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Research Article

Bioanalysis of bedaquiline in human plasma by liquid chromatography-tandem mass spectrometry: Application to pharmacokinetic study

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ABSTRACT

Introduction: A sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed for estimation of bedaquiline (BDQ) in human plasma using the deuterated analogue of the analyte, bedaquiline-d6 (BDQ-d6) as the internal standard.

Methods: The plasma sample of 50 μL was extracted by liquid–liquid extraction using methyl tertiary butyl ether (MTBE). The separation was achieved on Zodiac C_{18} (50 x 4.6 mm, 5 μm) column with a mobile phase consisting of methanol and 5 mM ammonium formate in 0.1 % formic acid (w/v) (90:10, v/v) at a flow rate of 1.0 mL/min. Protonated analyte and internal standard were detected on a triple quadrupole mass spectrometer using multiple reaction monitoring (MRM) mode.

Results: The linearity of the method was established in the concentration range of 5—–1800 ng/mL with correlation coefficient, $r^2 \geq 0.99$. All the validated parameters were found well within the limits.

Discussion: The method was applied for the first time to evaluate the pharmacokinetic parameters after single oral dose of BDQ 100 mg under fed conditions in healthy human volunteers, and the results were further authenticated by incurred sample reanalysis.

1. Introduction

Bedaquiline (BDQ), formerly known as TMC 207, is a diarylquinoline derivative used for the treatment of multidrug-resistant tuberculosis (MDR-TB) [1–3]. It exhibits anti-tubercular activity by inhibiting the proton pump of ATP synthase, which is an enzyme crucial for the synthesis of ATP in *Mycobacterium tuberculosis* [4–6]. When administered orally, it undergoes oxidative metabolism through Cytochrome P450 enzymes, resulting in a metabolite that is five times less active [7,8].

According to the available literature, several bioanalytical methods have been reported for the quantification of BDQ as a single analyte [9–13], as well as in combination with metabolites or other drugs [14–19], in various biological samples such as rat plasma [9,12], dog plasma [10], human serum [16], human hair [11], and human plasma [13–15,17–19], using LC-MS/MS. Additionally, an HPLC method was reported for the estimation of BDQ along with Delamanid in human plasma, with a total run time of 7 min [20]. It should be noted that the analysis of BDQ in biological samples from animals is only suitable for preclinical studies. Some of the methods reported by Hui ZHU *et al.* [13] and Svensson EM *et al.* [14] have low sensitivity in the concentration range of 100 – 5000 ng/mL and 10 – 5000 ng/mL, respectively. The reported method of Gray WA *et al.* [19] has a longer run time of 15.57

Abbreviations: AUC, area under the curve; BDQ, bedaquiline; BDQ-d6, bedaquiline-d6; CAD, collision activation dissociation; CC, calibration curve; C_{max}, peak plasma concentration; CV, coefficient of variation; DMSO, dimethylsulfoxide; HQC, high-quality control; ISR, incurred sample reanalysis; Kel, elimination rate constant; K_2-EDTA, dipotassium ethylenediamine tetraacetic acid; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLE, liquid-liquid extraction; LLOQ QC, lower limit of quantitation quality control; LQC, low-quality control; MDR-TB, multidrug-resistant tuberculosis; MQC, medium-quality control; MRM, multiple reaction monitoring; MTBE, methyl tertiary butyl ether; QC, quality control; RSD, relative standard deviation; SD, standard deviation; S/N, signal-to-noise ratio; t_{max}, time to peak plasma concentration; TMC, Tibotec medicinal compound; $t_{1/2}$, half-life; USFDA, United States Food and Drug Administration.

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min and low sensitivity with the concentration range of 20 – 6600 ng/mL. Moreover, the method proposed by Rustomjee R *et al.* [18] utilizes the protein precipitation technique for analyte extraction, which may lead to the accumulation of phospholipids on the chromatographic column, causing unpredictable elution behavior in subsequent analyses [21]. It is worth mentioning that none of the reported methods performed incurred sample reanalysis to prove their ruggedness.

