Received: 10 November 2019 | Revised: 11 February 2020 | Accepted: 25 February 2020

DOI: 10.1002/bmc.4816

RESEARCH ARTICLE

Biomedical Chromatography WILEY

LC–MS/MS determination of buparlisib, a phosphoinositide 3 kinase inhibitor in rat plasma: Application to a pharmacokinetic study

Jingyun Wang[1] | Meng Ming[2] | Lin Yu[1] | Guangliang Chen[3] | Nan Hao[3] | Yuqi Meng[4] | Lina Fang[4]

[1]College of Public Health, Shenyang Medical College, Shenyang, China

[2]Office of Academic Affairs, Shenyang Medical College, Shenyang, China

[3]College of Basic Medical Science, Shenyang Medical College, Shenyang, China

[4]College of Pharmacy, Shenyang Medical College, Shenyang, China

Correspondence
Lina Fang, College of Pharmacy, Shenyang Medical College, Huanghe North Street 146. Shenyang 110034, China.
Email: linafang1982@163.com

Funding information
General Financial Grant, Grant/Award Number: 2017M621162; Middle-aged and Young Scientific and Technical Talents Innovation Support Project of Shenyang City, Grant/Award Number: RC180303; Natural Science Foundation of Liaoning Provincial, Grant/Award Number: 20180550126

Abstract

Buparlisib is a selective phosphoinositide 3 kinase inhibitor currently evaluated in clinical trials. We developed and validated an LC–MS/MS coupled with a one-step protein precipitation extraction method for the quantitation of buparlisib in rat plasma. After protein precipitation with acetonitrile, the plasma sample was analyzed using a Cortecs UPLC C_{18} column, with acetonitrile–0.1% formic acid as the mobile phase system. Mass spectrometric detection was conducted in positive ionization mode, with target quantitative ion pair of m/z 411.2 → 367.2 for buparlisib. The calibration curve showed good linearity (1.0–3000 ng/ml), with acceptable accuracy (RE ranging from −6.2 to 5.9%) and precision (RSD within 8.2%) values at quality control concentrations. Extraction recovery from plasma was 80.9–88.7% and the matrix effect was negligible (92.6–95.2%). The validated method presented a simple quantification method of buparlisib in detail and utilized it for a pharmacokinetic study at three dose concentrations after oral administration in Wistar rats.

KEYWORDS

buparlisib, LC–MS/MS, pharmacokinetics, phosphoinositide 3 kinase

1 | INTRODUCTION

The activation of the phosphoinositide 3 kinase (PI3K) pathway promotes oncogenesis, cancer cell growth and survival (Engelman, Luo, & Cantley, 2006; Thorpe, Yuzugullu, & Zhao, 2015). The crucial role of PI3K in this signaling makes it an attractive antitumor target, especially in tumors harboring an overactivated PI3K pathway (Engelman, 2009; Niessner et al., 2016). Buparlisib (BKM120, Figure 1) is a selective, orally bioavailable pan-PI3K inhibitor that has been developed to inhibit all class I PI3K isoforms and shows preclinical efficacy in various PI3K pathway overactivated cancer models (Koul, Fu, Shen, Lafortune, & Yung, 2012; Maira et al., 2012; Ni et al., 2011; Tran et al., 2018). More than 60 clinical trials have been completed or are ongoing to comprehensively assess the therapeutic effects of buparlisib alone or in combination with other anticancer agents in patients with different types of cancer. A phase II clinical trial (NCT01852292) that enrolled 158 patients with recurrent or metastatic squamous cell carcinoma pretreated with platinum showed that, compared with paclitaxel, the combination of buparlisib and paclitaxel achieved an improved median progression-free survival with a controllable safety profile (Soulières et al., 2017). The positive outcomes of another two phase III clinical trials (NCT01610284, NCT01633060) proved the efficacy of buparlisib plus endocrine therapy in patients with advanced breast cancer, as well as patients with advanced breast cancer progressing on or after mTOR inhibition (Baselga et al., 2017; Di Leo et al., 2018).

