RESEARCH PAPER

Development and Validation of a Stability Indicating RP-HPLC method for Determination of Niraparib in Bulk Drug and its Pharmaceutical Dosage Form

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ABSTRACT

Background: Niraparib is selective poly (ADP-ribose) polymerase (PARP) inhibitor employed preliminary to mitigate ovarian, fallopian tube, or peritoneal cancer. Accurate and reliable analytical strategy is pivotal in quality control of niraparib in pharmaceuticals. Objective of current investigation is to develop as well as validate straightforward, rapid, precise, robust Reversed-phase high-performance liquid chromatography (RP-HPLC) strategy for quantitative determination of niraparib, with stability-indicating capability, in compliance with International Council for Harmonisation (ICH) guidelines.

Method: Chromatographic separation was accomplished employing Agilent Zorbax Bonus-RP column (4.6 mm × 250 mm, 5 µm particle size). Mobile phase consisted of 0.1% trifluoroacetic acid (TFA) in water and acetonitrile in a 75:25 v/v ratio, delivered in isocratic mode at flow rate of 1.0 mL/min. Detection wavelength was set at 240 nm, as well as injection volume was optimized at 20 µL. Method was validated for specificity, linearity, accuracy, precision, limit of detection (LOD), limit of quantification (LOQ), along with robustness.

Result: Niraparib eluted with good peak symmetry and resolution with retention duration of 5.18 minutes. With $R^2 > 0.999$, method revealed linearity in concentration range of 40–60 µg/mL. Results explored that LOD was 1.42 µg/mL and LOQ was 4.30 µg/mL. With Relative standard deviation (RSD) of less than 2%, intra- and inter-day precision results were within appropriate limits, demonstrating great precision. Additionally, approach exhibited outstanding accuracy and robustness under varied conditions.

Conclusion: Developed RP-HPLC strategy was straightforward, accurate, precise, sensitive, as well as reliable. It is apt for regular stability testing and quality control analysis of niraparib in pharmaceuticals and bulk drugs. Its potential to suggest stability guarantees that it may be availed to monitor drug stability under variety of stress conditions and identify degradation products.

Keywords: Niraparib, RP-HPLC, method development, validation, forced degradation study, stability-indicating method.

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1. Introduction

Niraparib is PARP inhibitor, used to mitigate ovarian cancer.[1,2] PARP inhibitors[3,4] are a revolutionary class of targeted therapies in oncology that selectively cytotoxically kill tumour cells via the exploiting deficiencies in DNA-repair processes.[5,6] Niraparib,[7,8] a potent and orally bioavailable PARP-1[9,10] and PARP-2[11,12] inhibitor, received regulatory approval for maintenance therapy in certain breast cancer indications.[13,14] Its clinical usefulness has been strengthened by its advantageous pharmacokinetic profile and blood–brain barrier crossing potential.[15,16] Accurate quantification of Niraparib in both bulk drug substance and formulated dosage forms is pivotal at every stage of drug development from synthetic route optimization and scale-up to quality control and stability assessment. [17,18] Drug's efficacy and safety profile[19,20] demands development of stability-

indicating RP-HPLC for its determination in bulk drug along with pharmaceuticals.[21,22]

Development of stability-indicating RP-HPLC method entails several key considerations, including selection of suitable stationary phase, mobile phase composition, and detection wavelength.[23,24] Developed method must hold potential to separate analyte from its degradation products, other impurities, simultaneously offering sensitivity, precision, accuracy.[25,26] In particular, RP-HPLC,[27,28] with its versatility in mobile-phase composition and column chemistries, is ideally apt for analysis of moderately polar, lipophilic small-molecule drugs like niraparib. [29,30]

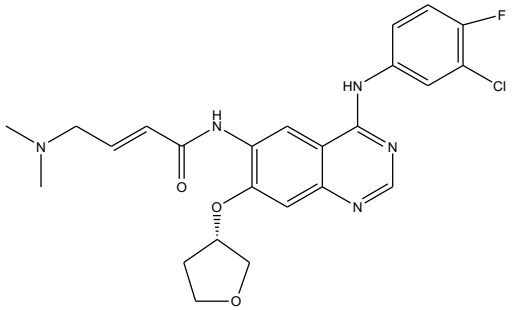

Figure 1 Structure of Niraparib

Stability-indicating assessment is vital for ensuring quality and efficacy of pharmaceuticals and hold potential to detect degradation products and impurities, rendering the assessment of drug stability under multiple conditions and separate Active pharmaceutical ingredient (API) from its potential degradants developed via forced degradation condition imparting acidic,[31] basic,[32] oxidative,[33] thermal stress.[34,35] In the context of niraparib, stability-indicating RP-HPLC would render quantification of drug in exitance of its degradation products, ensuring accuracy and reliability of the results.