Thus, it is imperative to develop a rapid, highly sensitive, and selective bioanalytical assay method to fulfill the requirements of pharmacokinetic, bioavailability, and bioequivalence studies following an oral dose of 100 mg of BDQ. The current method offers high sensitivity (5 ng/mL) with a short run time of 2 min, utilizing a 50 μL plasma sample that is extracted by a liquid–liquid extraction (LLE) technique. This method was successfully applied to a pharmacokinetic study involving healthy male subjects from South India. Additionally, the method's ruggedness was validated through incurred sample reanalysis (ISR).

2. Experimental

2.1. Chemicals and materials

Reference standards of BDQ and bedaquiline-d6 (BDQ-D6) were purchased from Vivan Life Sciences Pvt. Ltd. (Mumbai, India) and Simson Pharma Ltd (Mumbai, India), respectively. HPLC -grade water and analytical grade dimethylsulfoxide (DMSO) were supplied by Rankem (Gurugram, India). HPLC -grade methanol and methyl tertiary butyl ether (MTBE) were procured from RCI Labscan Ltd. (Bangkok, Thailand). Analytical-grade formic acid and ammonium formate were obtained from Merck Ltd (Mumbai, India). The control K_2-EDTA human plasma was procured from Deccan's Pathological Labs (Hyderabad, India).

2.2. Instruments and conditions

Quantitative analysis of BDQ in human plasma was conducted using a liquid chromatography (LC) system (Shimadzu, Kyoto, Japan) consisting of a binary LC-20AD prominence pump, an auto-sampler (SIL-HTC), and an online degasser (DGU-20A_3), coupled to a triple quadrupole mass spectrometer AB Sciex API 5500 (Foster City, CA, USA) equipped with Turbo Ion Spray™. Separation of the analyte and BDQ-D6 was performed on a Zodiac C_{18} (50 x 4.6 mm, 5 μm) column under isocratic conditions using a mobile phase composed of methanol and 5 mM ammonium formate in 0.1 % formic acid (w/v) (90:10, v/v), delivered at a flow rate of 1.0 mL/min. Eluents were detected in positive ion and multiple reaction monitoring (MRM) mode to monitor the transition from precursor ion to product ion, with *m/z* 556.10 to 58.10 and 562.20 to 64.40 for BDQ and BDQ-D6, respectively. System control and data acquisition were performed using Analyst Software Version 1.7.2.

The source-dependent parameters maintained for BDQ and BDQ-D6 were as follows: Gas 1 (nebulizer gas) at 30 psi, Gas 2 (heater gas) at 35 psi, ion spray voltage set to 5500 V, turbo heater temperature at 550 °C, entrance potential at 10 V, collision activation dissociation (CAD) at 8 psi, and curtain gas at 40 psi. The compound-dependent parameters, including declustering potential, collision energy, and cell exit potential, were set at 70 V, 70 eV, and 7 V, respectively, for both BDQ and BDQ-D6. Quadrupoles 1 and 3 were maintained at unit resolution, and the dwell time was set at 200 ms.

2.3. Preparation of calibration curve (CC) and quality control (QC) samples

The primary stock solution of BDQ (1000 μg/mL) was prepared in DMSO and then diluted using a mixture of HPLC-grade methanol and water (50:50, v/v; diluent) to obtain the working standard solutions. Similarly, the stock solution of BDQ-D6 (1000 μg/mL) was prepared in DMSO and a working standard solution (500 ng/mL) was prepared by dilution with the diluent.

CC standard solutions were prepared by spiking 950 μL of K_2EDTA human plasma with 50 μL of appropriate working standard solutions at ten non-zero concentrations: 4.99, 9.99, 24.99, 62.49, 152.41, 362.87, 725.74, 1083.19, 1444.25, and 1805.31 ng/mL. Furthermore, QC samples were prepared in a similar manner at concentrations of 4.99 ng/mL (lower limit of quantitation quality control, LLOQ QC), 14.18 ng/mL (low-quality control, LQC), 218.12 ng/mL (medium-quality control, MQC1), 778.99 ng/mL (MQC2), and 1391.06 ng/mL (high-quality control, HQC). All CC standards and QC samples were stored at a temperature of −70 ± 10 °C until analysis.

