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Efficient Determination of Abemaciclib Concentrations in Human Plasma Via LC-MS/MS: A Rapid and Reliable Approach

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KEYWORDS
Abemaciclib; Abemaciclib-D10; Human plasma; HPLC-ESI-MS/MS; Bioanalysis

ABSTRACT:

The quantification of Abemaciclib in human plasma was accomplished through a validated protein precipitation method employing HPLC-ESI-MS/MS, utilizing Abemaciclib-D10 as an internal standard (ISTD). Chromatographic separation was achieved on a Discovery® C18 HPLC Column (2 cm × 2.1 mm, 5 µm) with a mobile phase consisting of Methanol: Acetonitrile (20:80%, v/v, pH: 6.5 adjusted with diluted ammonia solution). The total analysis time was 3.0 min, and the flow rate was maintained at 0.7 ml/min. Mass transitions for Abemaciclib and Abemaciclib-D10 were recorded as m/z 507.32 →393.16 ansd 517.66 → 393.16, respectively. The standard curve exhibited a correlation coefficient (r2) exceeding 0.9983, covering a concentration range of 6.00-768.00 pg/ml using the linear regression model.

INTRODUCTION

Abemaciclib (ABEMA) stands as a potent oral cyclin-dependent kinase inhibitor (CDKi) that has garnered approval from both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) regulatory agencies. This approval is specifically for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) locally advanced and metastatic breast cancer [1].

While the three drugs varied in terms of toxicity and tolerance due to differences in target specificity and selectivity, ABEMA's antitumor activity in this patient population has been determined to be equivalent to that of the other licensed CDKi's [2]. ABEMA was initially approved by FDA for mono- and in a second stage for combination therapy with an aromatase inhibitor, such as letrozole (LETRO), or fulvestrant. In contrast to palbociclib and ribociclib, which have a three-week on/one-week off schedule, ABEMA is given twice daily and continuously under this second dosing regimen, with a beginning dose of 150 mg [3,4]. Therapeutic drug monitoring (TDM) has the potential to prevent or at least delay the loss of a therapeutic chance due to the close correlation between ABEMA exposure, efficacy, and toxicity, as has been reported by the FDA [3]. Adverse reactions to ABEMA are not experienced by all patients in the same way as those to the other CDK. However, in cases of severe toxicity, dose reductions and therapy discontinuation are necessary [3, 4]. This leads to a reduced quality of life. Specifically, MONARCH 2 study indicated that patients with neutropenia had increased exposure to ABEMA. Additionally, a positive correlation has been established between plasma concentration and tumor shrinkage, lower hazard of progression, and best objective response. Pharmacokinetic (PK) variability does not appear to be influenced by patient demographics [6–11]. Additionally, as was already mentioned, dose adjustments are made based on signs of toxicity [4,8–11], which may be anticipated and prevented with TDM-guided dosing, because there are no predictive biomarkers for response and/or tolerance to ABEMA [7].

An oral kinase inhibitor is called abelacilbiprofen. With a molecular weight of 506.59 and an empirical formula of C27H32F2N8, it is a white to yellow powder.

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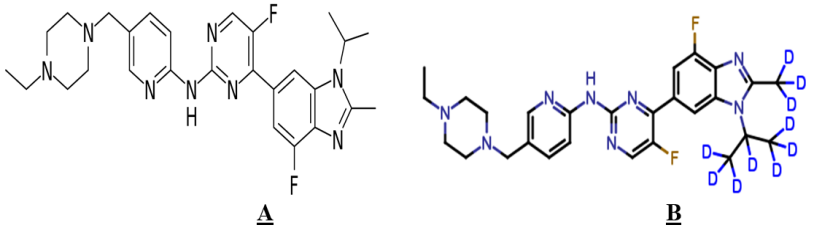
Abemaciclib is known by its molecular name, N-[5-[(4-Ethyl-1-piperazinyl) methyl][2-pyridinyl]5-fluoro-4-[1-methylethyl)-1H-benzimidazol-6-yl-1-fluoro-2-methyl-1-]-2-pyrimidinamine. The structure of Abemaciclib is as follows (Figure-1.0).