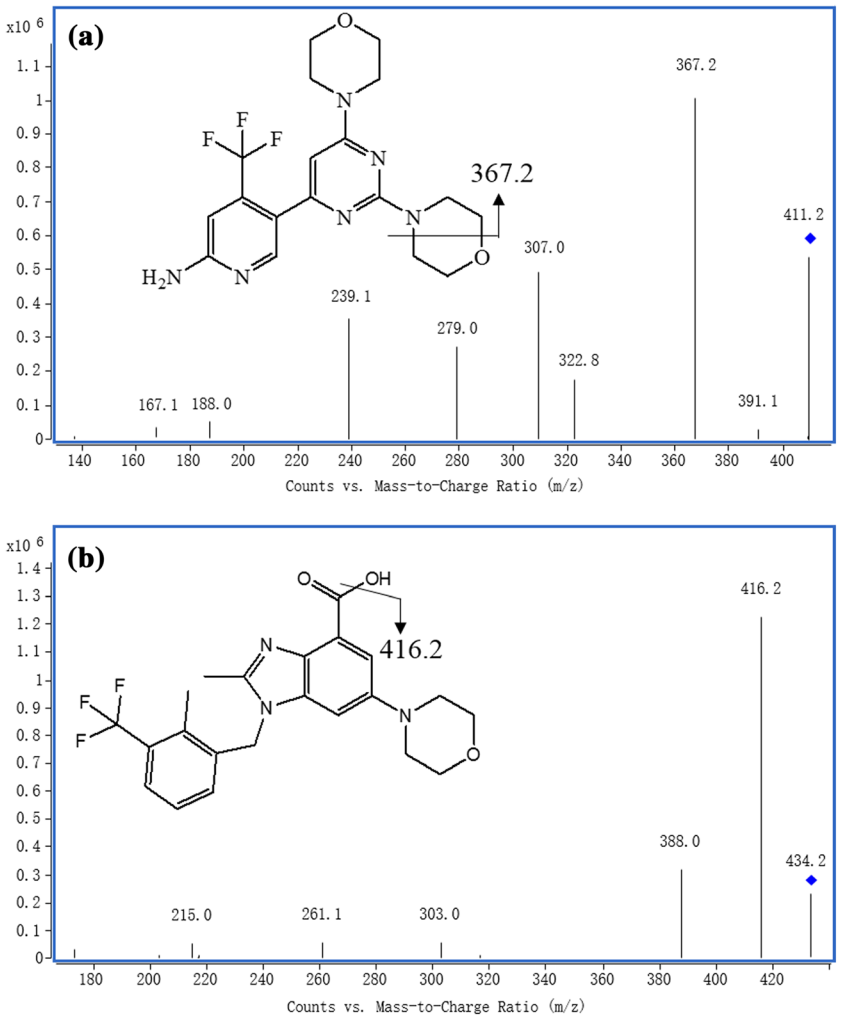

FIGURE 1 Chemical structures and MS^2 scan mass spectra of buparlisib (a) and IS (b)

Although buparlisib has been evaluated in numerous clinical trials, there is only one analytical method, a laser diode thermal desorption ion source (LDTD)–Atmospheric-Pressure Chemical Ionization (APCI)–MS/MS method, reported in detail for the determination of buparlisib in biological samples (Lanshoeft et al., 2014). Compared with the widespread use of the LC–MS/MS method (Fang et al., 2019; Wang et al., 2019), extensive application of LDTD is restricted owing to lack of access to the equipment. Another phase I study in subjects with hepatic impairment briefly described an LC–MS/MS method for the determination of buparlisib (Csonka et al., 2016), using stable labeled buparlisib as the internal standard. Although a stable isotope-labeled internal standard (IS) is the gold standard in developing bioanalytical methods using LC–MS, stable labeled buparlisib is not commercially available so far. In this work, we provide a simple and reliable LC–MS/MS method for the quantification of buparlisib in rat plasma and demonstrate its suitability for a pharmacokinetic study in rats. The method we have established is based on the use of a common instrument and employs a commercially available compound as the IS. It was fully validated with regard to linearity, accuracy, precision, extraction recovery, matrix effect and stability, making the present method a valuable reference for future works.

2 | EXPERIMENTAL

2.1 | Materials and reagents

Buparlisib (purity >98.5%) as well as GSK2636771 (purity >99.0%, internal standard) were provided by Shanghai Azbiochem Biotechnology Co. Ltd (Shanghai, China). All other reagents such as acetonitrile and methanol were of HPLC grade and obtained from Fisher Scientific (Fair Lawn, NJ, USA). Pure water was used in the experiment.

