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Research Article

Bioanalytical Method Development by LC-MS/MS and Liquid Chromatographic Techniques for the Assay and Validation of Olaparib

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Abstract

The present method was developed for the estimation of Olaparib in spiked human plasma using Liquid chromatography-mass spectroscopy. The liquid-liquid extraction method was adopted and chromatographic separation was performed on a waters symmetry shield, C18 (4.6 mm id x 50 mm) analytical column using (Acetonitrile: Ammonium bicarbonate, pH 4.2 in the volume ratio of 70:30) as mobile phase. Positive ion mode was selected to obtain the product m/z+515.200 (parent)→380.3 (product) for Olaparib and m/z+435.22 (parent)→322.700 (product) for internal standard. Calibration curve was linear over the range of 3 ng/ml-600 ng/ml. The intra and interday accuracy with % nominal 95→98.4%, precision %CV ≤ 2% in all quality control levels, The percentage extraction recovery (96.15%→98.34%), demonstrated excellent matrix and analyte selectivity (% interference=0), and satisfactory stability study results in all types (% nominal 93.91%→99.58%). Based on the experimental findings the current developed method was considered a novel validated bioanalytical method, and applied in blood samples for bioanalytical studies of marketed formulations.

Keywords: Olaparib; Bioanalytical study; LCMS/MS; Method development

Introduction

Olaparib, a highly selective potent Poly (Adp-ribose) Polymerase (PARP) inhibitor in advanced treatment of ovarian cancer. It is 4-[(3-{[4-cyclopropylcarbonyl) piperazin-1-yl]carbonyl}-4-luorophenyl)methyl] phthalazin-1(2H)-one. Molecular formula is $C_{24}H_{23}FN_4O_3$. Molecular weight is 434.471 g/mol. Olaparib is an innovative, first-in-class oral Poly ADP-Ribose Polymerase (PARP) inhibitor that exploits tumor DNA repair pathways deficiencies to preferentially kill cancer cells. It is indicated as monotherapy in patients with deleterious germline BRCA mutated advanced ovarian cancer after chemotherapy. Olaparib is available as oral tablets marketed under the brand name Lynparza and was initially indicated as a maintenance therapy or monotherapy for the treatment of adult patient with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. On January 2018, FDA expanded the approval for use of Lynparza to include chemotherapy-experienced patients with germline breast cancer susceptibility gene (BRCA) mutated, Human Epidermal Growth Factor Receptor 2 (HER2)-negative metastatic breast cancer. Olaparib is available as capsules for oral use, containing 50 mg of free olaparib and the recommended dose is 400 mg twice daily. Peak plasma concentrations achieved typically between 1 hour to 3 hours. It exhibits a non-linear pharmacokinetics in human following oral administration. Exhibited moderate plasma protein binding in human (81.9%-91.2%). CYP3A5 plays a role in the formation of the major metabolites of olaparib incubated in human liver microsomes. It was predominantly eliminated in faeces (41.8%) and urine (44.1%). A generic drug must contain the same active ingredients as the original formulation. According to the United State Food and Drug Administration (USFDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamic properties. There is a necessity of assessment of pharmacokinetic parameters of generic drug formulation. Also, assessment between the generic and innovator product is carried out by a study of bioequivalence. Bioanalysis of study samples is an important phase of Bioequivalence assessment and to study the pharmacokinetics. The analytical method used in an *in vivo* bioavailability or bioequivalence study to measure the concentration of the active drug ingredient in body fluids shall be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient achieved in the body [1-6].

Materials and Methods

Olaparib standard (99.95% pure) and telmisartan (98.61% pure) was kindly provided by Honour labs, Hyderabad, India, as a gift sample. Ammonium bicarbonate buffer: ACN was obtained from sisco research laboratories Pvt. Ltd, Aldrich, Hyderabad, India. LC-MS grade in house was procured form mili-Q-water.

High performance liquid chromatographic operating conditions

An isocratic elution technique was adopted with the mobile phase (Acetonitrile: Ammonium bicarbonate, pH 4.2 in the volume ratio of 70:30) derived at a flow rate of 0.8 µl/minute using waters Symmetry shield C18 column with 10 mm internal diameter, 3.5 µm particle size, 100A° pore size layer was transferred to pre-labeled tubes and evaporated to dryness at 40°C. Both prepared samples were reconstituted with 200 µl of mobile procedure, transferred to autosampler loading vials, and 20 µl of the sample was injected into the LC-MS/MS device.

