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Research Article

RP-HPLC Method Development and Validation for Abiraterone and Niraparib estimation in Tablet Dosage Form for Cancer Treatment

Daram Devi Sri Satya,[1] Dr. M Sudhakar[2]

1, M. Pharmacy, Department of Pharmaceutical Analysis, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Hyderabad, 500100, Medchal District

2, M. Pharmacy, PhD, Principal and Professor, Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Hyderabad, 500100, Medchal District

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ABSTRACT:
A simple, Accurate, precise method was developed for the simultaneous estimation of the Abiraterone and Niraparib in Tablet dosage form. Chromatogram was run through Kromasil 250 x 4.6 mm, 5µ. Mobile phase containing Buffer 0.01N potassium dihydrogen orthophosphate: Acetonitrile taken in the ratio 60:40 was pumped through column at a flow rate of 1 ml/min. Buffer used in this method was Potassium dihydrogen orthophosphate buffer. Temperature was maintained at 30°C. Optimized wavelength selected was 260.0 nm. Retention time of Abiraterone and Niraparib were found to be 2.125 min and 2.638 min. %RSD of the Abiraterone and Niraparib were and found to be 0.5 and 0.9 respectively. %Recovery was obtained as 99.51% and 99.61% for Abiraterone and Niraparib respectively. LOD, LOQ values obtained from regression equations of Abiraterone and Niraparib were 0.65, 1.96 and 0.03, 0.10 respectively. Regression equation of Abiraterone is y = 4033.6x + 173.05, and y = 10742x + 173.05 of Niraparib.

Key Words: Niraparib, Abiraterone, Rp Hplc, Validation.

INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide. In particular, prostate cancer represents a major health burden in men, especially in its advanced and treatment-resistant stages. For patients with metastatic castration-resistant prostate cancer (mCRPC), traditional androgen-deprivation therapies or chemotherapy often eventually fail, calling for novel therapeutic strategies. The combination of Niraparib and Abiraterone has recently emerged as a promising dual-mechanism therapy for such cases, particularly in patients with homologous recombination repair (HRR) gene alterations such as BRCA1 or BRCA2 mutations.[1,2] When combined — as in the fixed-dose regimen of Niraparib plus Abiraterone acetate (marketed as a dual-action therapy) — the two drugs deliver a "double hit" to cancer cells: impairment of androgen-dependent growth and simultaneous disruption of DNA repair capacity. This dual-mechanism strategy harnesses the tumor's dependency on both androgen signaling and DNA repair pathways, thereby increasing anti-tumor activity, especially in patients with HRR gene–altered mCRPC.[1,3]

Niraparib is an orally active poly (ADP-ribose) polymerase (PARP) inhibitor. By blocking the enzymes responsible for DNA repair, niraparib induces cytotoxicity in cancer cells.[4] Niraparib is selective towards PARP-1 and PARP-2.[5] it is Chemically written as 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide[6] and Abiraterone is an antiandrogen used in the treatment of metastatic castration-resistant prostate cancer and metastatic high-risk castration-sensitive prostate cancer. Abiraterone is a potent, irreversible, and selective inhibitor of 17 αhydroxylase/C17,20-lyase (CYP17), an enzyme expressed in testicular, adrenal, and prostatic tumour tissues, to regulate androgen biosynthesis.[7-10] Abiraterone has poor oral bioavailability and is susceptible to hydrolysis by esterase is Chemically known as (3aS,3bR,7S,9aR,9bS,11aS)-9a,11a-dimethyl-1-(pyridin-3-yl)-3H,3aH,3bH,4H,6H,7H,8H,9H,9aH,9bH,10H,11H,11aH-cyclopenta[a]phenanthren-7-ol.[7]

Address for Correspondence: Daram Devi Sri Satya, M. Pharmacy, Department of Pharmaceutical Analysis, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Hyderabad, 500100, Medchal District, Telangana, 502313.; **E-Mail:** devisridaram2001@gmail.com