2.2 | Instruments and LC–MS/MS conditions

An Agilent 1290 Infinity system (Agilent Technologies, Singapore) equipped with an autosampler was employed for sample separation with a Cortecs UPLC C_{18} column (2.1 × 100 mm, 1.6 μm, Waters, USA). The column temperature was set at 35°C and prepared samples were maintained at 4°C in the autosampler. The mobile phase included phase A, acetonitrile, and phase B, 0.1% formic acid in water at a gradient flow rate of 0.30 ml/min, as follows: 0–3.0 min, 10–80% B; 3.01–3.5 min, 80% B; 3.51–5.5 min, 10% B.

An Agilent Technologies 6460-triple quadrupole mass spectrometer (Agilent Technologies, Singapore) with a Jetstream electrospray source was used as the detector. The detection was performed via positive-mode ionization under multiple reaction monitoring modes with target quantitative ion pairs for buparlisib and IS of *m/z* 411.2 → 367.2 and 434.2 → 416.2, respectively (Figure 1). The settings of the other optimal parameters were as follows: gas temperature, 325°C; gas flow, 7 L/min; nebulizer, 35 psi; sheath gas heater, 350 units; and sheath gas flow, 11 units.

2.3 | Standard solution and quality control samples

Both of the stock solutions of buparlisib and the IS were separately prepared by dissolving the compounds in methanol at a final concentration of 1.0 mg/ml. The solution of buparlisib was serially diluted to obtain standard working solutions (10, 50, 200, 1000, 5000, 15,000 and 30,000 ng/ml) and quality control (QC) solutions (25, 2000 and 20,000 ng/ml) in methanol.

The analytical calibration standard samples (1.0, 5.0, 20, 100, 500, 1500 and 3000 ng/ml) were prepared by spiking 10 μl of standard working solutions into 100 μl blank rat plasma during the validation process. QC samples at low, medium and high concentrations (2.5, 200 and 2000 ng/ml) were produced independently in the same way. The working solution of the IS was prepared in methanol to obtain a final concentration of 400 ng/ml.

2.4 | Sample preparation

Plasma samples of 100 μl were spiked with 50 μl of the IS solution and mixed for 30 s. After adding 600 μl of acetonitrile, samples were mixed for 1 min and then centrifuged for 10 min at 5000 rpm. The supernatant (1 μl) was used for analysis after filtering.

2.5 | Method validation

To study whether there were endogenous matrix constituents or potential interferences, six different batches of drug-free plasma and spiked samples at the lower limit of quantitation (LLOQ) were produced and analyzed according to the US Food and Drug Administration guidelines (Department of Health and Human Services, US Food and Drug Administration, 2018). The linearity of the calibration curve was measured in triplicate to establish the calibration range. The correlation coefficient (*r*) should be at least 0.99, with the acceptable accuracy of the LLOQ less than ±20%. Six QC sample replicates at three concentration levels were assessed on three separate occasions to evaluate accuracy and precision. A mean accuracy (RE, %) of ±15% was accepted, and the precision (RSD) had to be <15%. The extraction recovery and matrix effect of buparlisib were assessed in samples of six different subjects at three QC levels as described in the guidelines. The experiment for assessing the dilution integrity of the method was conducted as follows. A spiked plasma sample with a concentration of 6000 ng/ml (twice the ULOQ) was prepared by adding a standard solution in blank plasma, then diluted 2-fold with blank plasma to achieve a final concentration within the linear range. The stability of buparlisib was evaluated as follows: 30 days at −20°C, after three freeze–thaw cycles, 12 h at room temperature and samples after preparation at 4°C for 12 h. The acceptable criteria of the stability had to be within ±15%, with precision <15%.

2.6 | Pharmacokinetic application

Male specific pathogen-free-grade Wistar rats (220–245 g) were provided by Liaoning Changsheng Biotechnology Co. Ltd, and fed in an environmentally controlled room. After acclimatization, 18 rats were randomly divided into three groups and given different dosages of oral treatments (buparlisib was dissolved in DMSO, and suspended with 0.5% CMC-Na; dosages were 10, 20 and 40 mg/kg, respectively). Blood from the suborbital vein (~0.4 ml) was collected at the intervals 0, 0.17, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12 and 24 h, and then centrifuged and separated immediately before storage.

The plasma concentrations of buparlisib are presented as mean ± SD. The time to peak concentration (T_{max}) is expressed as median (minimum, maximum), which are the measured values. Pharmacokinetic parameters including peak concentration (C_{max}), T_{max}, half-life ($t_{1/2}$), clearance (*CL/F*), *Apparent Volume of Distribution* (V_z/F), area under the concentration–time curve (AUC) and Area Under the Moment Curve (AUMC) were calculated using a noncompartmental model with Phoenix WinNonlin software (version 8.0).