A **B**

Fig.1. Chemical Structures of A) Abemaciclib B) Abemaciclib-D10

Abemaciclib has been the subject of several pharmacokinetic investigations [12–18], but none of these research included a method for estimating the amount of Abemaciclib in human plasma by LC-MS/MS using Abemaciclib-D10 as the internal standard.

Therefore, the purpose of this work was to reduce the chromatographic run time utilizing a more selective LC-MS/MS technique while also streamlining the sample preparation stage using protein precipitation. Furthermore, isotopically labeled Abemaciclib (Abemaciclib-D10) was utilized to decrease the matrix effect and increase reproducibility in order to increase the method's precision and accuracy. These advancements made it possible to create an LC-MS/MS method for determining the amount of Abemaciclib in human plasma that is quick, sensitive, and selective.

Developing an advanced bioanalytical technique that incorporates appropriate deuterated or analog-based internal standards is crucial for mitigating the matrix impact and enhancing reproducibility.

According to bioanalytical FDA guidelines [19–22], the current study details the development and validation of an isocratic LC-MS/MS with an extraction method that is straightforward, highly sensitive, specific, and efficient for quantitatively determining Abemaciclib in human plasma with minimal plasma usage.

MATERIALS AND METHODS

Materials:

Chemical Resources

Alsachim, France provided Abemaciclib and Abemaciclib-D10. Water (HPLC Grade). J.T. Baker in India provided the methanol and acetonitrile (HPLC grade), whereas Merck in India provided the formic acid (AR grade). The source of human plasma was Doctors labs Blood Blank in Hyderabad. The house Milli-Q system provided the Milli Q water.

Instrument Resources

Analyst® Software 1.4.1 was used for data gathering and processing on an API 4000 HPLC-ESI-MS/MS system (Applied Biosystems), a 1200 Series HPLC system (Agilent Technologies, Waldbronn, Germany), and data processing.

Methods:

Chromatographic conditions

Utilizing the Discovery® C18 HPLC Column, which measures 2 cm × 2.1 mm, 5 µm, the chromatographic separation was accomplished with Methanol: Acetonitrile (pH: 6.5, Adjusted with Distilled Ammonia) (20: 80, v/v), which produced the best peak shape and minimal baseline noise. The flow rate was adjusted to 0.7 ml/min, and the analysis took three minutes total. The column oven's temperature was set at 40°C. To improve ionization and chromatography, the sample volume for the mass spectrometry injection was changed to 10 µl.

Detection

In order to optimize mass parameters such as source temperature, IS, heater gas, nebulizer gas, curtain gas, CAD gas (all gas channels were purged with ultra high pure nitrogen gas), EP, DP, CE, FP, and CXP, the pure drugs Abemaciclib and Abemaciclib-D10 were prepared in acetonitrile (200.00 pg/mL) and injected at a flow rate of 10 µL/min into a positive ion mode mass spectrometer. Analysis was performed using MRM

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positive ion mode with mass transitions of 507.32 m/z (parent ion) to 393.16 m/z (product ion) for Abemaciclib. Likewise, mass transitions from 517.66 m/z (parent ion) to 393.16 m/z (product ion) were obtained for Abemaciclib-D10. Figures 2 and 3 showed the parent and product ion mass spectra.

