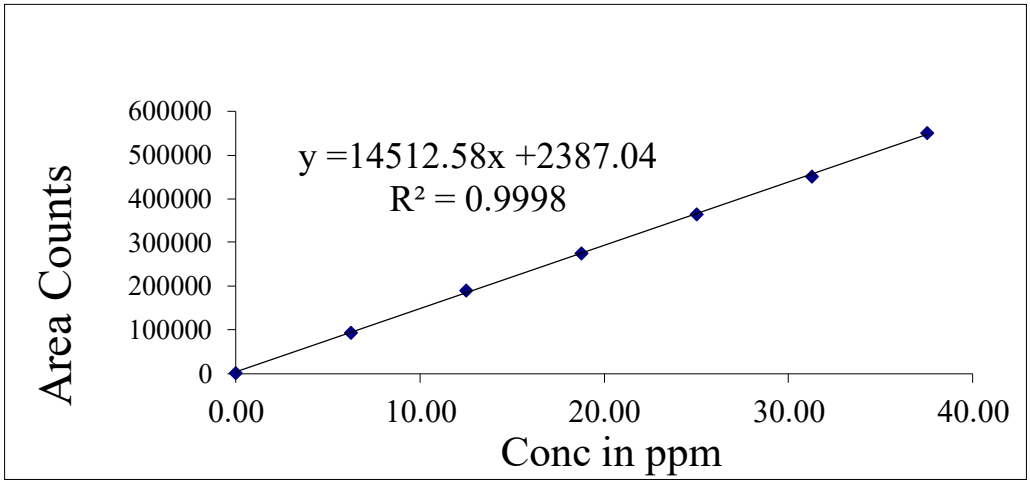


Figure 9: Calibration curve of Bevacizumab

Precision

Repeatability and intermediate precision are assessed by 6 determinations of sample solution Olaparib and Bevacizumab. The results are shown in Table 3. From the table it is observed that the results are within the limits as the %RSD values of peak areas for precision are found to be less than 2.

Table 3: Precision data of Olaparib and Bevacizumab

Peak Area	Repeatability (for sample)		Intermediate precision (method precision)	
	Olaparib	Bevacizumab	Olaparib	Bevacizumab
1	2537472	362893	2537472	363430
2	2545965	364560	2537472	362320
3	2512625	366195	2545965	360461
4	2530410	363591	2512625	362312
5	2505364	365786	2530410	365761
6	2520205	364268	2505364	364521
Mean	2525340	364549	2526367	363756
SD	15397.15	1263.22	16983.21	1483.32
% RSD	0.61	0.347	0.672	0.408

Accuracy

The % recovery is determined by spiking known quantities of standards (Olaparib and Bevacizumab) to pre-analyzed samples at 50%, 100% and 150% levels in triplicate. The results are shown in tables 4 and 5. From the results it is observed that the mean % recovery is found to be 99.7 for Olaparib and 100.1 for Bevacizumab and %RSD is less than 2 for both drugs.

Table 4: Accuracy data for Olaparib

% Conc. Level	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean % Recovery	%RSD
	1267441	75.00	75.28	100.4		
	1263234	75.00	75.03	100.0		
50%	1246126	75.00	74.02	98.7		0.89
	2525921	150.00	150.03	100.0		
	2536023	150.00	150.63	100.4		
100%	2517308	150.00	149.52	99.7	99.7%	0.37
	3772308	225.00	224.07	99.6		
	3761124	225.00	223.40	99.3		
150%	3753564	225.00	222.95	99.1		0.25

Table 5: Accuracy data for Bevacizumab

% Conc. Level	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean % Recovery	%RSD
50%	183053	12.50	12.58	100.6	100.1%	0.81
	181336	12.50	12.46	99.7		
	180124	12.50	12.38	99.0		
100%	366406	25.00	25.18	100.7		0.81
	368384	25.00	25.31	101.2		
	362467	25.00	24.91	99.6		
150%	545237	37.50	37.46	99.9		0.34
	547364	37.50	37.61	100.3		
	543759	37.50	37.36	99.6		

Limit of detection and Limit of quantitation

LOD is lowest quantity of drug in a sample that can be identified but cannot be quantify exactly. LOQ is the lowest quantity of a drug in an analyte which can be quantitatively estimated with a suitable accuracy and precision. The LOD and LOQ values were calculated from the linearity data by utilizing standard deviation and slope of the curve and is determined by considering the S/N ratio. The results are shown in table 6 and from the results this method is found to be sensitive within the concentration range.