2.4. Sample extraction procedure

To an aliquot of 50 μL of the spiked plasma sample, 50 μL of BDQ-D6 working standard solution and 100 μL of 5 mM ammonium formate in 0.1 % formic acid (w/v) were added and vortexed. Then, 2 mL of MTBE was added, and the mixture was vortexed again. The sample was then centrifuged for 5 min at 5 °C and 4000 rpm. The resulting supernatant was evaporated to dryness at 40 °C under a stream of nitrogen. The residue was reconstituted with 250 μL of mobile phase, and 15 μL of the solution was injected into the instrument for analysis.

2.5. Method validation

The validation of the developed method was performed as per USFDA guidelines [22] and our previous work [23].

The selectivity of the method was assessed by verifying the interference of the blank plasma sample at the retention times of both the analyte and the internal standard. Sensitivity was evaluated by injecting eighteen sets of LLOQ samples. To determine the matrix factor, the mean area response of post-extraction spiked samples was compared with that of aqueous samples at both the LQC and HQC levels.

In order to perform least square weighted ($1/x^2$) linear regression calculations, three batches of CC standards were injected, which included one blank plasma sample and an additional blank plasma sample spiked with the internal standard each time. Intra-day precision and accuracy were assessed by injecting six replicates of each batch of QC samples on the same day. For the evaluation of inter-day precision and accuracy, the third batch of QC samples was analyzed on the second day.

The extraction efficiency of the analyte was determined by comparing the mean detector response of six sets of pre-extraction plasma samples with that of aqueous samples at the LQC, MQC2 and HQC levels. The recovery of the internal standard was assessed at a concentration of 2000 ng/mL.

Benchtop stability was assessed by keeping the plasma samples at room temperature on the workbench for a specified period of time before processing. The final processed and reconstituted plasma samples for wet extract, reinjection and auto-sampler stability study were evaluated by keeping them for different times at different temperatures. Freeze-thaw stability was evaluated by subjecting the frozen plasma samples to a single cycle of thawing at room temperature for 1 h. Short-term and long-term stability were also tested by storing samples at −20 ± 5 °C and −70 ± 10 °C, respectively, for different time periods. To assess the ruggedness of the method, one Precision & Accuracy batch was evaluated using different columns and instruments of the same make, along with different sets of reagents.

2.6. Pharmacokinetic study design

A pharmacokinetic study of BDQ tablets at a dose of 100 mg was conducted in six healthy male subjects of South Indian origin. The study involved oral administration of the tablets under fed conditions. Prior to

enrollment, the volunteers underwent medical, biochemical, and physical examinations. Informed consent was obtained from each participant, and the study protocol was approved by the S2J Independent Ethics Committee in Hyderabad. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Following an overnight fast of 10 h and 30 min after serving breakfast, a single oral dose of BDQ was administered. A total of 21 blood samples were collected into K_2-EDTA vacutainer (5 mL) collection tubes (BD, Franklin, NJ, USA) at various time points: pre-dose (0 h) and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48, and 72 h [24]. The collected samples were centrifuged at 4000 rpm and 4 °C for 10 min, and the resulting plasma samples were stored at −70 ± 10 °C until analysis. Pharmacokinetic parameters were calculated using the non-compartmental model in WinNonlin® Software Version 8.3 (Pharsight Corporation, USA).

An ISR was performed by choosing two samples from each subject, one near the Peak plasma concentration (C_{max}) and the other at the elimination phase of Plasma concentration – Time profile of BDQ.

3. Results and Discussion

3.1. LC-MS/MS method development

Several methods are available to estimate BDQ in various biological matrices. However, the aim of the present work was to develop a rapid and highly sensitive method to meet the requirements of pharmacokinetic studies in healthy humans.

The composition of the mobile phase and the type of column were optimized to achieve satisfactory peak shape and response. The mobile phase, consisting of methanol, water, and formic acid, was selected to enhance the peak response. Additionally, 5 mM ammonium formate was added to obtain tailing-free peaks and good resolution. Different columns, such as C_8 and C_{18}, were tested, and the best conditions were achieved using the Zodiac C_{18} (50 x 4.6 mm, 5 µm) column.