All statistical analyses were performed with SPSS software 19.0. The statistical differences between pharmaceutical parameters were analyzed as follows: T_{max} and $t_{1/2}$ were calculated with the Kruskal–Wallis test and *CL/F* and V_z/F were calculated by one-way analysis of variance, with $p < 0.05$ considered statistically significant. Dose proportionality was assessed with Phoenix WinNonlin software (version 8.0) using the power model as follows (Smith et al., 2000): ln (*Y*) = β_0 + β_1*ln (dose), where *Y* is C_{max} or AUC, β_0 is the intercept and β_1 is the slope of the equation as dose-proportionality coefficient. Dose proportionality was concluded if the 90% confidence intervals (CIs) for β_1 fell completely within the acceptance criterion of 0.839–1.161.

3 | RESULTS AND DISCUSSION

3.1 | Method optimization

Both positive and negative modes were investigated, and positive ionization mode was selected because buparlisib could hardly be

detected (Q1) in negative ionization mode. Other parameters including ion transition, fragmentor voltage and collision energy (fragmentor voltage 220 V for buparlisib, 155 V for the IS; collision energy 40 V for buparlisib, 24 V for the IS) were optimized using automatic optimizer process.

GSK2636771 was chosen as the IS because its molecular mass is similar to that of buparlisib and it has the same or similar chemical structure units as buparlisib. Moreover, the two compounds exhibited similar chromatographical behavior and approximate extraction recovery.

In the reference method, 100 μl of plasma was mixed with 200 μl of acetonitrile containing the IS and then extracted with 100 μl of saturated sodium chloride solution (salting-out assisted liquid–liquid extraction). After mixing and centrifugation, the supernatant was transferred onto a 96-well plate and allowed to dry at room temperature prior to the LDTD–APCI–MS/MS analysis (Lanshoeft et al., 2014). This sample preparation involved many steps and was rather complicated, so we developed a one-step protein precipitation extraction method to pretreat the plasma sample prior to analysis. Acetonitrile and methanol were tested as the protein precipitation solvents. The recoveries with both of the solvents were >80%. Compared with methanol, acetonitrile achieved a smoother baseline which resulted in a higher signal-to-noise ratio of baseline and better sensitivity.

3.2 | Method validation

3.2.1 | Selectivity

The chromatographic retention times were 2.09 and 2.53 min for buparlisib and the IS, respectively. There was no significant co-elution interference detected at the same time, which proved the good selectivity of the method. Representative chromatograms of blank plasma sample, spiked sample with buparlisib at the LLOQ and the IS and rat plasma sample 0.5 h after administration of buparlisib are presented in Figure 2.

By adding 1.0% formic acid to the needle wash solvent (80% acetonitrile), the carryover of the ULOQ for the analyte was <6.8% of the LLOQ and <2.3% for the IS.

3.3 | Calibration curve and LLOQ

The correlation coefficients of the calibration curves were ≥0.9936 with a representative linear regression equation of $y = 0.0049x + 0.00422$ for buparlisib. The method was suitable for analysis buparlisib in rat plasma over the range of 1–3000 ng/ml, which is more sensitive and with a wider concentration range than the existing methods [calibration curve ranged from 5 to 2000 ng/ml, with an