Mass spectroscopy operating conditions

Mass spectrometry was performed using an API-4500 Q-TRAP mass spectrometer (AB SCIEX, Foster city, CA/concord, Ontario, Canada) was equipped with an Electrospray Ionisation Source (ESI), operating in the positive ion mode at 700°C dessolvation temperature. The ion source voltage was 5000 V, the source temperature was maintained 382°C. The entrance potential and collision energy was maintained 10 V and 38 V. All other tuning parameters was set for the olaparib and internal standard telmisartan. Detection of the ions were carried out in multiple reaction monitoring by monitoring the transition pairs of m/z+435.22 (parent)→366.00 (product) for olaparib and m/z+515.200 (parent)→276.16 (product) for internal standard [7,8].

Preparation of stock solutions

Olaparib: Accurately, about 5 mg of Olaparib was weighed and transferred into 25 mL volumetric flask. It was dissolved in Methanol, and the volume was made up to the mark with same solution to make approximately 200.000 µg/mL solution of Olaparib. The stock solution was labelled appropriately and was stored at 2°C to 8°C for further usage.

Note: Two different stocks were used for Calibration curve standards and Quality control samples.

Telmisartan: Accurately, about 2 mg of Telmisartan was weighed and transferred into 20 mL volumetric flask. It was dissolved in Methanol, and the volume was made up to the mark with same solution to make approximately 100.000 µg/mL solution of Telmisartan. The stock solution was labelled appropriately and was stored at 2°C to 8°C for further usage.

Concomitant drug: Concomitant drug stocks were prepared in 100% Methanol and further dilution was prepared in dilution solution and was labelled separately.

Preparation of solutions

Dilution solution: A mixture of Methanol and water was prepared in a reagent bottle in the volume ratio of 50:50 using measuring cylinder. Mix well using the Sonicator. The solution was stored at room temperature (25°C ± 5°C) and was used within 5 days from date of preparation and was labelled appropriately.

Rinsing solution: A mixture of Acetonitrile and water was prepared in a reagent bottle in the volume ratio of 50:50 using measuring cylinder. Mix well using the Sonicator. Use this solution within the solution was stored at room temperature (25°C ± 5°C) and was used within 5 days from date of preparation and was labelled appropriately.

Mobile phase buffer (10 mM ammonium bicarbonate): Accurately, about 790.60 mg of ammonium bicarbonate, was weighed and dissolved in 1000 ml water using measuring cylinder. Mix well using the Sonicator. The solution was stored at room temperature (25°C ± 5°C) and was used within 5 days from date of preparation and was labelled appropriately.

Mobile phase: Mixture of Acetonitrile and Mobile phase buffer was prepared in a reagent bottle in the volume ratio of 70:30 using measuring cylinder and was labelled appropriately. Mix well using the Sonicator. The solution was stored at room temperature (25°C ± 5°C) and was used within 5 days from date of preparation.

Preparation of calibration curve standards and quality control samples

Screened blank K2EDTA human plasma lots were pooled together and were spiked with analyte stock dilutions to give the target concentrations.

Method validation carry over effect

The autosampler was used to monitor the carryover effect of Olaparib and the internal standard (telmisartan). Six replicates of analytes and internal reference samples were analysed at the null, ULOQ, and LLOQ levels. The processed samples were inserted in a particular order, for example, LLOQ samples first, then ULOQ, then blank. At the retention of analytes and IS, the interfering peak response of blank samples should not exceed 5% of the average IS response.

Matrix effect

This research was done at the LQC and HQC levels. For this analysis, 2 haemolytic and 2 lipemic plasma lot were chosen. One set of each sample was spiked with blank matrices (haemolytic), while the other set (LQC and HQC) with internal standard was spiked with lipemic plasma. Six replicates of aqueous samples with final LQC and HQC concentrations were prepared by adding an internal standard to reconstituted olaparib and injecting each one separately. By dividing peak response area in the presence of matrix ion by mean peak area response ratio in the absence of matrix ion, an internal standard normalised matrix factor was determined. The IS-normalized factor's

variability, as determined by the coefficient of variance, should be less than 15%.

Precision and accuracy

Using several olaparib QC samples at the level of LLOQ, LQC, MQC (I and II), and HQC in 6 replicates, the precision (intra and interday) and accuracy were estimated, and the concentrations in these levels were measured, followed by standard deviation, percent CV for precision, and percent nominal for accuracy for each replicate. The acceptance requirements for accuracy (percent nominal) are 15% and 20% for LLOQ level, respectively, and precision (percent CV) should be within 15% and 20% for LLOQ sample, respectively.