Table 6: LOD and LOQ Results

Drug	LOD(µg/ml)	LOQ(µg/ml)
Olaparib	0.90	3.00
Bevacizumab	0.15	0.50

Robustness

It is performed by changing flow rate, 0.90 mL/min (−) and 1.1 mL/min (+) and mobile phase, acetonitrile and OPA 27: 73(−) and 33: 67 (+). The results are shown in Table 7 and 8. The % RSD values for peak areas are found to be within limits as they are less than 2. So the method is considered to be robust.

Table 7: Robustness data for Olaparib

Injection	Olaparib			
	FR (−)	FR (+)	MP (−)	MP (+)
1	2724125	2239920	2081154	2857986
2	2739254	2255843	2062754	2842715
3	2727558	2243254	2078485	2835456
Mean	2730312	2246339	2074131	2845386
SD	7931.67	8397.82	9942.74	11499.98
% RSD	0.291	0.374	0.479	0.404

Table 8: Robustness data for Bevacizumab

Injection	Bevacizumab			
	FR (−)	FR (+)	MP (−)	MP (+)
1	383866	323829	406612	304442
2	383214	322654	405564	303214
3	385654	322187	406412	302787
Mean	384245	322890	406196	303481
SD	1263.31	846.06	556.39	859.2
% RSD	0.329	0.262	0.137	0.283

Assay

5 µl of standard solution (of pure drugs) and sample solution (extracted from Capsules) are injected separately into the HPLC to record the chromatograms in triplicate. The percentage assay of the sample is calculated by comparing the areas of standard and sample and found to be 99.9% and 99.4% for Olparib and Bevacizumab respectively. The results are shown in Table 9.

Table 9: Assay data for Olaparib and Bevacizumab

Drug	Avg sample area (n=5)	Std. Conc. (µg/ml)	Sample Conc. (µg/ml)	Label amount (mg)	Std purity	Amount found (µg/ml)	% assay
Olaparib	2524138	150	150	150	99.8	149.93	99.9
Bevacizumab	361714	25	25	25	99.9	24.85	99.4

Forced degradation studies

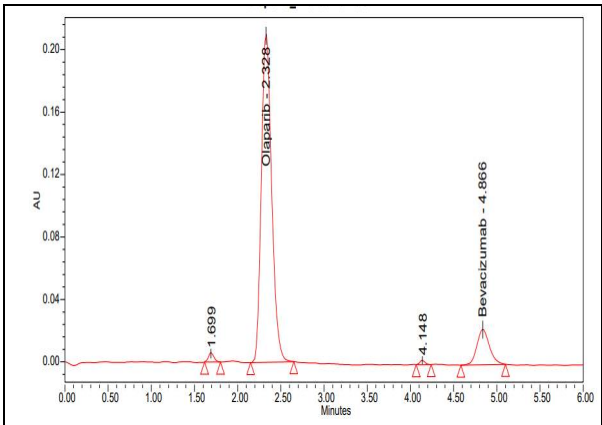
Forced degradation studies were conducted in accordance with ICH Q1A and Q1B guidelines to assess the stability of Olaparib and Bevacizumab under various stress conditions. Acidic degradation was performed by adding 1 mL of 2N hydrochloric acid to 1 mL of standard stock solution and refluxing the mixture at 60 °C for 30 minutes. For alkaline degradation, 1 mL of 2N sodium hydroxide was added to the stock solution and similarly refluxed. Oxidative stress was applied by treating the solution with 1 mL of 20% hydrogen peroxide under the same thermal conditions. Thermal degradation was evaluated by placing the stock solution in an oven at 105 °C for 1 hour to simulate dry heat exposure. Photolytic degradation was studied by exposing the solution to UV light in a UV chamber for 24 hours. Finally, neutral degradation was assessed by refluxing the drug in water at 60 °C for 1 hour to simulate hydrolysis under neutral pH.All the above solutions are diluted to obtain 150µg/ml Olaparib and 25 µg/ml Bevacizumab solutions, and 10 µl of each solution is injected into the system to assess the stability of the sample. The results are shown in Tables 10 and11. From the results obtained, it is found that drug samples are stable under all stress conditions. The chromatograms are shown in Figure 10.