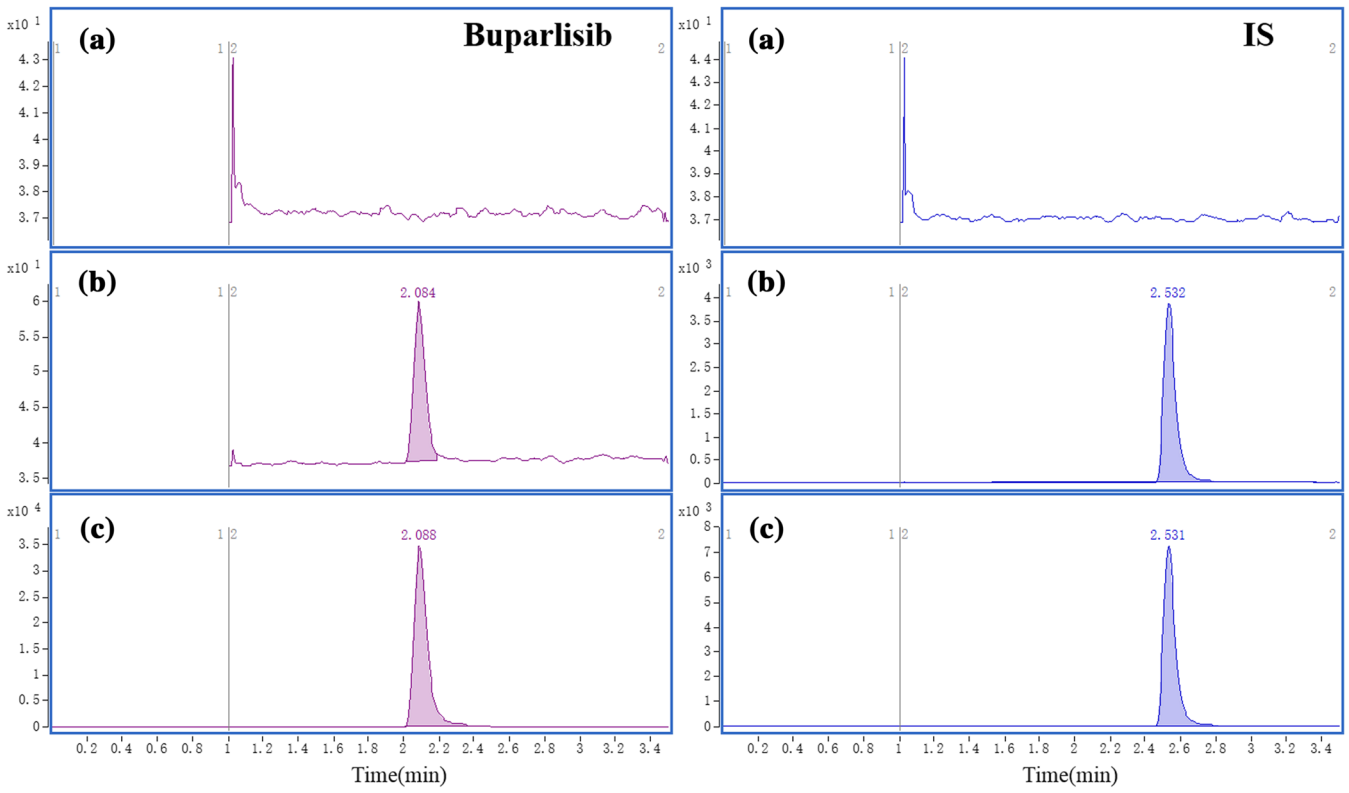

FIGURE 2 Representative chromatograms of: (a) blank rat plasma; (b) blank rat plasma spiked with buparlisib (LLOQ) and IS; and (c) rat plasma obtained 0.5 h after administration

TABLE 1 Precision, accuracy, matrix effect and recovery for analysis of buparlisib in rat plasma (n = 6)

Compound	Spiked concentration (ng/ml)	Intra-day		Inter-day		Matrix effect	Recovery
		RSD (%)	RE (%)	RSD (%)	RE (%)	(%, mean ± SD)	(%, mean ± SD)
Buparlisib	1.0	6.5	−7.9	13.9	−14.4	—	—
	2.5	8.2	−4.3	7.1	−6.2	92.6 ± 7.3	86.2 ± 6.7
	200	7.7	−5.8	6.8	5.9	95.2 ± 6.9	88.7 ± 7.9
	2000	6.1	3.6	6.3	4.0	94.1 ± 5.7	80.9 ± 5.8
IS	400	—	—	—	—	91.3 ± 6.4	89.7 ± 7.5

LLOQ of 5 ng/ml for reference (Lanshoeft et al., 2014), and from 1 to 1000 ng/ml, with an LLOQ of 1 ng/ml for reference (Csonka et al., 2016)].

3.4 | Accuracy, precision and dilution integrity

Data on accuracy and precision of the method are listed in Table 1. The range of QC sample-based accuracy was from −6.2 to 5.9%, and the intra- and inter-day precisions were ≤8.2%. Meanwhile, the precision and accuracy of LLOQ were all within ±14.4%. The results all met the acceptance criteria, which demonstrated the accuracy and reliability of the developed method. Diluted samples with six replicates were measured after diluting the concentration of 6000 ng/ml to 3000 ng/ml (2-fold), and the accuracy was 95.8 ± 7.3%.

