Heliyon 9 (2023) e17230

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Development and validation of an LC-MS/MS method by one-step precipitation for cinacalcet in human plasma

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ARTICLE INFO

Keywords:
Cinacalcet
One-step precipitation
LC-MS/MS
Human plasma

ABSTRACT

A sensitive, convenient, rapid and economic liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed to determine cinacalcet concentration in human plasma. A stable isotope cinacalcet (cinacalcet-D_3) was selected as internal standard and the analytes were extracted from plasma samples by a one-step precipitation procedure. Chromatography separation was conducted on an Eclipse Plus C18 column by gradient elution with mobile phase of methanol-water-ammonium formate system at a constant flow rate of 0.6 mL/min. Mass spectrometric detection was conducted by multiple reaction monitoring using positive electrospray ionization. Cinacalcet concentrations in human plasma were determined over the concentration range of 0.1–50 ng/mL. The accuracies of lower limit of quantification (LLOQ) and quality control samples were all within the range of 85–115%, and the inter- and intra-batch precisions (*CV*%) were all within 15%. The average extraction recovery rates were 95.67–102.88%, and the quantification was not interfered by the matrix components. The validated method was successfully applied to determined cinacalcet concentrations in human plasma from secondary hyperparathyroidism patients.

1. Introduction

Secondary hyperparathyroidism (SHPT) is a serious complication commonly presented in patients with chronic kidney disease (CKD) [1]. SHPT probably develops as a consequence of elevating Fibroblast Growth Factor 23 (FGF23) and serum phosphorus levels, and decreasing serum 1,25-dihydoxy vitamin D and calcium concentrations, which reduce the signaling through calcium-sensing receptor (CaSR) and increase parathyroid hormone (PTH) secretion. The elevating levels of PTH hence lead to the development of renal osteodystrophy [2–4]. The primary treatment options include calcium supplementation, active vitamin D analogues, phosphate binders and dietary phosphate restriction [2,4].

Cinacalcet is a second generation calcimimetic approved by FDA and EMA for the treatment of SHPT. It takes effect by modulate CaSR and increase extracellular calcium level, resulting in the decrease of PTH synthetize and secretion [4,5]. Pharmacokinetics (PK)

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https://doi.org/10.1016/j.heliyon.2023.e17230
Received 25 May 2023; Received in revised form 6 June 2023; Accepted 12 June 2023
Available online 12 June 2023

characteristics of cinacalcet have been investigated in healthy volunteers. The T_{max} in human plasma was 2–6 h after oral administration, with absolute bioavailabilities of 20–25% [6,7]. The terminal half-life of cinacalcet was 30–40 h and steady state concentrations (C_{ss}) were achieved within 7 days [6,7].

Different from traditional pharmacokinetics, population pharmacokinetics (PPK) is commonly investigated in a large group of patients to differentiate the interindividual and residual unexplained variabilities [8]. To establish a PPK model, a large number of subjects (generally at least 100 subjects) should be involved and sparse plasma concentrations should be obtained at both absorption and elimination stages. Therefore, a simple and rapid quantification method for target compounds is required to the PPK study of cinacalcet. Several liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods have been reported for the determination of cinacalcet in human or rat plasma [9–11]. In these methods, solid-phase extraction [9] and liquid-liquid extraction [10,11] were employed to prepare the plasma samples, which were time consuming and uneconomic. A protein precipitation method for the assay of cinacalcet has been reported that only 100 μL precipitant (methanol) was added in 50 μL plasma to performed satisfied sensitivity, and therefore a further filter under vacuum was required to prevent clogging of chromatographic column [12].

The present study describes an LC-MS/MS method by one-step precipitation for determination of cinacalcet in human plasma. The method was simple, rapid, economical and has been validated according to the recommendations of the Pharmacopoeia of the People's Republic of China (Edition 2020) and guidelines of FDA.