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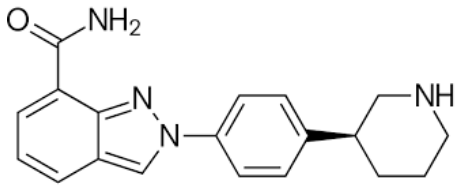

Figure 1: structure of Niraparib

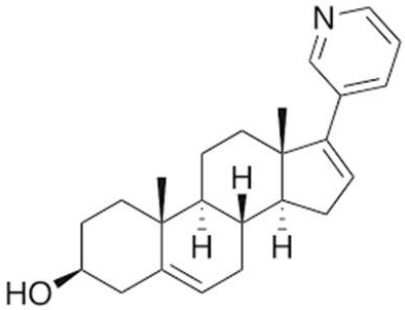

Figure 2: Structure of Abiraterone

Extensive literature research has unearthed a multitude of recorded analytical procedures, including the discovery of more economically efficient ways. Nevertheless, there is currently few documented approach for calculating stability studies. Hence, a reliable and cost-effective approach is suggested for assessing the stability of Niraparib, Abiraterone, and their medicinal dose form using RP-HPLC [10 - 16] must be validated and developed as per ICH guidelines

Materials and Methods: Spectrum pharma Research Solution provided with Niraparib and Abiraterone pure drugs (API) gift samples and Combination Niraparib and Abiraterone tablets (**Akeega**). The chemicals and buffers utilized in this estimation were obtained from Rankem, an Indian supplier.

Instrumentation: The development and method validation were conducted using a WATERS HPLC, specifically the model 2695 SYSTEM, equipped with a Photo diode array detector. The system also included an automated sample injector and the Empower 2 software.

Objective: In order to fulfill ICH standards, we need to design and test an HPLC technique that can detect Abiraterone and Niraparib in pharmaceutical formulations at the same time.

Table 1: Chromatographic Conditions

Mobile phase	Acetonitrile and KH_2PO_4 (60:40 v/v)
Flow rate	1 ml/min
Column	Kromosil C18 (4.6 x 250mm, 5µm)
Detector wave length	210 nm
Column temperature	30°C
Injection volume	10 mL
Run time	6.0 min
Buffer	KH_2PO_4

Buffer Preparation: 0.01N KH2PO4 Buffer: Accurately weighed 1.36gm of Potassium dihyrogen 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 5.0 with dil. Orthophosphoric acid solution.

API Preparation:

Preparation of Standard stock solutions: Accurately weighed 50mg of Abiraterone, 5mg of Niraparib and transferred to 50ml and 50ml individual volumetric flasks and 3/4 th of diluents was added to these flasks and sonicated for 10 minutes. Flask were made up with diluents and labeled as Standard stock solution. (1000µg/ml of Abiraterone and 100µg/ml Niraparib)**.** 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (10µg/ml Niraparib of and 100µg/ml of Abiraterone)

Formulation Preparation:

Preparation of Sample stock solutions: 10 tablets were taken each tablet weigh and calculate the mean of total 10 minutes then equivalent to average weight of 1 tablet (50mg and 500mg) of dosage form was transferred into a 100 ml volumetric flask, 50ml of diluents was added and sonicated for r the volume was made up with diluent and filtered by HPLC filters (5000µg/ml of Abiraterone and 500µg/ml Niraparib): 0.2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (100µg/ml of Abiraterone and 10µg/ml Niraparib)

System suitability parameters: Niraparib (10 ppm) and Abiraterone (100 ppm) standard solutions were prepared, injected six times, and metrics such as peak tailing, resolution, and USP plate count were measured in order to evaluate the system suitability parameters. The region of six standard injection results should have an RSD of no more than 2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. Therefore, this method was said to be specific.

Linearity: To test the drug's linearity, serial dilutions from 25% to 150% were prepared. A graph was used to demonstrate the link between peak area response and medication concentration. It was found to be linear at the indicated drug concentration. Dilution were as follows.