3.5 | Recovery and matrix effect

The extraction recoveries of buparlisib were all >80.9% at LLOQ and three QC levels. No significant matrix effects were found in the test samples. Meanwhile, recovery of IS was 89.7 ± 7.5% with a matrix effect calculated as 91.3 ± 6.4%. In a word, the results of the recovery and matrix effect of the assay were all within the acceptance criteria (Table 1).

3.6 | Stability

The assessment of stability of the QC samples was conducted under four different circumstances. The results demonstrated good stability at −20°C for 30 days, after three freeze–thaw cycles, 12 h at room temperature and at 4°C in the autosampler for 12 h after preparation (Table 2).

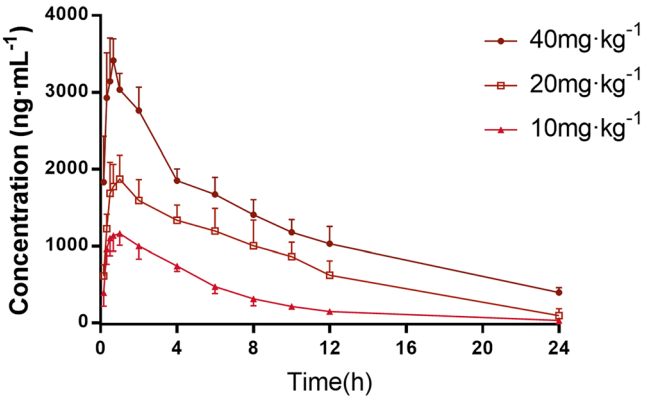

FIGURE 3 Mean plasma concentration–time profiles of buparlisib after oral administration at doses of 10, 20 and 40 mg/kg in rats (n = 6)

3.7 | Pharmacokinetic application

A pharmacokinetic study of buparlisib was carried out to prove the applicability of the established LC–MS/MS method. A single 10, 20 or 40 mg/kg dosage of buparlisib was administered to adult male Wistar rats. The mean plasma concentration–time curves are presented in Figure 3, and the main pharmacokinetic parameters are summarized in Table 3.

As shown in Table 3, C_{max} was detected as 1.19 ± 0.15, 1.92 ± 0.34 and 3.45 ± 0.26 μg/ml, and $AUC_{0\rightarrow\infty}$ was calculated as 7.84 ± 0.98, 19.27 ± 2.84 and 34.52 ± 3.42 h·μg/ml at dosages of 10, 20 and 40 mg/kg, respectively.

No statistically differences in the pharmacokinetic parameters of T_{max} and CL/F of buparlisib were observed between groups at different doses. However, there were statistically significant differences in the other parameters between low-, medium- and high-dose groups. Compared with the low-dose group, the $t_{1/2}$ of the high-dose group showed a significant difference ($p < 0.05$). In addition, the V_z/F of the

TABLE 2 Stability of buparlisib in rat plasma (n = 3)

Spiked (ng/ml)	Room temperature for 12 h		Frozen for 30 days		Three freeze–thaw cycles		4°C in autosampler for 12 h	
	RE (%)	RSD (%)	RE (%)	RSD (%)	RE (%)	RSD (%)	RE (%)	RSD (%)
2.5	−1.8	7.7	−2.9	7.0	−2.1	9.2	−0.9	9.5
200	4.7	5.6	7.3	6.2	5.5	6.3	7.2	6.3
2000	4.6	5.3	6.8	5.4	5.9	5.6	5.8	4.8

TABLE 3 Pharmacokinetic parameters of buparlisib with noncompartmental method (n = 6)

Parameters	Expressed as	Units	10 mg/kg	20 mg/kg	40 mg/kg
C_{max}	Mean ± SD	mg/ml	1.19 ± 0.15	1.92 ± 0.34	3.45 ± 0.26
T_{max}	Median (Min, Max)	h	0.67 (0.5, 1)	0.83 (0.5, 1)	0.67 (0.5, 0.67)
$t_{1/2}$	Mean ± SD	h	3.05 ± 0.97	4.64 ± 2.51	7.59 ± 1.53*
$AUC_{0\rightarrow 24h}$[a]	Mean ± SD	h·μg/ml	7.68 ± 0.86	18.38 ± 3.22	30.14 ± 2.34
$AUC_{0\rightarrow \infty}$[a]	Mean ± SD	h·μg/ml	7.84 ± 0.98	19.27 ± 2.84	34.52 ± 3.42
V_z/F	Mean ± SD	L	5.57 ± 1.55	7.04 ± 3.98	12.64 ± 1.92**/#
CL/F	Mean ± SD	L/h	1.29 ± 0.16	1.06 ± 0.15	1.17 ± 0.11
$AUMC_{0\rightarrow 24h}$	Mean ± SD	h^2·μg/ml	41.96 ± 7.35	130.6 ± 26.0	235.7 ± 29.1
$AUMC_{0\rightarrow \infty}$	Mean ± SD	h^2·μg/ml	46.49 ± 13.02	161.4 ± 52.1	391.0 ± 81.8