Linearity

The linearity of the current approach was also tested in the olaparib concentration range of 2.000 ng/ml to 1001.734 ng/ml. The CC (calibration curve) samples were prepared and processed by spiking human plasma. To produce the best fit for the concentration/response relationship, a regression equation with a weighing factor 1/(concentration ratio)2 of the drug to internal normal concentration was used to create the calibration curve. The r2 (coefficient of correlation) should be less than 0.9986 as an acceptance criterion for linearity.

Matrix selectivity and specificity

Olaparib matrix selectivity was tested by analysing plasma from 6 separate lots, including one haemolytic and one lipemic plasma, to see if the analytes' and internal standard's retention times interfered. The intervention at the drug retention times was assessed by comparing the response in blank plasma to the response of LLOQ. The intervention at the internal standard's retention time was also compared to the response of the extracted internal standard in the LLOQ study. The interfering substance's response will be considered appropriate if it is less than 20% of the mean drug response in the LLOQ sample and less than 5% in the internal norm.

Recovery study

This study was performed at 3 concentration levels: LQC, MQC-1, and HQC. The specimens, both extracted and non-extracted, have been packed. Internal criteria were applied at all stages, and samples were processed and injected. LQC, MQC-1, and HQC samples were freshly prepared for the preparation of extracted samples; internal criteria were applied at all stages, and samples were processed and injected and percent of recovery was measured separately for analytes and internal standard. It was determined what the average total recovery was.

Dilution integrity study

Prepare Dilution Integrity Quality Control (DIQC) spiked with about 1.5 to 1.8 times the concentration of the highest calibration curve standard (ULOQ). Process and analyse 6 samples each of the above dilution integrity quality control by diluting them 2 times and another 6 samples by diluting 4 times prior to extraction using acceptable blank matrix along with one set of calibration curve standards and quality control samples.

Ruggedness study

To assess the robustness of the established olaparib method, one accuracy and accuracy batch of samples was prepared and performed. These were injected into the LC-MS/MS system after being processed. To prepare the sample and mobile phase, different batch reagents (acetonitrile, ammonium bicarbonate, HPLC grade water) were used, as well as the same type of other column with the same make on different instruments.

Stability studies

Along with room temperature and refrigerator stock solution stability study of olaparib other stability tests of olaparib (Bench top, wet extract, freeze thaw, autosampler, short term and long term stability) were performed using freshly prepared calibration curve samples and quality control samples at low, middle, and high levels and analysed. The concentration of stability samples was calculated using data from concentration response linearity. Concentration response linearity data was collected and used to calculate the concentration of stability samples.

Room temperature stability study

It was conducted with a olaparib stock solution that had been ready for at least 6 hours. Analyte stock solution and internal standard were prepared from source. The stock solution (stability samples) and fresh stock solution (comparison sample) were diluted to their final concentrations, which is equivalent to the final middle quality control analytes and internal norm. The percent of stability was measured after 6 replicates of fresh and comparison samples were injected immediately.

Refrigerator stock solution stability

To test olaparib's stability, 6 replicates of the stock solution were prepared and stored in the refrigerator at 2°C-8°C for 4 days. On the day of the evaluation, a fresh reference stock solution (comparison sample) was prepared that was equal to the final MQC concentration of the analytes in reconstituted solution with the final concentration of the internal standard. Both stability and contrast samples were injected in correct away. For the analytes and internal normal, the percentage of stability for olaparib was determined.

Bench top stability

Six sets of LQC and HQC olaparib samples were taken from the deep freezer and left for 12 hr unprocessed. Following that, 6 sets of new quality control samples (low, middle, and high) as well as calibration samples were prepared. olaparib stability samples were processed and analysed alongside fresh samples. The linearity data was used to measure the concentration.

Auto sampler stability

To determine type stability, 6 sets of olaparib quality control samples were prepared at the LQC and HQC levels and kept in an auto sampler for 3 days. All stability samples were compared to freshly prepared spiked calibration curves and quality control samples at the low, middle, and high levels.

Freeze thaw stability

Four freeze-thaw cycles were used to determine it. olaparib LQC and HQC samples were prepared in 6 replicates and stored in a deep freezer at -25°C ± 5°C. The first 6 samples were removed after 24 h and thawed at room temperature before being frozen again. Similarly, the remaining samples were removed after the next 12 hr, and refrozen for another 12 h. After 4 cycles, all samples were processed. Olaparib stability samples were quantified at medium, mid, and high levels alongside freshly spiked calibration samples and quality control samples.