- 25 µg/mL: Take 0.25 mL of stock solution and dilute to 10 mL
- 50 µg/mL: Take 0.5 mL of stock solution and dilute to 10 mL
- 75 µg/mL: Take 0.75 mL of stock solution and dilute to 10 mL
- 100 µg/mL: Take 1.0 mL of stock solution and dilute to 10 mL
- 125 µg/mL: Take 1.25 mL of stock solution and dilute to 10 mL
- 150 µg/mL: Take 1.5 mL of stock solution and dilute to 10 mL

Accuracy: Accuracy was performed in triplicate for various concentrations equivalent to 50%, 100% and 150% of the standard amount were injected into the HPLC system per the test procedure. Dilution were as follows.

- 50 µg/mL: Take 0.1 mL of stock solution and dilute to 10 mL
- 100 µg/mL: Take 0.2 mL of stock solution and dilute to 10 mL
- 150 µg/mL: Take 0.3 mL of stock solution and dilute to 10 mL

Sensitivity

Limit of detection and Limit of Quantification

LOD and LOQ were calculated from the average slope and standard deviation from the calibration curve as per ICH guidelines. Based on the response's standard deviation and calibration curve's slope, the LOD and LOQ can be estimated.

Assay

The assay and % purity were calculated for brand Akeega with label claim Abiraterone 500g and Niraparib 100mg. The observed value was compared with that of standard value without interference from the excipients used in the tablet dosage form.

Degradation studies:

Oxidation: To 1 ml of stock solution of Abiraterone and Niraparib, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 600c. For HPLC study, the resultant solution was diluted to obtain 100µg/ml & 10µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Acid Degradation Studies: To 1 ml of stock s solution Abiraterone and Niraparib, 1ml of 2N Hydrochloric acid was added and refluxed for 30mins at 600c. The resultant solution was diluted to obtain 100µg/ml & 10µg/ml solution and 10 µl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

Alkali Degradation Studies: To 1 ml of stock solution Abiraterone and Niraparib, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 600c. The resultant solution was diluted to obtain 100µg/ml & 10µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Dry Heat Degradation Studies: The standard drug solution was placed in oven at 105°C for 1 h to study dry heat degradation. For HPLC study, the resultant solution was diluted to 100µg/ml & 10µg/ml solution and10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Photo Stability studies: The photochemical stability of the drug was also studied by exposing the 5000µg/ml Abiraterone &500µg/ml Niraparib solution to UV Light by keeping the beaker in UV Chamber for 1days or 200 Watt hours/m2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 100µg/ml & 10µg/ml solutions and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Neutral Degradation Studies: Stress testing under neutral conditions was studied by refluxing the drug in water for 1hrs at a temperature of 60ºC. For HPLC study, the resultant solution was diluted to 100µg/ml & 10µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Table 2: System suitability results

S.no	Niraparib			Abiraterone			
Inj	RT (min)	USP Plate Count	Tailing	RT (min)	USP Plate Count	Tailing	Resolution
1	2.127	2934	1.22	2.594	4174	1.29	4.8
2	2.127	2920	1.23	2.594	4056	1.28	4.8
3	2.128	2938	1.19	2.597	4118	1.28	4.8
4	2.129	2839	1.18	2.598	3905	1.26	4.7
5	2.134	3027	1.26	2.598	4179	1.32	4.9
6	2.144	2864	1.25	2.598	3898	1.26	4.7