*p < 0.05,
**p < 0.01, compared with the low-dose group
#p < 0.05, compared with the medium dose group
[a]Parameters showed a dose-dependent relationship at different doses.
AUMC, Area under the moment curve; C_{max}, peak concentration; T_{max}, time to peak concentration; $t_{1/2}$m half-life; AUC, area under concentration–time curve; CL/F, clearance; Vz/F, apparent volume of distribution.

high-dose group showed remarkable differences compared with both the low- and medium-dose groups (p < 0.01 vs. low-dose group, p < 0.05 vs. medium-dose group). Buparlisib is a lipophilic drug and easily distributed in fat-rich tissue and organs after administration, which explains the significant differences of V_z/F and $t_{1/2}$ of the high-dose groups compared with the other groups.

The slopes (90% CIs) were 0.772 (0.681, 0.864) for C_{max}, 0.988 (0.885, 1.090) for $AUC_{0\rightarrow 24h}$ and 0.987 (0.863, 1.112) for $AUC_{0\rightarrow \infty}$. The 90% CIs of $AUC_{0\rightarrow 24h}$ and $AUC_{0\rightarrow \infty}$ were within the acceptance interval (0.839, 1.161), whereas the value for C_{max} was inconclusive. Therefore, the $AUC_{0\rightarrow -24h}$, and $AUC_{0\rightarrow \infty}$ of buparlisib were observed to increase in a dose-proportional manner, but the dose proportionality of the C_{max} of buparlisib was not conclusively linear over the dose range tested (10–40 mg/kg).

4 | CONCLUSIONS

A robust, simple and reliable LC–MS/MS method has been developed and fully validated for the determination of buparlisib in rat plasma and has been utilized for a pharmacokinetic study after oral administration at three dose levels in rats. The method is based on a commonly available instrument and uses a commercially available IS, which makes it valuable as a reference in future works.

ACKNOWLEDGEMENTS

The present work was financially supported by Postdoctoral Science Foundation of China (2017 M621162), Natural Science Foundation of Liaoning Provincial (20180550126) and Middle-aged and Young Scientific and Technical Talents Innovation Support Project of Shenyang City (RC180303).

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ORCID

Lina Fang https://orcid.org/0000-0003-1462-5055

REFERENCES

Baselga, J., Im, S. A., Iwata, H., Cortés, J., De Laurentiis, M., Jiang, Z., & Campone, M. (2017). Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*, *18*(7), 904–916. http://doi.org/10.1016/s1470-2045(17)30376-5

Csonka, D., Hazell, K., Waldron, E., Lorenzo, S., Duval, V., Trandafir, L., & Kobalava, Z. D. (2016). A phase-1, open-label, single-dose study of the pharmacokinetics of buparlisib in subjects with mild to severe hepatic impairment. *The Journal of Clinical Pharmacology*, *56*(3), 316–323. http://doi.org/10.1002/jcph.590

Department of Health and Human Services, US Food and Drug Administration. (2018) Guidance for Industry—Bioanalytical Method Validation. https://www.fda.gov/media/70858/download

Di Leo, A., Johnston, S., Lee, K. S., Ciruelos, E., Lønning, P. E., Janni, W., & Bachelot, T. (2018). Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*, *19*(1), 87–100. http://doi.org/10.1016/s1470-2045(17)30688-5

Engelman, J. A. (2009). Targeting PI3K signalling in cancer: Opportunities, challenges and limitations. *Nature Reviews Cancer*, *9*(8), 550–562. https://doi.org/10.1038/nrc2664

Engelman, J. A., Luo, J., & Cantley, L. C. (2006). The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nature Reviews Genetics*, *7*(8), 606–619. https://doi.org/10.1038/nrg1879