2. Materials and methods

2.1. Chemical reagents

Cinacalcet HCL (97.67%) was obtained from Sinco Pharmchem Inc. (DE, USA). Cinacalcet-D_3 HCl (internal standard, IS) was supplied by TLC Pharmaceutical Standards Ltd. (Ontario, Canada). Acetonitrile and methanol (HPLC grade) were purchased from Merck KGaA (Darmstadt, Germany). Ammonium formate (MS grade) was supplied by Sigma-Aldrich Co., LLC (MO, USA). Ultrapure water (resistivity 18 MΩ) was prepared by a Milli-Q system (Millipore, Bedford, USA). Cinacalcet-free human plasma was obtained from consenting healthy volunteers in our lab.

2.2. Instrument and conditions

Chromatographic analysis was carried out on a Shimadzu 20A HPLC system, include two LC-20AD pumps, a DGU-$20A_{3R}$ degassing unit, an SIL-20A autosampler and a CTO-20A column oven (Shimadzu Corporation, Kyoto, Japan). Separations were conducted on an Eclipse Plus C18 column (particle size 3.5 μm, 4.6 × 100 mm, Agilent Technologies Inc., Santa Clara, CA, USA) at 35 °C. The mobile phase consisted of 75% methanol (v/v) and 5 mmol/L ammonium formate in water (phase A) and methanol (phase B), with gradient elution (Table 1). The flow rate was 0.6 mL/min and the injection volume was 10 μL.

Mass spectrometric detection was performed using an LCMS-8040 triple-quad mass spectrometer (Shimadzu Corporation) equipped with an electrospray ionization (ESI) source operating in positive mode. Detection was performed by multiple reaction monitoring (MRM). The ion transitions of cinacalcet and IS were m/z 358.2 → 155.1 (Fig. 1A) and m/z 361.2 → 158.1 (Fig. 1B), respectively. The collision energies were both −17 eV. Mass spectrometric conditions were optimized as follows: interface voltage 4.5 kV; conversion dynode voltage 6 kV; DL temperature 250 °C; heat block temperature 400 °C; nebulizing gas (nitrogen) 3 L/min; drying gas (nitrogen) 15 L/min; collision gas (argon) 230 kPa.

Data acquisition and processing were performed by Shimadzu LabSolutions Workstation (version 5.99 SP2, Shimadzu Corporation). Means, standard deviations (*SD*) and coefficients of variations (*CV*) were calculated by Microsoft Office Excel 2019 (Redmond, WA, USA).

2.3. Calibration standards and quality controls

Stock solutions of cinacalcet (1 mg/mL) were prepared in methanol and stored at 4 °C. Working solutions of calibration standards and quality controls were prepared by serial dilution of cinacalcet stock solution with 50% methanol water solution (v/v) to appropriate concentrations. 5 μL working solution was used to spiked with 95 μL cinacalcet-free human plasma to provide mimic plasma samples. The final concentrations of cinacalcet in plasma were 0.1, 0.2, 1, 5, 10, 20, 40, 50 ng/mL for calibration standards and 0.3, 5,

Table 1
Elution procedure for determination of cinacalcet.

Time (min)	Ratio of phase A[a] (%)	Ratio of phase B[b] (%)
0	100	0
1	100	0
1.5	10	90
3	10	90
3.5	100	0
5	100	0

[a] Phase A: 75% methanol (v/v) and 5 mmol/L ammonium formate in water.
[b] Phase B: Methanol.