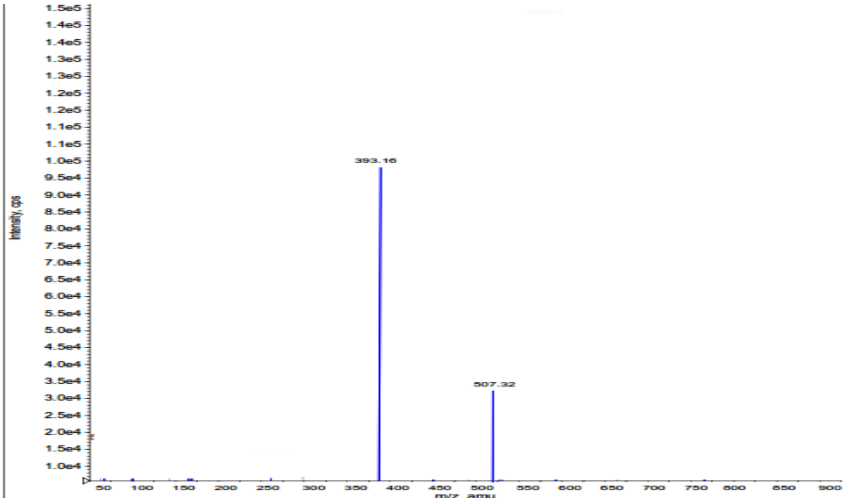

Figure.2: Parent ion mass spectra (Q1) and (Q3) of Abemaciclib

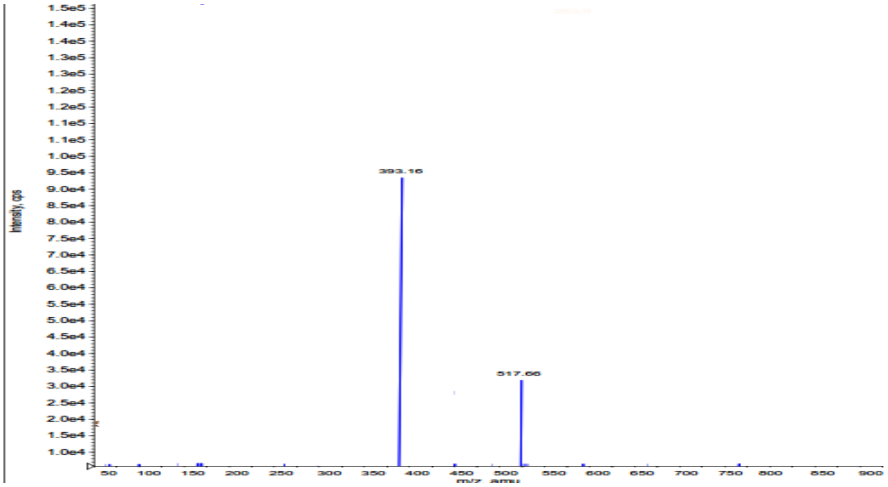

Figure.3: Parent ion mass spectra (Q1) and (Q3) of Abemaciclib-D10

Standard calibration and quality control samples preparation

Acetonitrile was used to create standard stock solutions of Abemaciclib (10.0 mg/mL) and Abemaciclib-D10 (10.0 mg/mL). The mobile phase solution (methanol:acetonitrile, pH:6.5, adjusted with diluted ammonia solution) (20:80%, v/v)) was used to prepare the IS spiking solution (200.0 pg/mL) from the Abemaciclib-D10 stock solution. Up until analysis, standard stock solutions and IS spiking solutions were kept in refrigerators between 2 and 8 degrees Celsius. To obtain concentration levels of 6, 12, 24, 48, 96, 192, 384, and 768 pg/mL for analytical standards and 6 (LLOQ), 18 (LQC), 360 (MQC), and 720 pg/mL (HQC) for quality control (QC) standards, standard stock solutions of Abemaciclib (10.0 mg/mL) were added to drug-free screened human plasma and stored in the freezer at -30ºC until analysis. The aqueous standards were made in a mobile phase solution (20:80%, v/v) of methanol and acetonitrile (pH:6.5, adjusted with diluted ammonia solution) and were kept chilled until analysis at 2–8ºC.

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Sample extraction

The separation of Abemaciclib and Abemaciclib-D10 from human plasma was accomplished by the protein precipitation method. To achieve this, 150 µL of plasma sample and 10 µL of Abemaciclib-D10 (200 pg/mL) were added to the labelled polypropylene tubes, and they were vortexed for a short while—roughly 10 minutes. After that, vortex 20µL of 0.1% formic acid for 30 seconds. After adding 1 mL of acetonrile extraction solvent, the mixture was vortexed for approximately 10 minutes.

The samples were then centrifuged for about five minutes at room temperature at 15000 rpm. A sample of the supernatant was taken from each and placed into labelled polypropylene tubes. It was then dried for a short time at 45ºC and reconstituted using a mobile phase solution of methanol:acetontile (pH:6.5, adjusted with diluted ammonia) (20:80, v/v). Finally, the sample was placed into autosampler vials and injected into the LC-MS/MS for analysis.