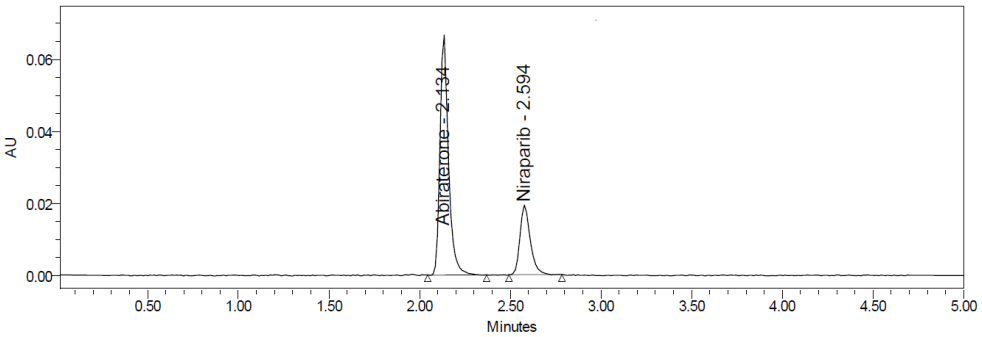

Figure 3: system suitability Chromatogram

Table 3: Specificity data

Sample name	Retention time	Area	Plate count	Tailing	Resolution
Niraparib	2.125	409916	3092.6	1.3	
Abiraterone	2.638	106454	4511.2	1.3	4.9

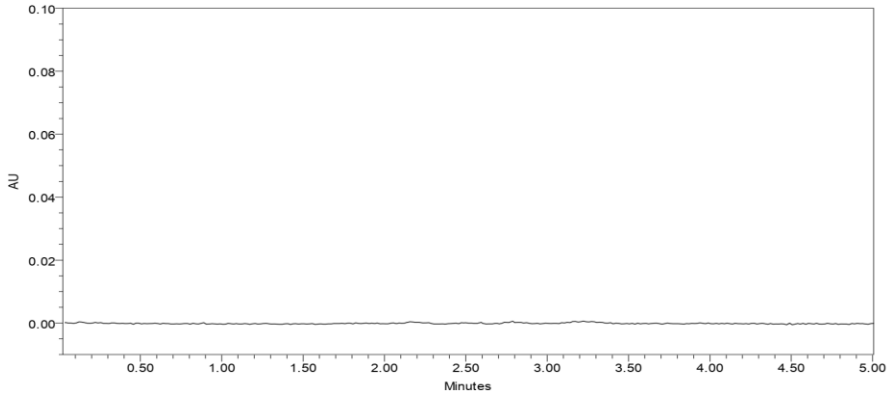

Figure.4 Specificity of Niraparib and Abiraterone

Linearity:

Calibration data is given in table 4 and regression data in table 5 and calibration curve in figure 5, 6

Table 4: Calibration data of Niraparib and Abiraterone

Niraparib		Abiraterone	
Conc (µg/mL)	**Peak area**	**Conc(µg/mL)**	**Peak area**
0	0	0	0
25	101479	2.5	26945
50	206524	5	53930
75	301071	7.5	80855
100	405310	10	107571
125	500621	12.5	135381
150	608812	15	160468