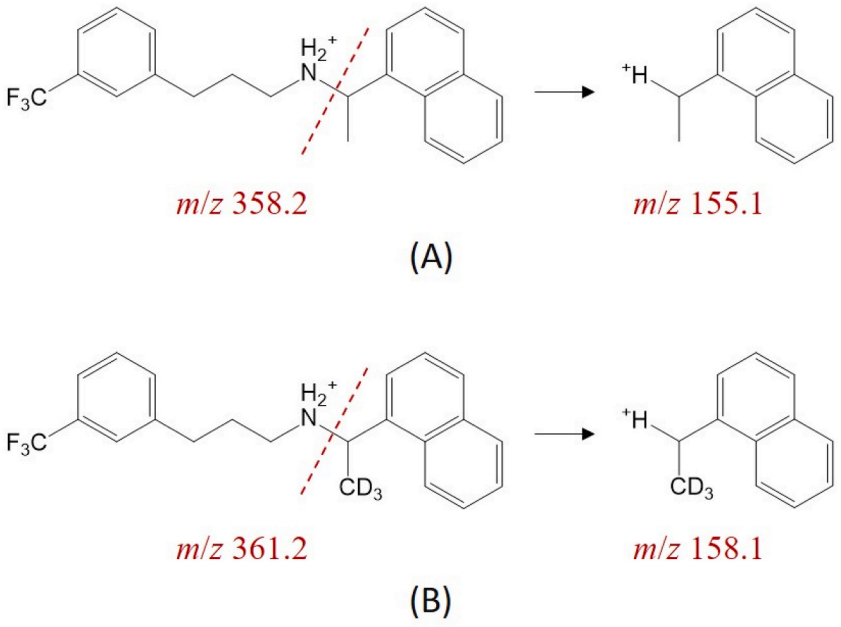

Fig. 1. Ion transitions of cinacalcet (A) and cinacalcet-D_3 (B).

20, 35 ng/mL for quality controls. Stock solutions of cinacalcet-D_3 (1 mg/mL) were prepared in methanol and diluted with 50% methanol water solution (v/v) to provide IS working solution (50 ng/mL).

2.4. Plasma sample preparation

Cinacalcet was extracted from plasma by one-step precipitation. In brief, 100 μL plasma was spiked with 20 μL IS working solution and 500 μL acetonitrile. After vortexed mixing for 15 s the mixture was centrifuged at 20,000 *g* for 5 min. The supernatant was collected for LC-MS/MS determination.

2.5. Method validation

Validation of the LC-MS/MS method was performed in compliance with the recommendations of the Pharmacopoeia of the People's Republic of China (Edition 2020) and guidelines of FDA, including linearity, sensitivity, specificity, accuracy, precision, matrix effect, recovery, carryover and stability.

2.5.1. Specificity, sensitivity and linearity

Specificity for cinacalcet and isotope-labeled IS (cinacalcet-D_3) was tested in cinacalcet-free human plasma (blank plasma). Blank plasma samples from six different subjects were prepared and detected as described in Section 2.4. Endogenous substances at the retention time of cinacalcet should be less than 20% of the peak areas for LLOQ, and less than 5% for that of IS. Sensitivity of the LC-MS/MS method was defined by LLOQ samples of cinacalcet, with acceptable signal-to-noise ratio (S/N $\geq$ 10), accuracy (80–120%) and precision ($CV \leq 20\%$). For the assess of linearity, peak ratios against concentration ratios of cinacalcet and cinacalcet-D_3 were plotted to establish the calibration curve at 0.1–50 ng/mL of cinacalcet. The regression equation was fitted by least-squares method with a weighting factor of $1/x^2$.

2.5.2. Precision and accuracy

The intra-batch precisions and accuracies of the method were investigated by assessing six replicate QC samples at five concentration levels including 0.1 ng/mL (LLOQ), 0.3 ng/mL (LQC), 5 ng/mL (GMQC), 20 ng/mL (MQC) and 35 ng/mL (HQC). Three batches of the above QC samples were determined at different days to assessed the inter-batch precisions and accuracies. *CV* was calculated to evaluate intra- and inter-batch precisions, which were accepted within 15% for LQC, GMQC, MQC and HQC, while within 20% for LLOQ. Intra- and inter-batch accuracies were accepted at the range of 85–115% for LQC, GMQC, MQC and HQC, and 80–120% for LLOQ.

2.5.3. Matrix effect and recovery

The matrix effect on the determination of cinacalcet was assessed by comparing relative responses of post-spiked samples (cinacalcet and IS working solutions were added to post-extracted blank biological matrix residues) with same concentration of solution