When a tuning solution of 10 ng/mL was infused into the mass spectrometer, the Q1 mass spectra of BDQ and BDQ-D6 showed abundant protonated molecular ions at *m/z* 556.00 and *m/z* 562.20, respectively. Tandem mass spectra yielded highly stable and intense product ions at *m/z* 58.10 and *m/z* 64.20 (Fig. 1), corresponding to the formation of the N,N-dimethylmethyleneiminium ion and its deuterated analogue, respectively, through the fragmentation of the parent ions.

The lipophilic nature of the analyte made it suitable to use a liquid–liquid extraction (LLE) technique for isolating BDQ from plasma samples. The extraction was assessed using ethyl acetate, diethyl ether, and MTBE. A reproducible recovery was obtained with MTBE, which was further improved from 51 % to 74 % by adding 5 mM ammonium formate in 0.1 % formic acid (w/v).

3.2. Selectivity and chromatography

Blank plasma samples and spiked plasma samples containing BDQ-D6 after extraction were evaluated for selectivity. Fig. 2A demonstrates the selectivity of the method, showing no interference from endogenous components at the retention times of the analyte and internal standard. Additionally, there was no interference from the internal standard on the MRM channel of BDQ (Fig. 2B).

3.3. Matrix effect and extraction efficiency

The matrix effect was tested in different sources of human plasma, including lipemic and hemolyzed plasma at two QC levels of LQC and HQC. No significant matrix effect was observed.

The extraction efficiency was evaluated at LQC, MQC-2, and HQC levels in six replicates using the LLE technique, which consistently and reproducibly recovered the analyte and BDQ-D6. The results of the matrix effect and recovery are shown in Table 1.

3.4. Linearity and sensitivity

The calibration curves (n = 3) showed good linearity over the established concentration range of 5 to 1800 ng/mL ($r^2 \geq 0.99$). Linearity was calculated using the least-squares regression with a weighting factor of $1/x^2$. The mean linear equation established was y = 0.0019x − 0.0006. The signal-to-noise ratio (S/N) was found to be ≥ 10, with the LLOQ QC level of the BDQ, demonstrating the method sensitivity (Fig. 2C).

3.5. Precision and accuracy

The intra-day and inter-day precision and accuracy results are shown in Table 2. The precision (%CV) and accuracy were in the range of 0.62 % to 6.06 % and 94.86 % to 104.20 %, respectively.

3.6. Stability and ruggedness

Various stability studies carried out along with the results obtained are shown in Table 3 at LQC and HQC levels.

The ruggedness of the method was shown with accuracy and precision (%CV) in the range of 88.33 % to 103.21 % and 0.99 % to 5.02 %, respectively.

3.7. Pharmacokinetic study and incurred sample reanalysis

The validated method was applied to analyze the plasma samples (Fig. 2D) for the pharmacokinetic study of BDQ 100 mg in healthy male volunteers under fed conditions. However, lack of female subjects is the limitation of the study. The mean plasma concentration–time profile is shown in Fig. 3, and the estimated pharmacokinetic parameters are illustrated in Table 4. The C_{max} and time to peak plasma concentration (t_{max}) were found to be 1159.47 ng/mL and 4.58 h, respectively, which are comparable to 1208 ng/mL and 4.10 h as reported by Rustomjee R *et al.* [18].

The variation between the average area response of BDQ-D6 in accepted CC standards, QC samples, and subject samples was less than 20 %, thus proving insignificant internal standard response variability.

The percent difference in the concentration of BDQ between the

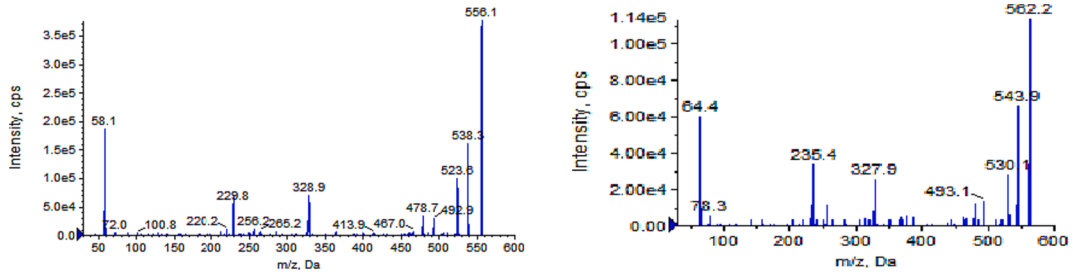

Fig. 1. Product ion mass spectra of BDQ (left panel) and BDQ-D6 (right panel).