Table 10: Degradation data for Olaparib

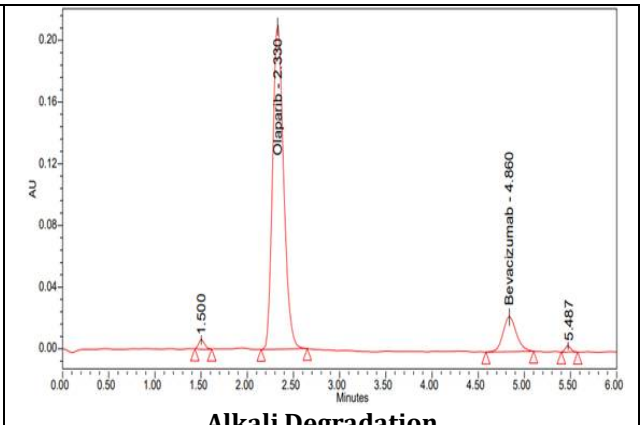
S.no	Degradation condition	Peak area	% Recovery	% Drug degradation	Peak purity		
					Purity angle	Purity threshold	Pass /Fail
1	Acid	2204763	87.3	12.7	0.407	4.035	Pass
2	Alkali	2172274	86	14	0.101	4.055	Pass
3	Peroxide	2102715	83.2	16.8	0.373	4.054	Pass
4	Reduction	2263289	89.6	10.4	0.122	4.065	Pass
5	Thermal	2496377	98.8	1.2	0.122	4.057	Pass
6	Photo	2439561	96.6	3.4	0.154	4.021	Pass
7	Neutral	2464172	97.5	2.5	0.136	4.079	Pass

Table 11: Degradation data for Bevacizumab

S.no	Degradation condition	Peak area	% Recovery	% Drug degradation	Peak purity		
					Purity angle	Purity threshold	Pass /Fail
1	Acid	315670	86.8	13.2	1.53	6.341	Pass
2	Alkali	317863	87.4	12.6	1.442	6.195	Pass
3	Peroxide	307113	84.4	15.6	1.365	6.742	Pass
4	Reduction	322184	88.6	11.4	1.298	6.258	Pass
5	Thermal	361412	99.4	0.6	1.154	6.323	Pass
6	Photo	355854	97.8	2.2	1.253	6.264	Pass
7	Neutral	358746	98.6	1.4	1.183	6.357	Pass