According to literature very few bioanalytical strategies and only one RP-HPLC for impurity profiling assessment of niraparib are available.[36,37] No reported analytical methods for determination of niraparib in bulk drug and its formulation was noted in literature. Despite several reported HPLC[38] and LC–MS/MS[39,40,41] methods for quantifying niraparib in plasma and biological matrices,[42] there is a lack of published, fully validated, stability-indicating RP-HPLC approach rendering routine analysis of bulk drug as well as formulated dosage form. Thus, the authors attempted to develop stability indicating RP-HPLC for determination niraparib along with its formulation in compliance with ICH guidelines that addresses gap in analytical methodology, promoting comprehending degradation profiling, quality assurance, and regulatory compliance.

2. Materials and methods

Drug and reagent: Niraparib was purchased from Baladi Pharma (Hyderabad), Acetonitrile and analytical grade TFA were purchased from Molychem, HPLC grade water from Indian Lab Q Ultra by Ion Exchange Pvt Ltd. Pharmaceutical dosage form was procured from local Pharmacy.

Instrumentation: HPLC experiment is performed on Agilent 1260 Infinity II with DAD Detector. Analytical column was employed for analysis (250 mm x 4.6 mm) x 5.0 µm (RP Agilent Zorbax Bonus). Other instruments employéd were Ultrasonicator (Remi), Analytical balance (OHUAS), pH meter (Lab India).

2.1 Solution preparation

2.1.1 Mobile phase (0.1% TFA): 1 ml TFA was added in 1000 ml HPLC grade water, mixed, sonicated and degassed.

2.1.2 Diluent: it was prepared by mixing of ratio of 0.1% TFA:Acetonitrile (70: 30 v/v).

2.1.3 Standard

Standard stock solution (NSSS-I) was prepared by adding 5 mg niraparib into 10 ml volumetric flask and 5ml Acetonitrile and sonicated for 5 minutes finally volume was made up with acetonitrile. (Niraparib, NSSS-1 Con. 500 µg/ml).

Niraparib standard solution was prepared by adding 1 ml of NSSS-1 into 10ml volumetric flask then 5ml diluent and vortexed, volume made up with diluent. (Niraparib Standard Solution Conc. 50 µg/ml).

2.1.4 Sample (Drug product assay)

Niraparib 20 tablets (Zejula 100 mg) were weighed; average weight was calculated, and then all tablet were powdered.

Powdered material equivalent to 5mg niraparib, was added to 10ml volumetric flask and 5ml acetonitrile was added, sonicated for 5mim; volume made up with acetonitrile. (Niraparib Conc. 500 µg/ml).

2.1.5 Above 1ml solution was transferred in 10 ml volumetric flask; added 5ml diluent and vortexed then volume made up with diluent.

2.1.6 Detector wavelength selection: DAD detector wavelength 200-400nm was employed for scanning sample solution. 240 nm was selected as appropriate wavelength for assessment.

2.1.7 Chromatographic condition

HPLC experiment were carried employing Agilent 1260 Infinity II with DAD Detector. Separation was done on 5.0 µm (250 x4.6) Agilent zorbax bonus RP where mobile phase 0.1% TFA and Acétonitrile (75 :25 v/v) in isocratic elution mode with flow rate 1.0 ml/min. Oven temperature 30°C and peak was monitored at 240 nm, injection volume 10 µl, diluent used was mixture of 0.1% TFA:Acetonitrile (70:30 v/v) for sample preparation. Total run time for analysis was 15min.

3. Method development

Standard drug and formulation prepared in TFA:Acetonitrile (70:30 v/v) Standard were injected into HPLC system with mobile phase 0.1% TFA:Acetonitrile in isocratic elution mode with different ratio but only (75:25 v/v) better separation achieved at 240 nm. Then developed method selected for validation as per ICH guidelines.