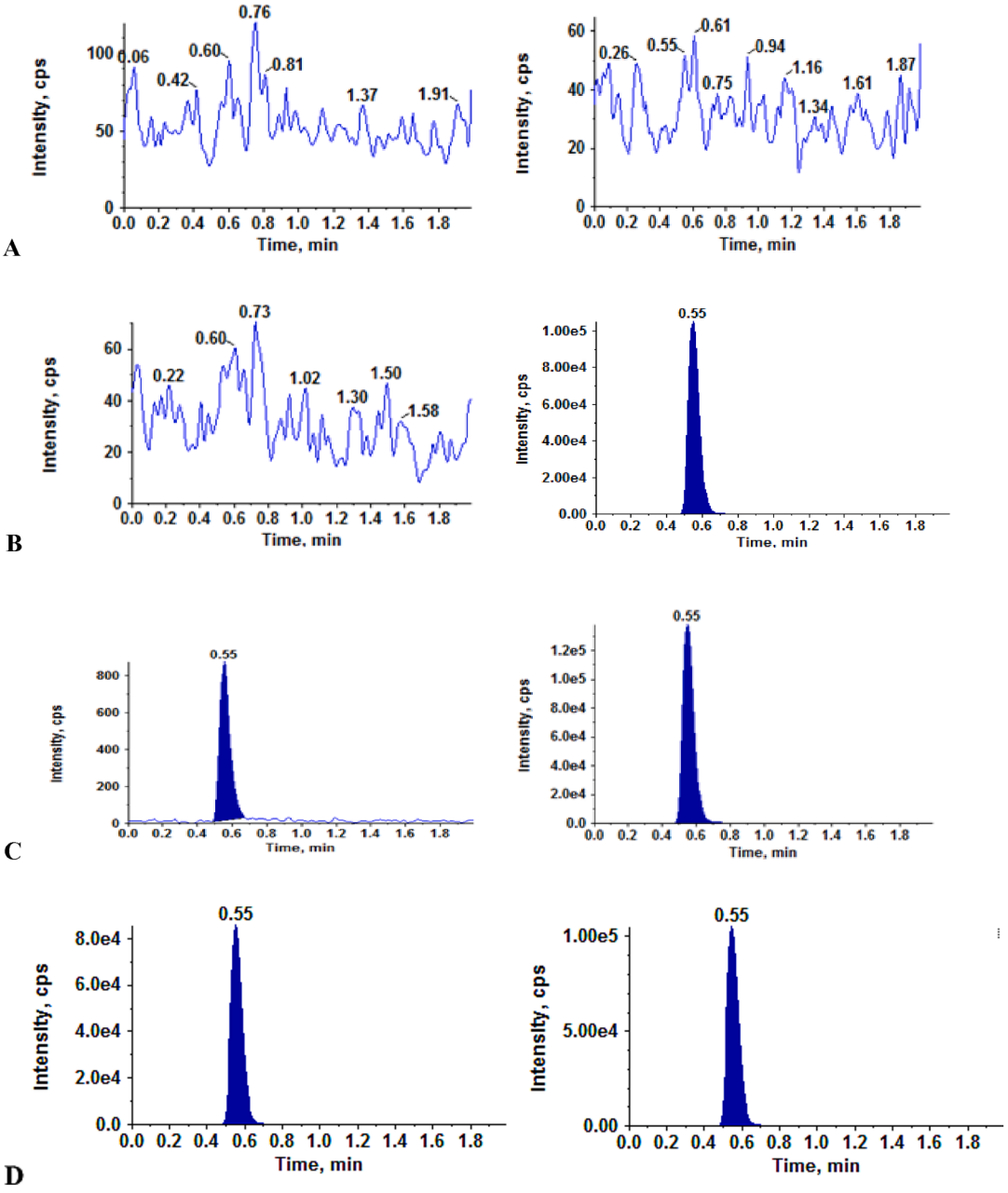

Fig. 2. Typical MRM chromatograms of BDQ (left panel) and BDQ-D6 (right panel) in (A) double blank plasma (without BDQ and BDQ-D6), (B) blank plasma with BDQ-D6, (C) LLOQ QC sample and (D) real subject sample after 6.0 h of administration of 100 mg dose of BDQ.