Acid Degradation



Alkali Degradation

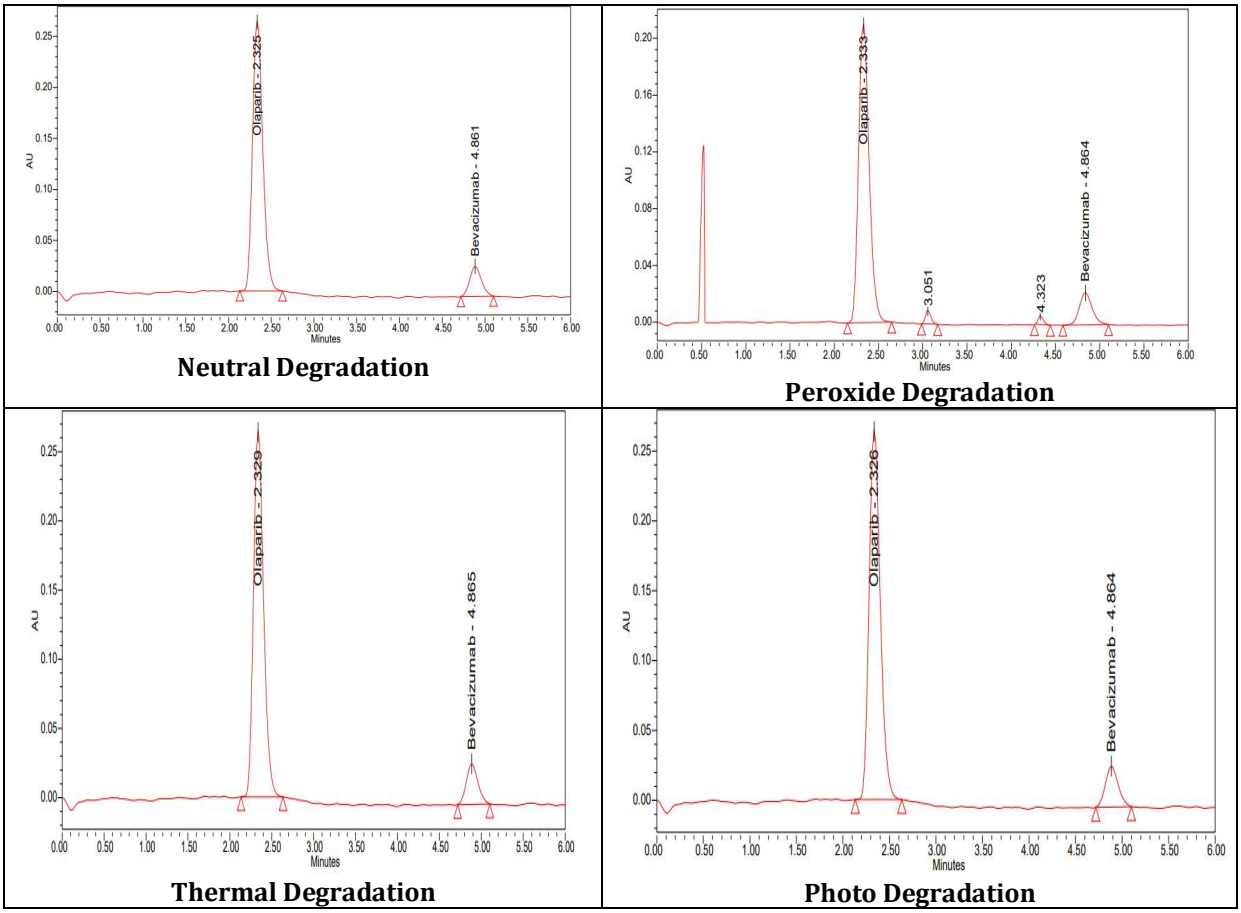


Figure 10: Forced degradation chromatograms for Olaparib and Bevacizumab

CONCLUSION

The developed HPLC method is simple, rapid, economical, specific and reliable for the estimation of Olaparib and Bevacizumab. The retention times of Olaparib and Bevacizumab are found to be 2.336 min and 4.873 min, respectively. The statistical evaluation of the proposed method showed good linearity and all validation parameters were performed as per ICH guidelines and are found to be in agreement with the acceptance criteria. Forced degradation studies were performed by applying various stress conditions to the sample to evaluate the stability-indicating nature and robustness of the developed method and it is found that sample drugs are stable and %RSD is less than 2 indicating the method is robust. This method can be used successfully in the routine laboratory analysis for the simultaneous estimation of Olaparib and Bevacizumab in the bulk and pharmaceutical dosage forms.

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