4. Validation: validated by RQ2 (R1) ICH guidelines.

5. Result

5.1 Specificity and assay

Working standard of niraparib and sample initially was prepared (50 µg/m) then injected in HPLC system which observed, diluent peak not interfering with main chromatographic peak. Table 1 provides assay results for niraparib. Following formula was used for calculation of assay.

$$\%\ Assay = \frac{\text{Area of Sample}}{\text{Area of Standard}} x\ 100 \quad \ldots\ldots\ldots$$

Equation 1

Table 1 Assay results for niraparib

Niraparib			
Sample	**RT**	**Area**	**Assay**
Working Standard	5.18	3672766	-
Sample Solution	5.18	3661967	99.71

5.2.System suitability and repeatability

Retention time demonstrated excellent reproducibility and higher consistency with zero standard deviation. Theoretical palates and asymmetry factor were within acceptable limits suggesting good column efficiency and peak shape. Peak purity of 1.00 for all injections inferred that the analyte peak is spectrally homogenous and aided in methods specificity.

Table 2 System suitability results

Injection	Retention time	Theoretical plates	Asymmetry factor	Peak Purity
1	5.18	7077	1.19	1
2	5.18	7223	1.13	1
3	5.18	7289	1.18	1
4	5.18	7451	1.07	1
5	5.18	7155	1.15	1
6	5.18	7058	1.21	1

Table 3 Repeatability results for niraparib

Injection	Working standard area
1	3672766
2	3661776
3	3663205
4	3662555
5	3671283
6	3663705
Average area	3665882
Standard deviation	4824.813
% RSD	0.13

5.2 Linearity and range: After passing system suitability parameter, linearity assessment was conducted by injecting 6 different concentrations of niraparib working standard solution in HPLC 40, 45, 50, 55, 60 ug/ml respectively. Calibration curve was plotted. Figure 1 presents linearity profile and with its values in Table 4.

Table 4 Calibration curve

Conc (ug/ml)	Area ()
40	2921892
45	3314293
50	3672766
55	4040360
60	4404589

n= six replicated

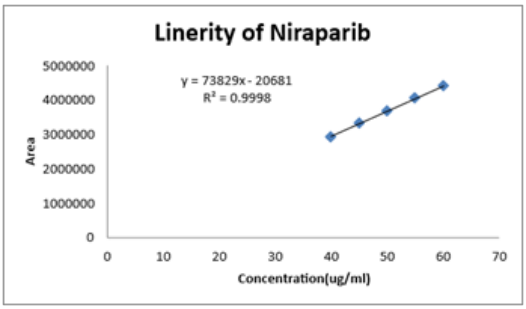

Figure 2 Calibration curve of niraparib

Peak area is increased proportionally as the concentration of niraparib increased from 40 to 60 ug/ml suggesting good linearity. R^2 was found to be 0.9998 explored linearity over given range.

5.3 Precision

Precision study was conducted as per ICH guidelines for developed method where intraday precision study injected six replicated standard solution morning and evening intraday precision, second day same standard solution injected compared the result with morning inter-day precision. Then relative standard was calculated.

Table 5 Intraday precision

Day 1	Sample ID	Area	Assay
Morning	Working Standard	3672766	-
	Sample Solution	3661967	99.71
Evening	Working Standard	3674509	-
	Sample Solution	3656563	99.51

Both sample injection yielded assay value within the close range 99.71-99.51%. The minor variability explored high repeatability. Thus, it can be concluded that results demonstrated excellent intraday precision. % RSD of inter-day precision was 0.10% suggested minimal variation between assay performed on different day thus inferred excellent interday precision of the method.

Table 6 Interday precision

Day	Sample ID	Area	Assay
Day 2	Working Standard	3665555	-
	Sample Solution	3653513	99.67
% RSD			0.10

5.5 Ruggedness

6 Sample of same concentration were prepared by different analyst and injected and area of all 6 samples was obtained and % RSD was calculated and was found to be 0.01% which was within the acceptable limits for assay methods. Thus, it demonstrated excellent precision and reproducibility.

Table 7 Ruggedness results

Standard solution injection	Area
1	3674401
2	3675377
3	3675161
4	3674782
5	3675377
6	3674509
Average	3675041.2
STDEV	384.1538754
RSD	0.01

5.4 LOD and LOQ: ANOVA technique was used for calculation. LOD & LOQ by following formula

$LOD = \frac{3.3 * Response\ of\ SD}{Slope}$ …… Equation 2

$LOQ = \frac{10 * Response\ od\ SD}{Slope}$ …… Equation 3

LOD as well as LOQ were noted to be 1.42 µg/ml, 4.30 µg/ml respectively.