Method Validation [19-22]

The new method was validated over a linear concentration range of 6.0–768.0 pg/ml. The validation parameters include selectivity and specificity, LOQ, Linearity, precision and accuracy, matrix effect, recovery, stability (freeze–thaw, auto sampler, bench top, long term) was tested under validation section.

Selectivity and Specificity

Six lots of interference-free blank plasma samples were chosen from ten lots of samples for analysis in order to determine the selectivity and specificity. Less than 20% of the LLOQ peak area of the Abemaciclib retention time and less than 5% of the Abemaciclib-D10 retention time are required for the endogenous/potentially interfering peak regions for blank samples.

Limit of Quantification (LOQ)

In a screened plasma lot, six LLOQ standards and IS (6.00 pg/ml) were created. Using analyst software, the signal to noise ratio (S/N) was computed.

Linearity

The linearity range of 6, 12, 24, 48, 96, 192, 384, and 768 pg/ml was achieved by preparing calibration standards, which were then analyzed in five duplicates on five separate days.

Precision & Accuracy

Calibration standards and quality control standards, encompassing Lower Limit QC (6.00 pg/ml), Low QC (18.00 pg/ml), Mid QC (360.00 pg/ml), and High QC (720.00 pg/ml) concentrations, were meticulously prepared in screened plasma. Each set of standards underwent analysis with six replicates on a single day (Intra-day) and was further assessed over five distinct days (Inter-day). This comprehensive approach ensures the robustness and reliability of the analytical method by evaluating both within-day and between-day variations across the specified concentration levels.

Matrix Effect

The un-extracted concentration of mid-QC (360.00 pg/ml) was added to six extracted blank plasma samples in three repetitions, and the results were compared to un-extracted standards at the same concentration.

Recovery

Protein precipitation was the technique used to recover the samples. At three different concentrations: low (18.00 pg/ml), medium (360.00 pg/ml), and high (720.00 pg/ml), the extraction recovery was ascertained in sextuplicate by comparing the extracted and un-extracted QC standards.

Stability studies

Bench top Stability (Room Temperature Stability, 48 h)

Six duplicates of BT stability samples—low and high quantities spiked—were kept at room temperature for a maximum of 48 hours. The samples underwent processing, and newly made low and high concentrations (comparison samples) were used for comparison.

Freeze and thaw stability (after 3rd cycle at -30°C)

In order to compare the FT stability samples, six replicates of low and high concentrations were frozen at -30°C and then went through three freeze-thaw cycles lasting 24, 36, and 48 hours (-30°C to room temperature).

Autosampler stability/ Processed Stability (2-8°C, 70 h)

Six replicates of both high and low concentrations (AS stability samples) were kept in the auto-sampler at 2–8°C for up to 70 hours. Newly made low and high concentrations (comparison samples) were compared to stability samples.

Long-term Stability (-30°C, 90 Days)

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After completion of the stability period stored at -30 °C (90 days) six duplicates of low and high concentrations (LT stability samples) were compared with newly generated low and high concentrations (comparison samples).

RESULTS AND DISCUSSION

Method development

HPLC-MS/MS was chosen as the preferred approach in the process of developing a straightforward and easily applicable method for determining the amount of Abemaciclib in human plasma. Chromatography (mobile phase composition, column, flow rate, injection volume, sample volume), mass spectrometry, sample extraction, and internal standard parameters were all logically and sequentially optimized during the technique development process in order to produce the best results.

Several brands of RP-HPLC C18 columns were used to separate the Abemaciclib. A low response was seen during the first separation, which was carried out using isocratic elution of formic acid, ammonium acetate, and ammonium formate combined with organic phases such methanol and acetonitrile was chosen as a mobile phase in various combinations. The best reaction was obtained using a mobile phase of Methanol: Acetonitrile (20:80, v/v); nevertheless, unsatisfactory peak shape was noted.