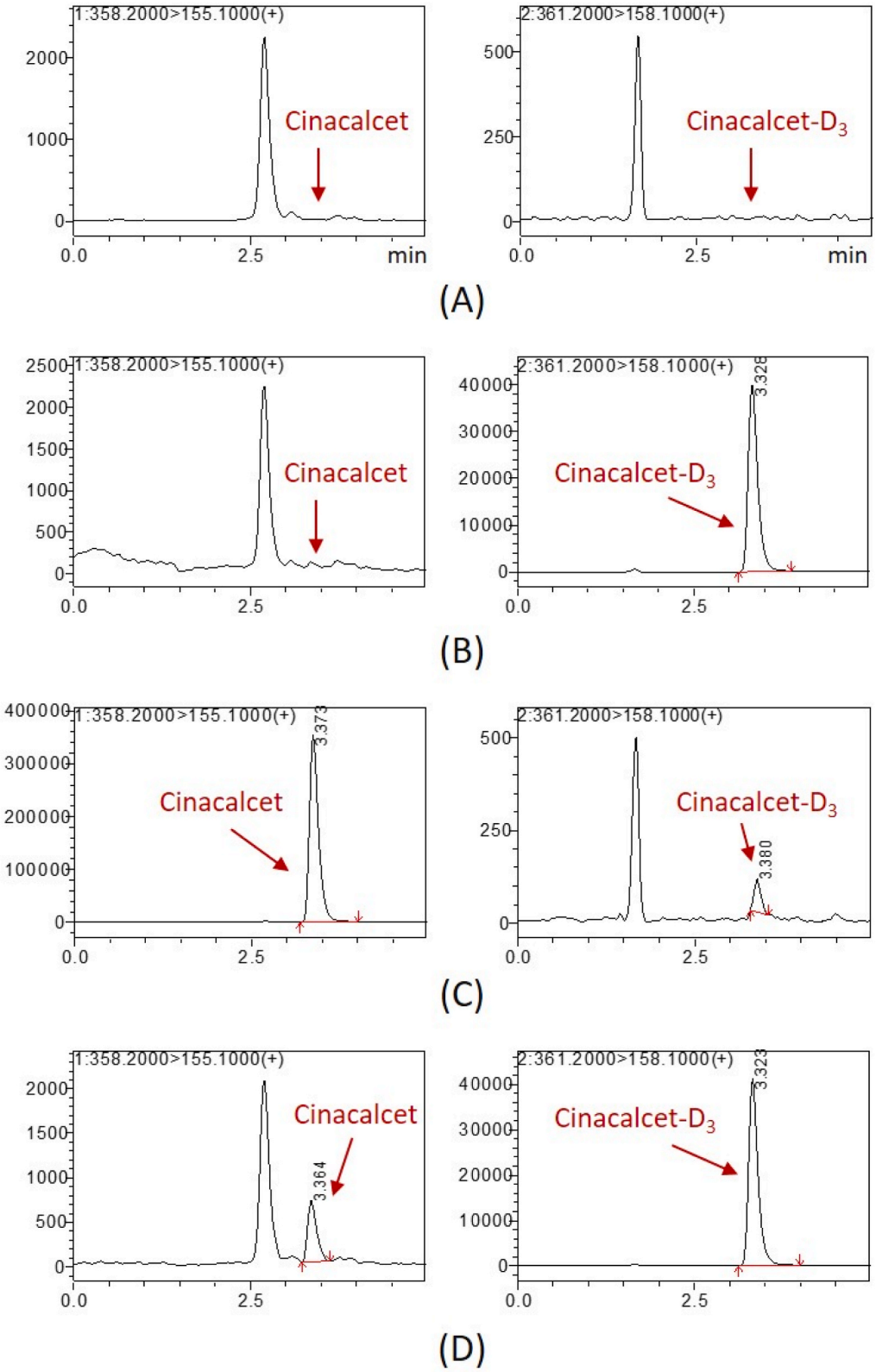

Fig. 2. Representative chromatograms of blank plasma (A), blank plasma spiked with 10 ng/mL of IS (B), blank plasma spiked with 50 ng/mL of Cinacalcet (C) and LLOQ plasma samples (D).

samples at 4 QC levels. Blank plasma samples from six different subjects were evaluated and IS-normalized matrix factors were used to expressed the matrix effect. Extraction recovery rates of cinacalcet and IS were determined by comparing responses of extracted samples (plasma QC samples prepared as described in Section 2.4) with same concentration of post-spiked samples at 4 QC levels with 6 replicates.