Wet extract stability

Six replicates of LQC and HQC samples were prepared, analysed, and held at room temperature (20°C ± 5°C) for one day to investigate olaparib wet extract stability. The samples were injected with freshly spiked calibration curve samples and quality control samples at medium, middle, and high levels after a suitable stability time. In comparison to freshly prepared samples, the sum of analytes in stability samples was measured.

Short term stability at -20°C

After spiking, 6 sets of olaparib quality control samples at low and high levels were prepared and frozen at -20°C in a deep freezer. The samples were processed 3 days later on the day of the evaluation, along with freshly prepared quality control samples at all stages and calibration curve samples. The stability samples' concentrations were measured in contrast to freshly prepared samples.

Long term stability at -70°C

Olaparib LQC and HQC samples were held at -70°C for 30 days to examine this. Six sets of long-term quality control samples (LQC and HQC) were removed and processed with freshly prepared calibration curves and quality control samples on the day of the assessment. The calibration curve data was used to quantify all of the stability samples. All stability samples must have a mean percent nominal concentration of between 85% and 115% at each quality control level, with precision of less than 15% of the CV percent. At least 67% of the stability QC samples must be within 15% of their nominal values.

Results

Mass spectrometry

The initial LCMS-MS was specified by proper tuning of all parameters in order to develop the method. The parameters were listed in detail in Table 1. Olaparib and internal standard telmisartan created a simple parent ion in positive ion mode. olaparib was found to have a m/z of 435.22 while telmisartan had a m/z of 515.200. The parent ion in the Q1 segment was protonated olaparib, and the internal standard [M+H]+ ion was used as a precursor ion to obtain Q3 product ion spectra.

Table 1: MRM acquisition parameters for analyte, metabolite, and ISTD

Parameter	Analyte	ISTD
DP (Declustering potential)	-92.00	-94.00
EP (Entrance potential)	-10.00	-10.00
CE (Collision energy)	-22.00	-22.00
CXP (Collision cell exit potential)	-14.00	-14.00
Dwell Time (m sec)	200.00	200.00
ESI source parameter	Settings	
CUR (psi)	30.00	
CAD (psi)	5.0	
IS (psi)	-4500.00	
TEMP(ºC)	500.00	
GS1 (psi)	45.00	
GS2 (psi)	50.00	
Note:- Olaparib (analyte): 435.22/366.000 (m/z) Telmisartan (ISTD): 515.200/276.16 (m/z)		

Tuning of the analyte

Compound depend parameters and Source depend parameters: Method development: Several chromatographic trials were carried out to develop the method, utilising different mobile phases with varied volume ratios. During the initial studies, several combinations of acetonitrile, methanol, ammonium bicarbonate and buffers were utilised. During the early experiments, the observed peaks of the analyte olaparib were similarly unsatisfactory due to a large number of splits and a high amount of base line noise. Finally, a waters symmetry shield, C18 (4.6mm id × 50mm) analytical column (waters Milford, MA, USA) with a mobile phase of acetonitrile and ammonium bicarbonate. Even at very low quality control samples, the peak shape for analyte and internal standard was determined to be excellent in this optimised setting. To find a good internal standard, numerous compounds were explored. Finally. the telmisartan was chosen since the retention time and other values were very selective and did not interfere with analytes. The retention time of olaparib was found to be 0.96 min at this optimised setting, and the retention time of the internal standard was found to be 1.23 min, as shown in the MRM chromatograms in Figures 1 and 2.