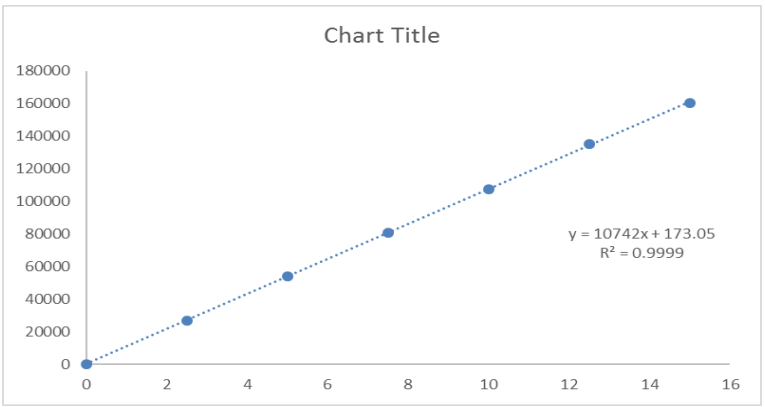

Figure 5 Calibration curve of Niraparib

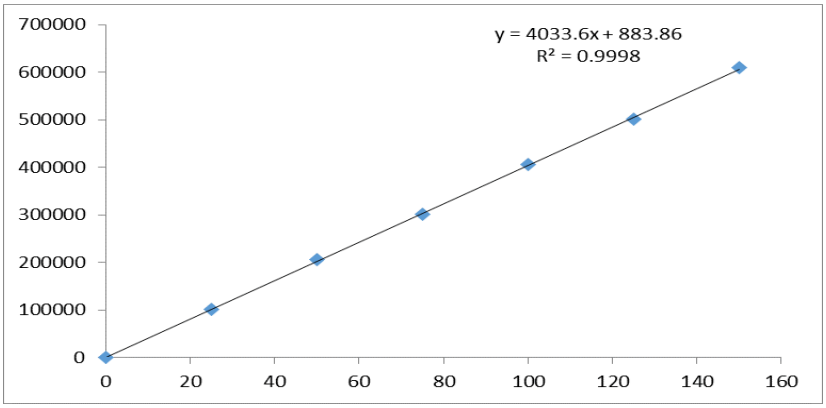

Figure 6 Calibration curve of Abiraterone

Table 5: regression data

Parameter	Niraparib	Abiraterone
Conc range (µg/mL)	2.5 – 15 µg/ml	25-150 µg/ml
Regression Equation	y = 10742x + 173.05	y = 4033.6x + 883.86
Co-relation	0.999	0.999

Accuracy:

Recovery data shown in table 6

Table 6: recovery data of Niraparib and Abiraterone

	Niraparib			Abiraterone		
% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**
50%	40	4.96	99.26	10	49.54	99.07
		4.98	99.68		50.12	100.24
		4.99	99.71		49.75	99.51
100%	80	9.96	99.63	20	99.86	99.86
		9.95	99.47		99.35	99.35
		9.99	99.89		100.07	100.07
150%	120	15.01	100.05	30	148.94	99.30
		14.91	99.39		148.67	99.11
		14.91	99.43		148.67	99.11
% recovery	**99.61**			**99.51**		

System precision was performed and the data was shown in table 7

Table 7: System precision of Niraparib and Abiraterone

S. No	Area of Niraparib	Area of Abiraterone
1.	106993	404610
2.	109264	407226
3.	107896	406097
4.	108763	403277
5.	106821	402127
6.	107723	402793
Mean	107910	404355
S.D	961.6	1995.4
%RSD	0.9	0.5

The % RSD for the peak areas of Niraparib and Abiraterone obtained from six replicate injections of standard solution was within the limit.

Method Precision: The precision of the method was determined by analyzing a sample of Niraparib and Abiraterone and shown in table 8.

Table 8: method Precision

S. No	Area of Niraparib	Area of Abiraterone
1.	108309	404454
2.	107428	408885
3.	107645	404517
4.	108644	406561
5.	108499	404200
6.	108018	405767
Mean	108091	405731
S.D	482.4	1793.7
%RSD	0.4	0.4

From the above results, the % RSD of method precision study was within the limit for Niraparib and Abiraterone.

Robustness: Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.0ml/min), mobile phase minus (65A:35B), mobile phase plus (55A:45B), temperature minus (27°C) and temperature plus(33°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

Table 9: Robustness data for Niraparib and Abiraterone.

Condition	%RSD of Niraparib	%RSD of Abiraterone
Flow rate (-) 0.9ml/min	0.9	0.2
Flow rate (+) 1.1ml/min	0.6	1.0
Mobile phase (-) 65A:35B	0.1	0.3
Mobile phase (+) 55A:45B	0.6	0.1
Temperature (-) 27°C	0.1	0.7
Temperature (+) 33°C	0.6	0.8

Sensitivity:

Table 10: sensitivity of Niraparib and Abiraterone

Molecule	LOD	LOQ
Niraparib	0.03 µg/ml	0.10 µg/ml
Abiraterone	0.65 µg/ml	1.96 µg/ml

Force Degradation Studies: table 11 shows degradation conditions and table 10 shows the obtained degraded data and purity plot chromatogram in figure 8, 9.