Following a number of experiments, different mixtures of methanol and acetontile were attempted as the mobile phase. The Ascentis Discovery® C18 HPLC Column, 2 cm × 2.1 mm, 5 µm analytical column with a flow rate of 0.7 ml/min and a shorter runtime of 3 minutes, produced the best signal along with a noticeable improvement in the peak shape and low baseline noise when used in conjunction with a mobile phase containing methanol: Acetontile (pH: 6.5, Adjusted with diluted ammonia) (20: 80, v/v). The temperature of the auto sampler was maintained at 4°C, while the column oven was kept at a consistent 38°C. A 10 µl sample was injected at a different volume to improve chromatography and ionization. Tenofovir, Emtricitabine, and Efavirenz were tested using ideal mobile phase and column conditions in order to choose an internal standard. Ultimately, Abemaciclib-D10 was chosen as the internal standard due to its superior extractability and chromatography.

With a runtime of three minutes, the retention times of the internal standard (Abemaciclib-D10) and analyte (Abemaciclib) were eluted at 1.38±0.02 min and 1.39±0.02 min, respectively. Various processes were optimized, including LLE (liquid-liquid extraction), SPE (solid phase extraction), and PPT (protein precipitation). All things considered, it was found that the LLE was the most appropriate because of its easy extraction, high recovery, and minimal impact of ion suppression on the medication and internal standard.

For this method, electron spray ionization (ESI) was selected since it offered a maximum responsiveness as compared to air pressure chemical ionization (APCI) mode. The device's sensitivity and signal stability were maximized during the analyte's infusion into the continuous mobile phase flow to the electron spray ion source, which was running at a 20 µL/min flow rate. In contrast to the negative ion mode, bemaciclib responded more in the positive ion state.

To produce high intensive productions source dependent parameters were optimized as nebulizer gas flow 30 psi, CAD gas and curtain gas flow 25 psi, ion spray voltage 5500 V, and temperature 500°C. The compound dependant parameters such as the declustering potential (DP), focusing potential (FP), entrance potential (EP), collision energy (CE), cell exit potential (CXP) were tuned during tuning as 35, 25, 10, 20, 12 eV for Abemaciclib and Abemaciclib-D10, respectively. Nitrogen gas was used to set the collision activated dissociation (CAD) gas at 4 psi. Quadrupole-1 and quadrupole-3 were both kept at a unit resolution and dwell duration was set at 200 ms for Abemaciclib and Abemaciclib-D10.

The MH+ ions at m/z 507.32 m/z (parent ion) and 517.66 m/z (parent ion) respectively correspond to the main peaks in the primary ESI spectra of Abemaciclib and Abemaciclib-D10. Following a collision with nitrogen in quadrupole-2, the productions of Abemaciclib and Abemaciclib-D10 scanned in quadrupole-3 with m/z values of 393.16 m/z (product ion) and 393.16 m/z (product ion), respectively. Figures 2 and 3 displayed the parent and production mass spectrums of Abemaciclib and Abemaciclib-D10.

Method validation

Limit of Quantification, Selectivity and Specificity (LOQ)

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When comparing the retention durations of Abemaciclib and Abemaciclib-D10 in blank plasma to LLOQ and blank with IS samples, no discernible change was seen. The lowest concentration of the calibration curve, which was determined to be 6.0 pg/ml, was the limit of quantification for this method. In Figures 4 and 5, represent chromatograms were displayed.