Table 1
Recovery and matrix effect data.

Analyte/IS	Level	Recovery				Matrix effect
		Mean area response		Recovery (%)	Mean recovery (%)	IS normalized matrix factor
		Extracted QC	Post extracted QC			
BDQ	LQC	$2.40x10^4$	$3.32x10^4$	72.4	74.1	1.02
	MQC2	$1.42x10^6$	$1.79x10^6$	79.0		–
	HQC	$2.45x10^6$	$3.45x10^6$	71.1		1.00
BDQ-D6	–	$8.72x10^5$	$1.13x10^6$	77.4	–	–

initial results of subject samples and the reanalysis results was less than 11 % (Table 5). This evidence supports the ruggedness of the current method.

4. Conclusion

In conclusion, the development of a simple, rapid, and sensitive LC-MS/MS technique for the quantification of BDQ in human plasma is a

Table 2
Intra- and Inter-day accuracy and precision data.

Analyte		Intra-day accuracy and precision (n = 12; 6 from each batch)			Inter-day accuracy and precision (n = 18; 6 from each batch)		
QC	Conc. Spiked (ng/mL)	Conc. Found (mean ± SD; ng/mL)	Accuracy (%)	Precision (% CV)	Conc. Found (mean ± SD; ng/mL)	Accuracy (%)	Precision (% CV)
LLOQ	5.00	5.14 ± 0.31	103	6.06	5.21 ± 0.28	104	5.41
LQC	14.9	14.1 ± 0.49	94.9	3.48	14.1 ± 0.43	95	3.06
MQC1	219	224 ± 2.1	102	0.94	222 ± 5.5	101	2.46
MQC2	782	798 ± 6.1	102	0.76	790 ± 16	101	2.07
HQC	$1.40x10^3$	$1.42x10^3$ ± 8.8	102	0.62	$1.42x10^3$ ± 16	102	1.15

Table 3
Stability data (n = 6).

Stability	Storage condition	Level	Conc.spiked (ng/mL)	Conc. Found(mean; ng/mL)	%Stability	Precision (%CV)
Wet extract stability	Room temperature (69 h)	LQCHQC	14.9 $1.40x10^3$	15.3 $1.47x10^3$	97.899.4	0.980.82
Re-injection stability	65 h at 5 ^{0}C	LQCHQC	14.9 $1.40x10^3$	14.5 $1.45x10^3$	102101	2.611.18
Auto-sampler stability	Auto-sampler temperature (5 ^{0}C, 64 h)	LQCHQC	14.9 $1.40x10^3$	15.3 $1.47x10^3$	97.898.8	4.212.12
Freeze-thaw stability	After 5th cycle at −70 ± 10 ^{0}C	LQCHQC	14.9 $1.40x10^3$	15.3 $1.45x10^3$	97.798.0	1.801.79
Short term stability	77 h at −20 ± 5 ^{0}C	LQCHQC	14.9 $1.40x10^3$	15.6 $1.48x10^3$	100 100	3.971.39
Long term stability	41 days at −70 ± 10 ^{0}C	LQCHQC	14.9 $1.40x10^3$	15.1 $15.1x10^3$	10197.8	1.189.63
Benchtop Stability	Room temperature (13 h)	LQCHQC	14.9 $1.40x10^3$	15.3 $1.46x10^3$	97.998.5	1.76 1.65