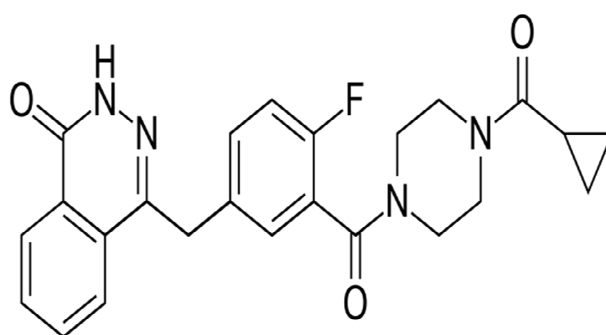

Figure 1: Chemical structure of Olaparib

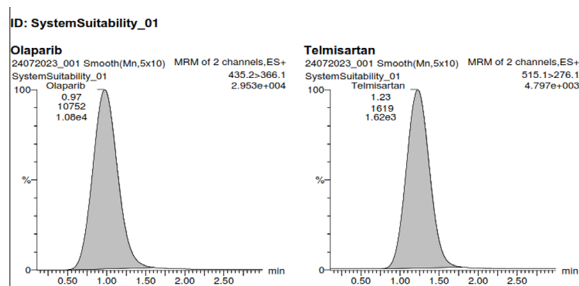

Figure 2: System suitability

Validation

Using the developed improved approach, several validation parameters according to USP requirements were investigated for olaparib. The results of the carryover research reveal that at the ULOQ and LLOQ levels, there was no interference in the retention period of olaparib and the internal standard telmisartan. The obtained answer for blank samples is 0 and the computed percent carry over is also 0%, indicating that the acceptance conditions were met. The internal standard normalized factor for the analyte in the presence of matrix ion was determined as a result of the matrix effect. Acceptance criteria were met when the percent CV of the normalized factor was found to be 8.19% for LQC samples and 8.24% for HQC samples. When comparing the mean response of extracted LLOQ samples with the blank matrix, no interference was discovered at the retention time of analyte and internal standard, and the response of interfering peaks at the retention time of analyte and internal standard was found to be 0% of the mean drug response. The intraday within batch precision (% CV) of LLOQ, LQC, MQC-I, MQC-II, and HQC samples of olaparib were reported to be 6.78, 1.23, 0.35, 0.75, and 0.46, respectively, in a study of intraday within batch precision (% CV). LLOQ, LQC, MQC-I, MQC-II, and HQC had intraday accuracy of 98.15%, 91.98%, 94.05%, 96.23%, and 94.24%, respectively. The batch accuracy (% Nominal) results for the levels of LLOQ, LQC, MQC-I, MQC-II, and HQC were in the range of 97.85% to 94.34%, and precision (% CV) values were in the range of 0.002 to 1.69. Table 2 summarizes the results. The linearity investigation used a regression equation with a weight factor of 1/(concentration ratio)2 of medicines to internal standard concentration for olaparib calibration curve samples in the concentration range of 0.5 ng/ml to 100 ng/ml. The correlation coefficient (r2) for olaparib was determined to be 0.998. In a recovery analysis of olaparib and internal standard QC samples, the mean overall recovery of olaparib was 95.96% and 94.07% for internal standard, with a precision (% CV) range of 0.65 to 1.8 and a percent difference between height and lowest percent recovery of 7.26 for olaparib and 6.92 for telmisartan, respectively. The results were within acceptable bounds. Olaparib dilution integrity was measured at the ULOQ level in this investigation [9,10]. In comparison to the undiluted calibration curve samples, % CV and percent nominal were found to be 1.16 and 96.92% at 2 times dilution and 1.36 and 96.10% at 4 times dilution. Within batch precision (% CV) was reported to be 2.15, 1.54, 0.97, 0.57, and 5.91 for the ruggedness investigation. At the LLOQ, LQC, MQC-I, MQC-II, and HQC levels, the accuracy values were 96.44%, 96.43%, 98.35%, 98.51%, and 92.37%, respectively Figures 3 and 4.

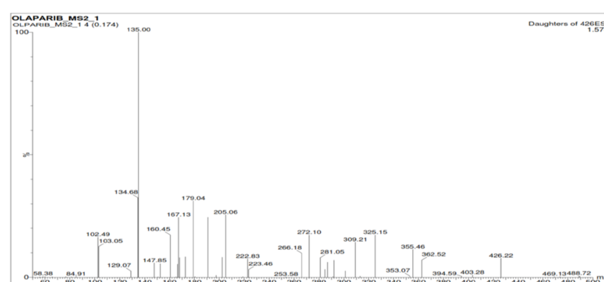

Figure 3: Mass Spectrum of Olaparib

Table 2: Accuracy and precision for determination of Olaparib in human plasma

Q.C Level	Olaparib measured concentration (ng/ml)				
	Run*	Mean	SD	% CV	% Nominal
Between the batch intra day					
LLOQ	1	1.958	0.091	4.65	97.90
	2	1.955	0.121	6.19	97.75
LQC	1	5.486	0.092	1.68	91.63
	2	5.730	0.112	1.95	95.71
MQC-1	1	417.655	1.656	0.40	94.18
	2	406.888	5.042	1.24	91.76
HQC	1	729.663	2.702	0.37	94.15
	2	725.011	6.318	0.87	93.55
Within batch inter day					
LLOQ	-	18	18	18	18
LQC		1.957	5.567	414.066	728.112
MQC-1		0.099	0.152	6.044	4.643
MQC-II		5.06	2.73	1.46	0.64
HQC		97.85	92.98	93.37	93.95