2.5.4. Carryover

Carryover effect was evaluated by analyzing a blank plasma sample following an upper limit of quantification (ULOQ, 50 ng/mL) sample. Carryover evaluation was performed in 3 replicates. Peak areas of cinacalcet in blank plasma samples within 20% of LLOQ, and that of IS within 5% were accepted.

2.5.5. Stability

Mimic human plasma LQC and HQC samples were quantified by freshly prepared calibration standard samples. To prove the stability of cinacalcet over different storage periods, the mean actual concentrations should be 85–115% of the nominal concentrations. Benchtop stability of cinacalcet in plasma was measured by storing LQC and HQC plasma samples at room temperature for 24 h. Long-term stability was evaluated by storing LQC and HQC plasma samples at −20 °C for 185 days. Post-extraction stability was investigated by storing LQC and HQC extracted samples in the autosampler for 24 h. To evaluated freeze-thaw stability, LQC and HQC plasma samples were subjected to 3 freeze-thaw cycles (from −20 °C to room temperature).

2.5.6. Plasma cinacalcet concentrations in SHPT patients

The validated LC-MS/MS method was applied to determined plasma concentrations in SHPT patients treated with cinacalcet. 22 plasma samples from 15 consenting SHPT patients at Zhujiang Hospital of Southern Medical University were assessed. All clinical procedures were approved by the Independent Ethics Committee of Zhujiang Hospital of Southern Medical University (2022-KY-215-02) and conducted in accordance with Chinese Good Clinical Practice and the Declaration of Helsinki.

3. Results and discussion

3.1. Method development

A C18 column was selected to separate the analytes from plasma matrix. During the development process, methanol-water and acetonitrile-water, with ammonium formate as buffer, were employed to optimized the elution program, in which methanol-water system offered a high response and well peak shape for cinacalcet. At a high ratio of methanol in the mobile phase, cinacalcet was eluted quickly and the response was significantly affected by the matrix components, while reducing the methanol ratio, cinacalcet was well separated with matrix components but exhibited a pool peak shape. A gradient elution process was thus employed to acquire both high response and well chromatographic peak.

Several LC-MS/MS methods for quantification of cinacalcet has been reported and the plasma samples were prepared by frequently used processes such as solid-phase extraction, liquid-liquid extraction and protein precipitation [9–12]. The LLOQs of the published methods were 0.1 ng/mL, except that reported by Li, which was 0.05 ng/mL with liquid-liquid extraction [11]. According to the pharmacokinetic characteristic of cinacalcet, an LLOQ of 0.1 ng/mL was sufficient [6,7]. In consideration of the large sample size for PPK modeling, the quantitative method for plasma samples was expected to be simple and rapid. Solid-phase extraction and liquid-liquid extraction were more sensitive compared to protein precipitation, while the preparation processes were time consuming and uneconomic. A protein precipitation method with an LLOQ of 0.1 ng/mL for determination of cinacalcet has been described by Cangemi [12]. In Cangemi's study, methanol was selected to be the precipitant, and the ratio of precipitant and plasma sample was only 2:1, which was insufficient for complete precipitation of plasma proteins. To protect the chromatographic column, a further filter under vacuum was required, which increased the processing time and final cost.

In the present work, acetonitrile was employed to prepare plasma samples with a precipitant-plasma ratio of 5:1. Only one-step precipitation was required during the plasma preparation process, which was quite simple, rapid and economic. In common with solid-phase extraction and liquid-liquid extraction, the LLOQ of the present method was 0.1 ng/mL at the detected condition described in Section 2.2. The method was validated and met the criterion of the Pharmacopoeia of the People's Republic of China (Edition 2020) and guidelines of FDA.