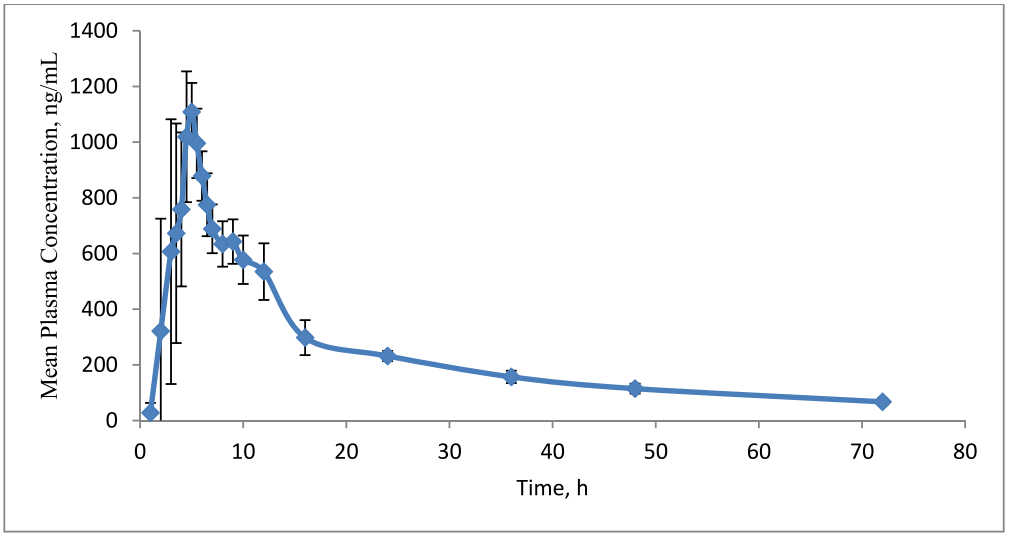

Fig. 3. Mean ± SD plasma concentration–time profile of BDQ after oral administration of 100 mg dose.

Table 4
Pharmacokinetic parameters data (n = 6).

Parameter	Mean ± SD
C_{max} (ng/mL)	$1.16x10^3$ ± $1.2x10^2$
t_{max} (h)	4.58 ± 0.86
$AUC_{0\rightarrow t}$ (ng h/mL)	$1.70x10^4$ ± $2.0x10^3$
$AUC_{0\rightarrow\infty}$ (ng h/mL)	$2.00x10^4$ ± $2.2x10^3$
$t_{1/2}$ (h)	30.9 ± 6.7
Kel (h^{-1})	0.02 ± 0.01

significant advancement in the field of analytical chemistry. The use of an LLE technique has resulted in minimal interference and reproducible recovery, making this method highly reliable and accurate for measuring BDQ levels in plasma samples. The method's short run time of only 2 min and high sensitivity make it a highly efficient and effective option for conducting bioavailability/bioequivalence studies for BDQ 100 mg in humans. This means that a larger number of samples can be analyzed quickly and accurately, allowing for high-throughput analysis. The use of this method can significantly improve the efficiency and reliability of BA/BE studies, ultimately leading to a better understanding and evaluation of the drug's performance in the human body. As such, this method is highly recommended for use in studying BDQ 100 mg to ensure its safety and efficacy in treating tuberculosis.

Table 5
Incurred sample reanalysis data.

Subject No.	Sampling point (h)	Initial conc. (ng/mL)	Re-assay conc. (ng/mL)	Mean	Difference[a] (%)
1	5.50	999	979	989	2.04
1	72.0	63.6	61.3	62.5	3.65
2	4.50	941	943	942	−0.18
2	48.0	104	104	104	0.31
3	5.00	942	926	934	1.78
3	72.0	74.6	77.0	75.8	−3.03
4	5.00	$1.25x10^3$	$1.26x10^3$	$1.26x10^3$	−1.17
4	48.0	113	106	109	6.56
5	6.50	931	936	933	−0.58
5	72.0	74.8	70.6	72.7	5.71
6	5.50	$1.08x10^3$	$1.20x10^3$	$1.14x10^3$	−10.6
6	72.0	79.5	81.7	80.6	−2.68

[a] Expressed as [(initial conc. – re-assay conc.)/mean] x 100.

CRediT authorship contribution statement

Viritha Bezawada: Conceptualization, Methodology, Data curation. **Padma Mogili:** Supervision. **Srinivasa Rao Polagani:** Visualization, Investigation. **Sireesha Dodda:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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