Table 11: degradation conditions

Stress condition	Solvent	Temp(^{0}C)	Exposed time
Acid	2N HCL	60^{0}c	60 mins
Base	2N NAOH	60^{0}c	60 mins
Oxdation	20% H_2O_2	60^{0}c	60 mins
Thermal	Diluent	105^{0}c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^{0}c	60 mins

Table 12: degradation data

Type of degradation	Niraparib			Abiraterone		
	area	%recovered	% degraded	area	%recovered	% degraded
Acid	102320	94.63	5.37	389956	96.25	3.75
Base	102602	94.89	5.11	388920	95.99	4.01
Peroxide	102199	94.52	5.48	388369	95.85	4.15
Thermal	104196	96.37	3.63	393841	97.21	2.79
Uv	105668	97.73	2.27	400486	98.85	1.15
Water	107352	99.28	0.72	402294	99.29	0.71

Acid degradation chromatogram

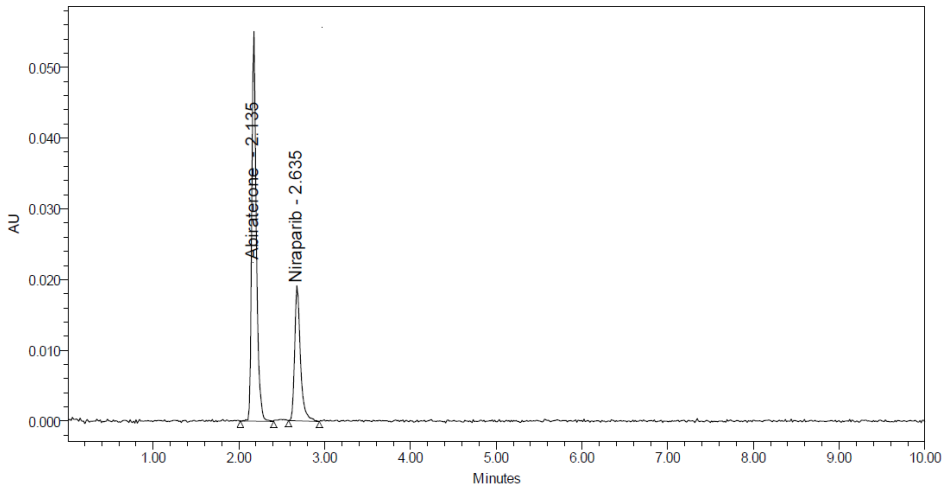

Fig 7 acid

Base degradation chromatogram

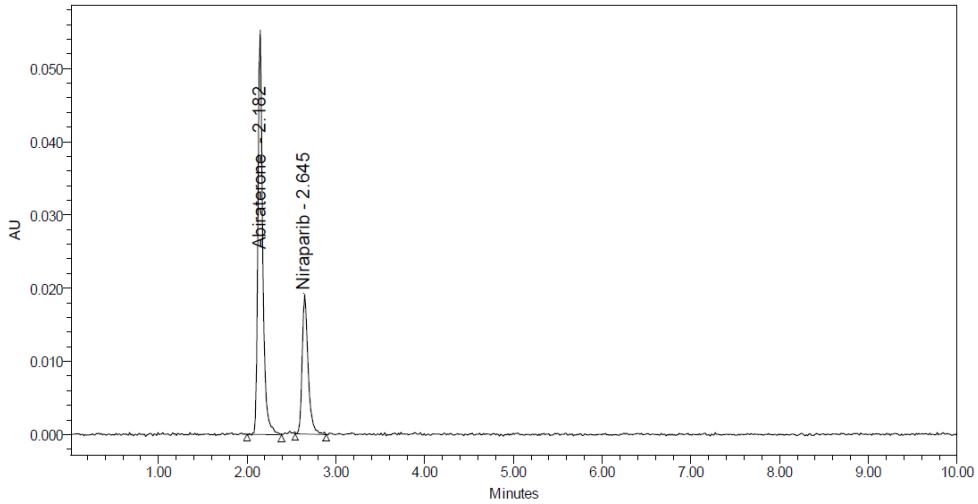

Fig 8 base

Peroxide degradation chromatogram

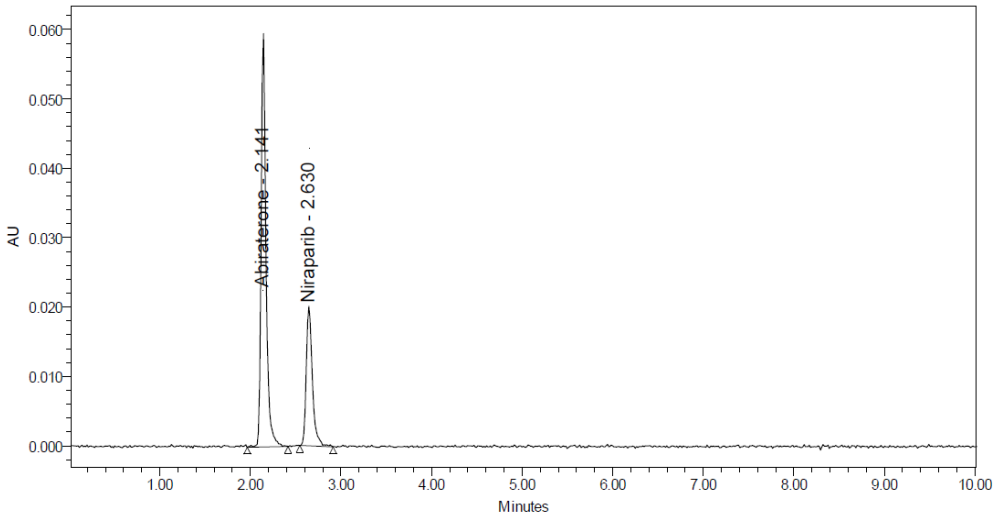

Fig 9 peroxide

Thermal degradation chromatogram

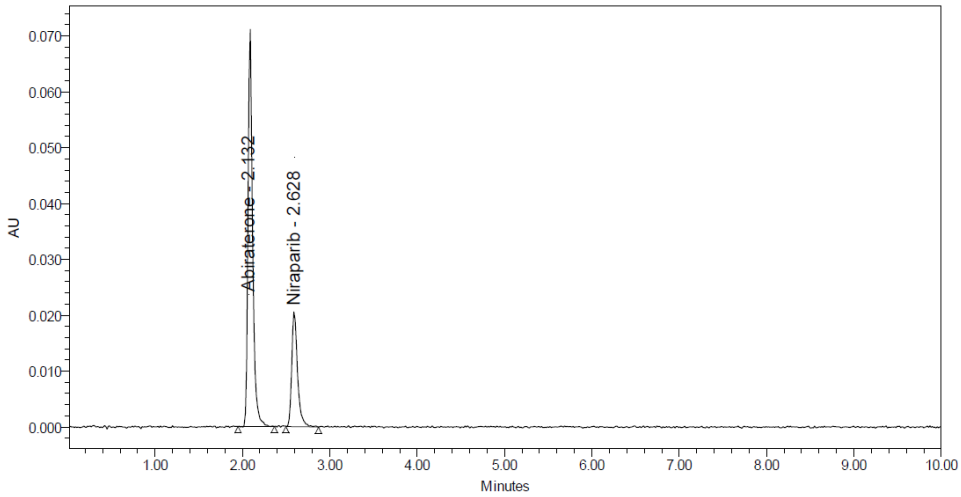

Fig 10 thermal

UV degradation chromatogram

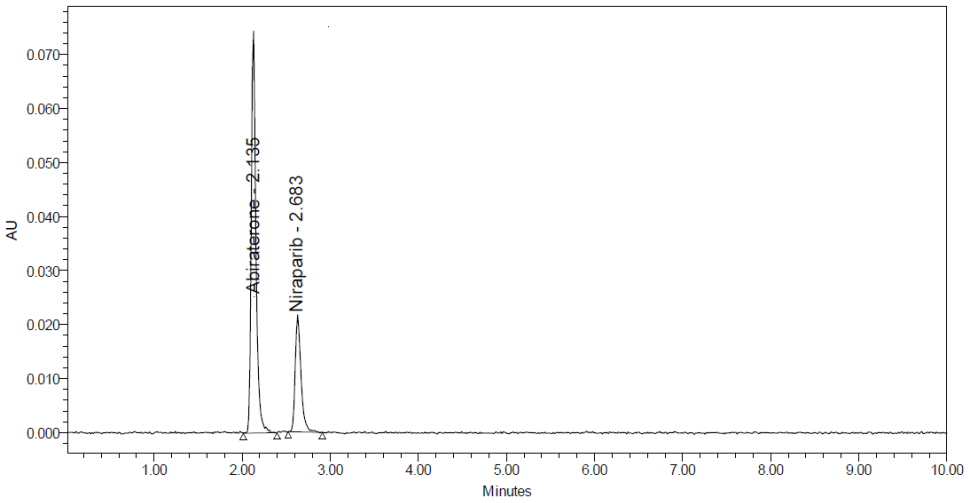

Fig 11 UV

Water degradation chromatogram

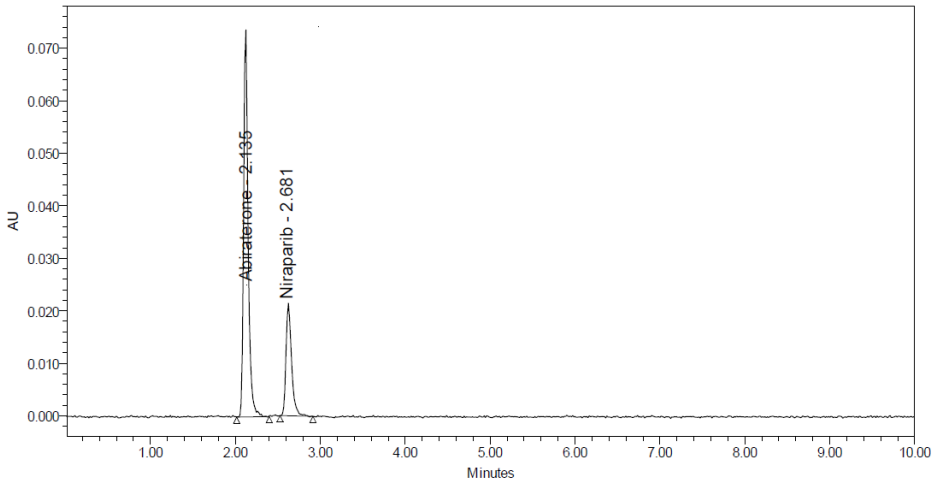

Fig 12 water

Assay: Akeega, bearing the label claim Niraparib 100mg, Abiraterone 500mg. Assay was performed with the above formulation. Average % Assay for Niraparib and Abiraterone obtained was 99.97% and 100.15% respectively.

Table 13: assay data

Formulation	Label claim(mg)	% Assay*
Akeega	Abiraterone 500mg.	100.15%w/w
	Niraparib 100mg	99.97%w/w

CONCLUSION:

The study's findings will be very helpful in evaluating the quality of reasonably priced medications that contain Abiraterone and Niraparib. This could be as a result of the study's straightforward sample preparation method, which required little mobile phase and a brief analytical period. The findings of assessing two drugs combined in a single dosage revealed that the freshly devised analytical technique was almost fully successful.

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