*SD= Standard deviation

5.5 Robustness

This parameter was performed by varying column temperature ± 2°C and detector wavelength ± 2 nm. % Assay was calculated for every injection for each condition, % RSD was found to be less than 2. Table 6 presents robustness results. Robustness results explored that minor variation in column over temperature ± 2°C and detector wavelength ± 2 nm didn't significantly affect the performance of process thus demonstrated robustness of the process.

Table 8 Robustness results

Column Oven temperature		
Normal	**Decreased**	**Increased**
30°C	28°C	32°C
Wavelength		
Normal	**Decreased**	**Increased**
240 nm	238 nm	242 nm

Sample Level	Injection	Actual added (ug/ml)	Peak Area	Amt Recovered (ug/ml)	% Recovery	Average	SD	% RSD
80%	1	39.988	2921892	39.84	99.63	99.66	0.028893	0.03
	2	39.988	2923582	39.86	99.69			
	3	39.988	2922628	39.85	99.66			
100%	1	49.985	3672766	50.08	100.19	100	0.163001	0.16
	2	49.985	3661776	49.93	99.89			
	3	49.985	3663205	49.95	99.93			
120%	1	59.982	4404589	60.06	100.13	100.2	0.054041	0.05
	2	59.982	4406247	60.08	100.16			
	3	59.982	4409609	60.13	100.24			

Table 9 Accuracy results

5.7 Accuracy

Accuracy result was assessed by recovery study by standard addition at concentration levels 80%, 100%, 120% of target assay concentration. Each level was analyzed in triplicate, % recovery along with % RSD were computed to assess accuracy. % recovery ranged from 99.66-100.20% across all the levels. Recovery values were within acceptable range of 99.63-100.24% inferred the accuracy and reliability over range of concentration. Method consistently recovered niraparib close to 100% thus rendered it apt for routine quantitative analysis.

Forced degradation

Acid hydrolysis: 5 mg niraparib was transferred to 10ml flask and 1ml 1N HCl was added then stored for 10 minutes at room temperature after diluted with acetonitrile. 1ml of aforementioned solution was pipetted; added into another 10 ml volumetric flask, volume was made with diluent. Table 9 and Figure 2 demonstrate results.

Base hydrolysis: 5 mg Niraparib was transferred to 10 ml flask and 1ml 0.1N NaOH was added, then stored 10 minutes at room temperature after dilution with acetonitrile. 1ml of aforementioned solution was pipetted; added into another 10 ml volumetric flask; volume was made with diluent.

Oxidation: 5 mg niraparib was transferred to 10 ml flask and 1ml 30 % hydrogen peroxide was added, then stored 10 minutes at room temperature after dilution with acetonitrile. 1ml of aforementioned solution was pipetted; added into another 10 ml volumetric flask, volume made with diluent.

Dry Heat:5 mg niraparib was transferred to 10 ml flask; stored for 4 hours at 100 °C and diluted with acetonitrile. 1ml of aforementioned solution was pipetted; added into another 10 ml volumetric flask; volume was made with diluent.

UV:5 mg niraparib was transferred to 10 ml flask; flask was exposed to UV light at 254 nm for 4 hours and diluted with acetonitrile. 1ml of aforementioned solution was pipetted; added into another 10 ml volumetric flask, volume was made with diluent.