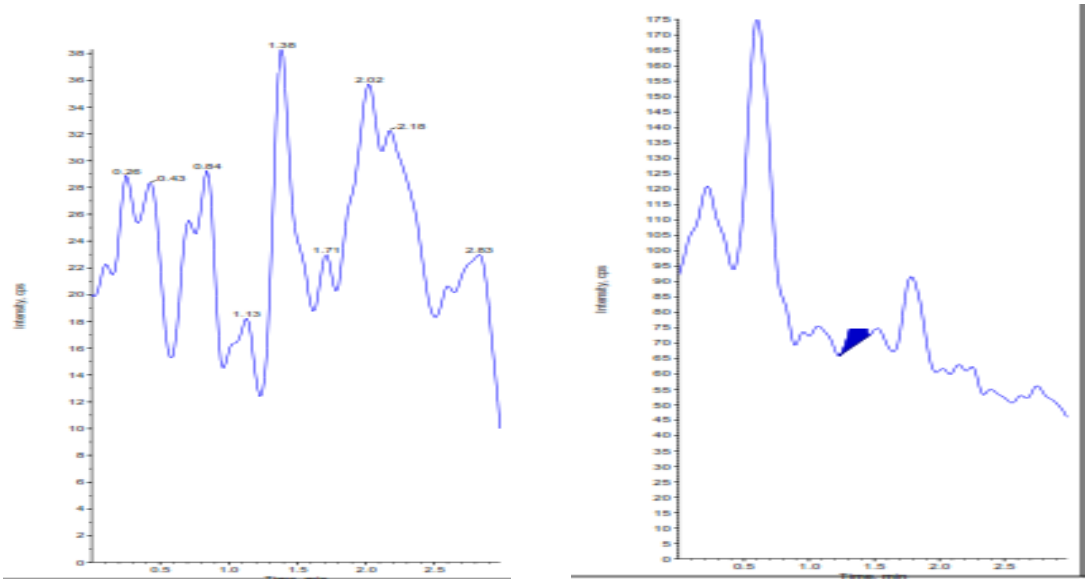
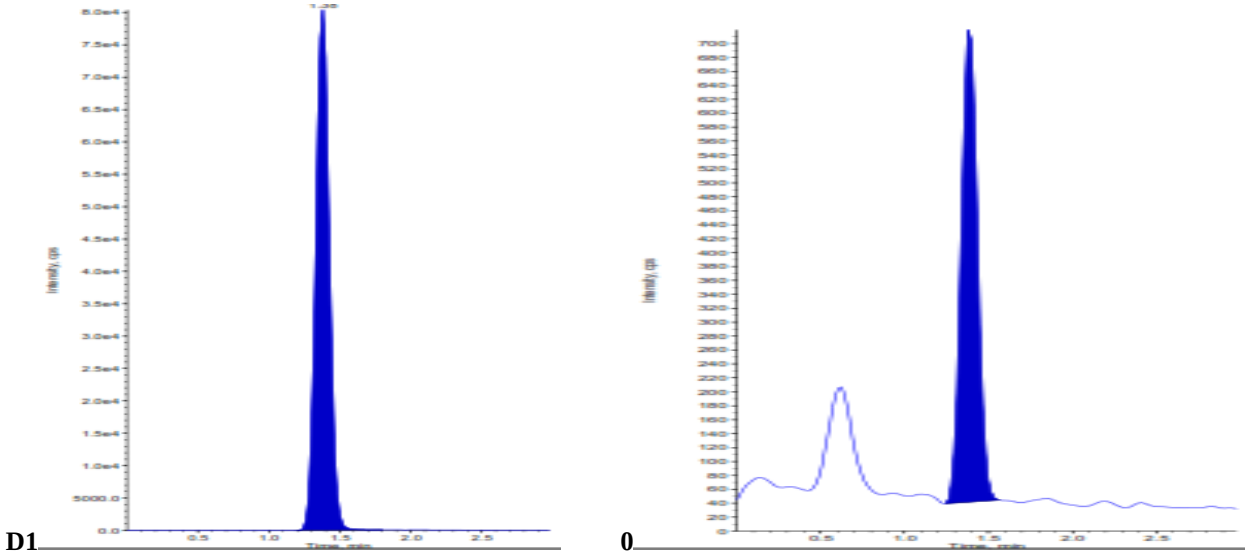


Fig.4-Blank plasma chromatogram for interference free Abemaciclib and Abemaciclib-



D1 0

Fig.5- Chromatogram of LLOQ sample (Abemaciclib and Abemaciclib-D10).

Linearity

Abemaciclib concentration (pg/ml) on the x-axis and peak area ratio (Abemaciclib peak area / Abemaciclib-D10 peak area) on the y-axis were used to plot linearity. For Abemaciclib, calibration curves were shown to be consistently precise and accurate over a linearity range of 6 to 768.00 pg/ml. Abemaciclib has a correlation coefficient greater than 0.99980. The mean accuracy varied from 96.83 to 100.52%, with a CV of less than 15%. Table 1 displayed the findings.