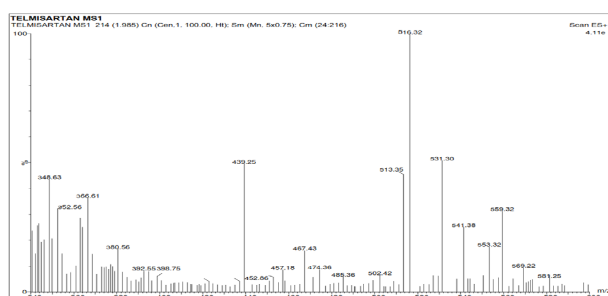

Figure 4: Mass Spectrum of Telmisartan

Stability studies

The percent stability for olaparib and the internal standard were 102.93% and 97.53%, respectively, according to the results of a room temperature (20°C ± 5°C) stock solution stability analysis. The calculated percent of stability for olaparib and 100.39 for the internal standard was found in a refrigerator stock solution stability study at 2°C-8°C for 7 hours. At the LQC level, the percent stability for Bench top stability research results was 96.58%, and at the HQC level, it was 96.83%. The auto sampler stability research (2 days 2 hours of acceptable stability period in auto sampler) revealed 90.50% and 94.08% at the LQC and HQC levels, respectively. Olaparib has a wide range of acceptability at both the LQC and HQC levels, with percentage stability of 96.58% and 96.83%, respectively, according to the results of a seven-cycle freeze-thaw stability sample. In dry extract stability testing, the percent nominal value for olaparib was 95.29% for LQC and 96.49% for HQC. Olaparib computed percent stability was more than 89.93% at LQC and 94.26% at HQC, which met the short-term stability study's acceptability level. The percentage stability for LQC samples was 92.42% and 93.71% for HQC samples in the long-term stability testing (25 days 17 h at 25°C+-5°C). The findings of all stability investigations are summarized (Table 3).

Table 3: Stability study data of Olaparib

Q.C Level	Type of stability	Olaparib			
-		Mean	SD	% CV	% Nominal
LQC	Bench Top	5.782	0.089	1.54	96.58
	Freeze thaw	5.591	0.074	1.32	93.39
	Autosampler	5.418	0.071	1.31	90.50
	Dry extract	5.705	0.045	0.79	95.29
	Whole Blood	4.964	0.063	1.27	100.32
	Long term	5.533	0.124	2.24	92.42
HQC	Bench Top	750.421	5.784	0.77	96.83
	Freeze thaw	731.298	5.111	0.70	94.36
	Autosampler	729.098	1.875	0.26	94.08
	Dry extract	747.790	4.243	0.57	96.49
	Whole Blood	4.964	0.063	1.27	100.32
	Long term	726.206	3.860	0.53	93.71

Discussion

The present bioanalytical method for olaparib has been developed after successful trials to optimised the parameters for both chromatographic and mass spectrophotometric analysis. Initially the LC-MS parameters has been tuned to obtained the product ion mass spectra of olaparib and internal standard telmisartan. Using the same tuned condition MRM chromatograms of olaparib and telmisartan has been optimized using acetonitrile and ammonium bicarbonate, pH 4.2 in the volume ratio of 70:30. The obtained MRM chromatograms of both olaparib and internal standard was highly selective with excellent peak shape with great sensitivity. The results of all the validation parameters are within the acceptance criteria as per US-FDA bio analytical method development guidelines [10]. The result of carry over test shows 0% carryover of LLOQ and ULOQ samples of analyte and internal standard which satisfied the acceptance criteria [11,12]. The results of the matrix and analyte selectivity analysis revealed that the olaparib developed method is selective.

Conclusion

The current method has a highest output than the previously published HPLC and LCMS/MS method. With less run time, the total analysis time is required to be much less. This method became more practical and cost effective thanks to a simple liquid-liquid extraction procedure. Empirical evidence of all validation results showed that the method is highly validated and simple, as all parameters are within the US-FDA guidelines' acceptance limits. As a result, this current attractive, simple, and reliable novel method is unquestionably highly applicable for Olaparib quantitative analysis during clinical trials, preclinical trials, forensic, and toxicological studies.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement

None.

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