3.2. Specificity and sensitivity

Specificity of the method for determination of cinacalcet was assessed by evaluating background noise or potential interference at the retention times of cinacalcet and cinacalcet-D_3 from endogenous substances. Representative MRM chromatograms of blank plasma, blank plasma spiked with 10 ng/mL of IS, blank plasma spiked with 50 ng/mL of cinacalcet and LLOQ plasma samples were obtained (Fig. 2). The retention times of cinacalcet and IS were approximately 3.3–3.4 min. No significant interfered response attributable to the matrix component of human plasma was observed at the retention time of the analytes (Fig. 2A). No chromatographic peak inferencing the determination of cinacalcet was occurred in blank plasma spiked with IS (Fig. 2B), while a small interfered response was appeared on the MRM chromatography of IS in blank plasma spiked with cinacalcet (Fig. 2C). The area ratio of interfered peak compared to IS was 0.16% (<5%), indicating that the interference of cinacalcet to IS was negligible. LLOQ (0.1 ng/mL) plasma samples were prepared to evaluate the sensitivity of the method. Chromatography peaks of LLOQ samples (Fig. 2D) were satisfied and signal-to-noise ratios (S/

N) were over 10.

3.3. Linearity and carryover

Calibration curves ranging 0.1–50 ng/mL in human plasma were assessed to evaluate the linearity. The correlation coefficients (R^2) of all routine calibration curves were greater than 0.995. Calibration accuracies of back-calculated concentrations for all calibrated levels were within ±15% bias. Slopes and intercepts of the calibration curves were 1.623 ± 0.048 and −0.001468 ± 0.000908, respectively. No apparent carryover was observed on the MRM chromatograms of blank plasma samples injected following the analyses of ULOQ plasma samples.

3.4. Precision and accuracy

Three analyze batches (six replicates for each batch) of human plasma samples at different days over five concentration levels (LLOQ, LQC, GMQC, MQC and HQC) were employed to investigate the precision and accuracy for the determination of cinacalcet. Intra- and inter-batch precisions for all concentration levels were satisfied with *CV*s below 15%. Meanwhile, intra- and inter-batch accuracies were all met the criterion of 85–115% (Table 2).

3.5. Matrix effect and recovery

Matrix effect was performed to investigate the possible suppression or enhancement of cinacalcet ionization interfered by endogenous substance in plasma. Mean IS-normalized matrix effects of cinacalcet at four QC levels were 99.17–102.22% with *CV*s within 15% (Table 3). The mean extraction recoveries of cinacalcet at 0.3, 5, 20 and 35 ng/mL were over the range of 95.67–102.88% (Table 3), and that of IS at 10 ng/mL was 98.80 ± 3.54%.

3.6. Stability

The recoveries of cinacalcet from plasma samples were investigated under different storage and processing conditions and the results were summarized in Table 4. All the recoveries of LQC and HQC samples were in the range of 85–115%, suggesting that cinacalcet was stable for at least 24 h during benchtop preparation, 185 days of storage at −20 °C, 3 cycles of freeze-thaw from −20 °C to room temperature, or 24 h after extracted and stored in the autosampler.

3.7. Method application

Concentrations of cinacalcet in 22 plasma samples from 15 SHPT patients were determined. The dose regimens, blood sampling times and cinacalcet concentrations were summarized in Table 5. Cinacalcet concentrations of all plasma samples (range 0.5818–25.47 ng/mL) were within the linear range of the calibration curve, 12 samples of which were obtained during steady state after multiple administration. The dose relative concentrations (plasma concentration divided by daily dose) of the steady state samples were 0.1091 ± 0.0678 ng/mL/mg. The current method was successfully applied to determine cinacalcet plasma concentrations of SHPT patients. For further investigation, at least 100 subjects were planned to be involved to detect sparse plasma concentrations and finally objective to establish a PPK model of cinacalcet.

4. Conclusion

A convenient, rapid and economic LC-MS/MS method for quantification of cinacalcet in human plasma has been successfully developed and validated. A one-step protein precipitation process using acetonitrile was employed to prepare plasma samples. C18 column was selected and methanol-water system with ammonium formate as buffer was employed to separate the analytes by gradient elution. The present method was fully validated and demonstrated well specificity and sensitivity, absence of matrix interference and

Table 2
Precision and accuracy for the determination of cinacalcet.