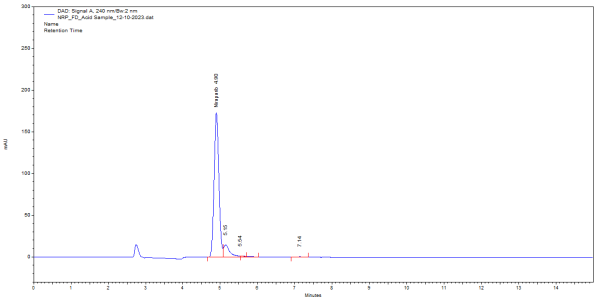

Figure 3 Acid degradation chromatogram

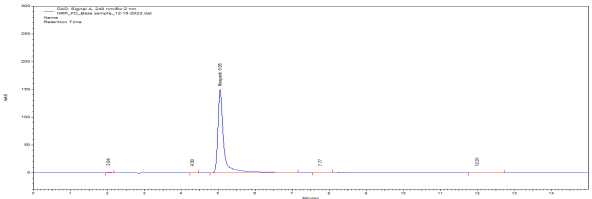

Figure 4 Base degradation Chromatogram

Sample ID	Condition	Wt (mg)	Area	% Assay	% Deg	Results
Working Standard	Control	5	3714131	100	-	-
Acid Sample	1 ml Stock + 1 ml 1N HCl for 10 min at RT	5	2994480	80.6	19.4	Degradation
Base Sample	1 ml Stock + 1 ml 0.1N NaOH for 10 min at RT	5	3398273	91.47	8.53	Degradation
Peroxide Sample	1 ml Stock + 1 ml H2O2 for 10 min at RT	5	3465686	93.28	6.72	Degradation
Heat Sample	5 mg API + 100C for 4 hours	5.1	3651734	96.36	3.64	Degradation
UV Sample	5 mg API + 254 nm for 4 hours	5.1	3624748	95.68	4.32	Degradation

Conclusion

Robust, accurate, precise, stability indicating RP-HPLC was successfully developed as well as validated for quantitative estimation of niraparib in bulk drug along with pharmaceutical dosage forms in current investigation. Method employed Agilent Zorbax Bonus-RP column with optimized mobile phase composition at 240 nm offering sharp and symmetrical peaks with consistent retention time of 5.18 minutes. Method validation was performed in compliance with ICH Q2 (R1) guidelines. Linearity was established in the concentration range of 40-60 ug/ml with 0.9998 as R^2. Precision exhibited % RSD below 2% suggesting high reproducibility. Accuracy was demonstrated at three concentration levels 80%, 100%, 120 % exhibited recovery from 99.66-100.20% across all the levels. Robustness results explored that minor variation in column over temperature ± 2°C and detector wavelength ± 2 nm didn't significantly affect the performance of process thus demonstrated robustness of the process. Method demonstrated stability indicating potential confirmed by capability to separate niraparib from its degradation products. Thus, it was inferred that developed RP-HPLC was simple, rapid, sensitive, as well as reliable rendering it highly suitable

for quality control assay along with stability testing assay in both formulated and bulk dosage forms.

Discussion

The present study aimed to develop and validate a simple, accurate, precise, and stability-indicating reverse-phase high-performance liquid chromatography (RP-HPLC) method for the quantitative determination of Niraparib in bulk drug and pharmaceutical dosage forms. Analytical method development is an essential component in pharmaceutical research and quality control to ensure the identity, purity, and potency of drug substances and formulations. Niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor widely used in the treatment of ovarian cancer, requires a reliable and sensitive analytical method for routine quality control and stability studies. Therefore, an RP-HPLC method was optimized and validated according to ICH guidelines to establish its suitability for routine pharmaceutical analysis.

During method development, several chromatographic conditions were investigated to obtain a well-resolved peak with good symmetry, adequate retention time, and satisfactory system suitability parameters. Different mobile phase compositions, flow rates, and detection wavelengths were evaluated to optimize the chromatographic performance. The final optimized conditions provided a sharp and symmetrical peak for Niraparib with minimal tailing and satisfactory theoretical plate count. The retention time obtained under the optimized conditions was appropriate for routine analysis, allowing rapid separation and reduced analysis time. These results indicate that the selected chromatographic parameters are suitable for the accurate determination of Niraparib.

The linearity of the developed method was assessed over a specific concentration range to determine the relationship between the drug concentration and the corresponding chromatographic response. The calibration curve demonstrated excellent linearity with a high correlation coefficient (R^2), indicating that the method is capable of producing proportional responses across the selected concentration range. This confirms the suitability of the method for quantitative analysis of Niraparib in bulk drug and pharmaceutical formulations.

Precision is an important validation parameter that reflects the reproducibility and reliability of an analytical method. In the present study, the precision of the developed method was evaluated in terms of repeatability (intra-day precision) and intermediate precision (inter-day precision). The results showed very low percentage relative standard deviation (%RSD) values, indicating that the method provides consistent and reproducible results under the same experimental conditions as well as on different days. These findings demonstrate that the developed RP-HPLC method possesses excellent precision and can be reliably used for routine analysis.