Fang, L. N., Mao, M. Q., Zhao, X. H., Yang, L., Jia, H., & Xia, S. Y. (2019). Development and validation of a UPLC-MS/MS method for quantification of doxofylline and its metabolites in human plasma. *Journal of Pharmaceutical and Biomedical Analysis*, *174*, 220–225. http://doi.org/10.1016/j.jpba.2019.05.039

Koul, D., Fu, J., Shen, R., Lafortune, T. A., & Yung, W. K. A. (2012). Antitumor activity of NVP-BKM120-A selective pan Class I PI3 kinase inhibitor showed differential forms of cell death based on p53 status

of glioma cells. *Clinical Cancer Research*, *18*(1), 184–195. https://doi.org/10.1158/1078-0432.CCR-11-1558

Lanshoeft, C., Heudi, O., Leuthold, L. A., Schlotterbeck, G., Elbast, W., Picard, F., & Kretz, O. (2014). Laser diode thermal desorption atmospheric pressure chemical ionization tandem mass spectrometry applied for the ultra-fast quantitative analysis of BKM120 in human plasma. *Analytical and Bioanalytical Chemistry*, *406*(22), 5413–5423. http://doi.org/10.1007/s00216-014-7966-6

Maira, S. M., Pecchi, S., Huang, A., Burger, M., Knapp, M., Sterker, D., & Wiesmann, M. (2012). Identification and characterization of NVP-BKM120, an orally available pan-class I PI3-kinase inhibitor. *Molecular Cancer Therapeutics*, *11*(2), 317–328. https://doi.org/10.1158/1535-7163.MCT-11-0474

Ni, Z. J., Knapp, M., Hendrickson, T., Atallah, G., Pfister, K., Zhang, Y., & Wagman, A. (2011). Identification of NVP-BKM120 as a potent, selective, orally bioavailable class I PI3 kinase inhibitor for treating cancer. *ACS Medicinal Chemistry Letters*, *2*(10), 774–779. https://doi.org/10.1021/ml200156t

Niessner, H., Schmitz, J., Tabatabai, G., Schmid, A., Calaminus, C., Sinnberg, T., & Schittek, B. (2016). PI3K pathway inhibition achieves potent antitumor activity in melanoma brain metastases *in vitro* and *in vivo*. *Clinical Cancer Reserch*, *22*(23), 5818–5828. https://doi.org/10.1158/1078-0432.CCR-16-0064

Smith, B. P., Vandenhende, F. R., DeSante, K. A., Farid, N. A., Welch, P. A., Callaghan, J. T., & Forgue, S. T. (2000). Confidence interval criteria for assessment of dose proportionality. *Pharmaceutical Research*, *17*(10), 1278–1283. https://doi.org/10.1023/a:1026451721686

Soulières, D., Faivre, S., Mesía, R., Remenár, É., Li, S. H., Karpenko, A., … Nagarkar, R. (2017). Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): A randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet Oncology*, *18*(3), 323–335. http://doi.org/10.1016/S1470-2045(17)30064-5

Thorpe, L. M., Yuzugullu, H., & Zhao, J. J. (2015). PI3K in cancer: Divergent roles of isoforms, modes of activation and therapeutic targeting. *Nature Reviews Cancer*, *15*(1), 7–24. https://doi.org/10.1038/nrc3860

Tran, D. C., Moffat, A., Brotherton, R., Pague, A., Zhu, G. A., & Chang, A. L. S. (2018). An exploratory open-label, investigator-initiated study to evaluate the efficacy and safety of combination sonidegib and buparlisib for advanced basal cell carcinomas. *Journal of the American Academy of Dermatology*, *78*(5), 1011–1013 e1013. https://doi.org/10.1016/j.jaad.2017.11.031

Wang, J., Yao, W., Fan, D., Qiu, Z., Song, J., Pan, K., & Hang, T. (2019). An LC-MS/MS method for quantification of HR011303, a novel highly selective urate transporter 1 inhibitor in beagle dogs and the application to a pharmacokinetic study. *Biomedical Chromatography*, *33*(10), e4604. http://doi.org/10.1002/bmc.4604

How to cite this article: Wang J, Ming M, Yu L, et al. LC–MS/MS determination of buparlisib, a phosphoinositide 3 kinase inhibitor in rat plasma: Application to a pharmacokinetic study. *Biomedical Chromatography*. 2020;34:e4816. https://doi.org/10.1002/bmc.4816