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Table. 1 - Calibration curve details of Abemaciclib

Spiked plasma Concentration (pg/ml)	Concentration measured (pg/ml) (Mean±S.D)	%CV (n=5)	%Accuracy
6.00	5.81± 0.62	10.68	96.83
12.00	11.64 ± 1.11	9.57	96.97
24.00	23.56 ± 1.27	5.40	98.17
48.00	46.99 ± 1.00	2.12	97.90
96.00	96.49 ± 1.17	1.21	100.52
192.00	191.13 ± 1.98	1.03	99.55
384.00	383.33 ± 1.01	0.26	99.83
768.00	768.16 ± 0.30	0.004	100.02

Precision & Accuracy

Abemaciclib's intra- and inter-batch percentage accuracy ranged from 97.33 to 99.58 and from 100.48 to 104.27. Its CV was 0.39 to 3.68 and between 0.28% and 3.18%. Table 2 displays the results.

Table.2-Precision and accuracy (Analysis with spiked samples at three different concentrations) of Abemaciclib

Spiked Plasma Concentration (pg/ml)	Within-run (Intra-day)			Between-run (Inter-Day)		
	Concentration measured (n=6;pg/ml;mean±S.D)	%CV	%Accuracy	Concentration measured (n=6;pg/ml;mean±S.D)	%CV	%Accuracy
18.00	17.52±0.65	3.68	97.33	18.77±0.60	3.18	104.27
360.00	366.62±6.40	1.75	101.84	361.73±1.01	0.28	100.48
720.00	716.94±2.78	0.39	99.58	721.72±5.31	0.74	103.24

Recovery

The average percentage of recovery for the Abemaciclib LQC, MQC, and HQC samples was 98.12%, 99.27%, and 97.24%, in that order. For Abemaciclib, the overall mean percentage recovery and percentage CV are 2.30% and 98.21% across all QC levels. The mean percentage of recovery and percentage of CV for the Abemaciclib-D10 (internal standard) are 94.31% and 4.82%.

Matrix Effect

Abemaciclib and Abemaciclib-D10 tests on several sources of rat plasma revealed no discernible matrix impact. 1.98 was determined to be the %CV.

Stability (freeze–thaw, auto sampler, bench top, long term)

Table 3 displays the long-term stability information and the quantification of Abemaciclib in plasma after it was subjected to three freeze-thaw cycles (-30°C to room temperature), processed by an autosampler, and room temperature (Benchtop).

Table. 3 - Stability studies of Abemaciclib in spiked plasma samples

Spiked Plasma concentration (pg/ml)	Room temperature Stability		Processed sample Stability		Long term stability		Freeze and thaw stability	
	48h		70h		90 days		Cycle (48h)	
	Concentration measured (n=6;pg/ml; mean±S.D)	%CV (n=6)	Concentration measured (n=6;pg/ml; mean±S.D)	%CV (n=6)	Concentration measured (n=6;pg/ml; mean±S.D)	%CV (n=6)	Concentration measured (n=6;pg/ml; mean±S.D)	%CV (n=6)
18.00	18.44±0.90	4.88	18.33±0.48	2.63	18.67±0.71	3.82	18.03±0.88	4.87
720.00	721.28±1.71	0.24	720.33±0.39	0.05	723.22±2.90	0.40	722.4±2.15	0.30

Conclusion

The approach presented in this publication has been developed and verified in human plasma throughout a concentration range of 6.0–768.0 pg/ml. With values constantly below 6.0% and %accuracy falling between 98.9% and 102.4 percent, intra- and inter-batch precision (%CV) showed impressive stability. Both Abemaciclib and Abemaciclib-D10 showed a total recovery rate of more than 90%. The method's fitness for the specified study is confirmed by its selectivity,

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sensitivity, precision, and accuracy taken together. In conclusion, this study's methodology is praiseworthy for its excellent selectivity, accuracy, precision, and stability. It is also simple and quick to use. The process is attractive for high-throughput bioanalysis of Abemaciclib due to its simplicity and quick protein precipitation extraction, which takes only 4.0 minutes per sample.

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Conflict of Interest

The authors certify that they have no competing interests.

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