The accuracy of the method was evaluated using recovery studies performed by the standard addition technique. Known quantities of Niraparib were added to pre-analyzed samples at different concentration levels, and the percentage recovery was calculated. The results of the recovery studies were found to be within the acceptable range, demonstrating that the method is accurate and capable of determining the true concentration of the drug in pharmaceutical formulations without interference from excipients. This confirms that the developed analytical method can be effectively applied for the quantitative estimation of Niraparib in dosage forms.

Robustness testing was carried out to evaluate the reliability of the method when small, deliberate variations in chromatographic conditions were introduced. Parameters such as flow rate, detection wavelength, and mobile phase composition were slightly modified to assess their effect on retention time, peak area, and overall chromatographic performance. The results indicated that these minor changes did not significantly affect the analytical performance of the method. The %RSD values remained within acceptable limits, demonstrating that the developed RP-HPLC method is robust and capable of producing consistent results even under slight variations in analytical conditions.

System suitability testing was performed to verify the performance of the chromatographic system before analysis. Parameters such as theoretical plate count, tailing factor, and retention time were evaluated. The obtained values met the acceptable criteria, confirming that the chromatographic system was functioning properly and that the developed method is suitable for analytical purposes.

A critical aspect of this study was the evaluation of the stability-indicating capability of the developed RP-HPLC method. Forced degradation studies were conducted under various stress conditions, including acidic, alkaline, oxidative, thermal, and photolytic degradation. These stress conditions are commonly used to evaluate the stability behavior of pharmaceutical compounds and to determine the ability of an analytical method to separate the drug from its

degradation products. The results demonstrated that Niraparib undergoes degradation under certain stress conditions, particularly in acidic and oxidative environments. However, the developed RP-HPLC method was able to effectively separate the drug peak from the peaks corresponding to degradation products. The chromatographic separation obtained during forced degradation studies confirmed that the developed method is stability-indicating in nature. The Niraparib peak remained well resolved and free from interference by degradation products, indicating that the method can accurately quantify the drug even in the presence of degraded components. This property is particularly important for stability studies and quality control analysis during pharmaceutical product development and shelf-life determination.

Furthermore, the method demonstrated adequate sensitivity for the detection and quantification of Niraparib, making it suitable for routine pharmaceutical analysis. The combination of simplicity, short analysis time, and reliable performance makes this method advantageous compared to more complex analytical techniques. The method can therefore be effectively applied for routine quality control testing in pharmaceutical laboratories as well as for stability studies during drug development.

Overall, the results obtained from method development and validation confirm that the proposed RP-HPLC method meets all the requirements specified in ICH guidelines for analytical method validation. The method exhibited excellent linearity, accuracy, precision, robustness, and stability-indicating capability. These characteristics make it highly suitable for the quantitative determination of Niraparib in bulk drug substances and pharmaceutical dosage forms.

Conclusion

In the present study, a simple, rapid, precise, and stability-indicating RP-HPLC method was successfully developed and validated for the quantitative determination of Niraparib in bulk drug and pharmaceutical dosage forms. The optimized chromatographic conditions produced a well-resolved and symmetrical peak with satisfactory system suitability parameters. The developed method demonstrated excellent linearity within the selected concentration range with a high correlation coefficient, confirming its suitability for quantitative analysis.

The validation results showed that the method is accurate, precise, and reproducible, as indicated by acceptable percentage recovery and low %RSD values for both intra-day and inter-day precision studies. Robustness testing confirmed that small variations in chromatographic parameters did not significantly affect the analytical performance of the method. Forced degradation studies under acidic, alkaline, oxidative, thermal, and photolytic conditions demonstrated that the method is capable of effectively separating Niraparib from its degradation products, confirming its stability-indicating nature.

Therefore, the developed RP-HPLC method is reliable and suitable for routine quality control analysis, stability studies, and pharmaceutical formulation analysis of Niraparib in research laboratories and pharmaceutical industries.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the research work presented in this report.

Consent for Publications

All authors have read and approved the final version of this manuscript for publication.

Availability of Data and Material

All data generated or analyzed during this study are included in the manuscript and are available within the document.

Authors' Contributions

Mr. Pravin Sake[1] designed and conducted the research work, performed data analysis, and prepared the manuscript.

Dr. Minal Ghante[2] supervised the research design, guided the experimental work, and reviewed and approved the final version of the manuscript.

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