Nominal concentration (ng/mL)	Intra-batch			Inter-batch		
	Measured concentration (ng/mL)	Accuracy (%)	Precision (*CV* %)	Measured concentration (ng/mL)	Accuracy (%)	Precision (*CV* %)
0.1	0.10 ± 0.00	97.08 ± 3.65	3.76	0.10 ± 0.00	100.45 ± 4.61	4.59
0.3	0.30 ± 0.01	98.98 ± 3.13	3.17	0.29 ± 0.01	97.11 ± 2.90	2.99
5	4.87 ± 0.13	97.31 ± 2.62	2.69	4.84 ± 0.09	96.87 ± 1.73	1.79
20	21.85 ± 0.32	109.26 ± 1.60	1.47	20.43 ± 1.06	102.15 ± 5.29	5.18
35	36.25 ± 1.27	103.56 ± 3.63	3.50	35.23 ± 1.10	100.65 ± 3.14	3.12

Table 3
Matrix effect and extraction recovery for the determination of cinacalcet.

Nominal concentration (ng/mL)	Matrix effect		Extraction recovery	
	IS-normalized matrix effect (%)	CV (%)	Recovery rate (%)	CV (%)
0.3	99.99 ± 5.09	5.09	101.04 ± 4.48	4.43
5	101.32 ± 2.33	2.30	101.50 ± 5.49	5.41
20	99.17 ± 1.91	1.93	102.88 ± 4.78	4.65
35	102.22 ± 1.02	0.99	95.67 ± 5.44	5.69

Table 4
Stability of cinacalcet in different conditions.

Storage condition	Recovery (%)	
	LQC (0.3 ng/mL)	HQC (35 ng/mL)
Benchtop stability (24 h)	89.64 ± 2.54	105.52 ± 2.83
Long-term stability (−20 °C, 185 days)	90.79 ± 5.09	105.29 ± 2.85
Freeze-thaw stability (3 cycles)	91.94 ± 2.22	102.06 ± 3.23
Post-extracted stability (24 h)	102.06 ± 2.09	99.12 ± 0.54

Table 5
Dose regimens, sampling times and cinacalcet concentrations of SHPT patients.

Subject	Dose regimen	Stage	Time (h)[a]	Concentration (ng/mL)
001	50 mg qd	Steady state	9.3	6.15
	50 mg qd	Steady state	14.1	6.22
002	25 mg qd	Second dose	9.8	0.58
	25 mg qd	Steady state	10.8	1.96
003	25 mg qd	Steady state	14.7	2.07
	25 mg qd	Steady state	10.0	2.61
	25 mg qd	Steady state	10.5	1.35
004	50 mg qd	Steady state	19.1	1.46
	50 mg qd	Steady state	2.5	5.37
	50 mg qd	Steady state	2.8	5.47
005	25 mg qd	First dose	10.7	1.04
006	25 mg qd	First dose	8.7	5.01
	25 mg qd	Second dose	1.0	6.31
007	100 mg qd	Third dose	8.5	25.47
008	25 mg qd	First dose	8.4	1.53
009	25 mg qd	First dose	2.8	1.74
010	25 mg qd	First dose	4.1	1.88
011	25 mg qd	Steady state	9.6	4.74
012	25 mg qd	First dose	14.1	1.61
013	25 mg qd	First dose	6.9	8.03
014	75 mg qd	Steady state	46.1	4.04
015	75 mg qd	Steady state	10.4	18.88

[a] The sampling times were calculated from the last administrations.

appropriate recovery rate. The accuracy and precision were satisfied over the concentration range of 0.1–50 ng/mL. The validated method was successfully used to the determination of cinacalcet in SHPT patients, which would be further applied to PPK modeling of cinacalcet.

Author contribution statement

Xin Wen: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Haoyang Lu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Tingting Guo: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Shanqing Huang; Yuandan Li: Performed the experiments.

Yuguan Wen: Analyzed and interpreted the data.

Dewei Shang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

The data used to support the findings of this study are included within the article.

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.

Acknowledgments

We are grateful to all participants for their willingness to participate in this study. Haoyang Lu and Tingting Guo are considered as co-first authors, and Xin Wen and Dewei Shang are considered as co-corresponding authors. This work was supported by President Foundation of Zhujiang Hospital, Southern Medical University (grant number yzjj2022qn15); Natural Science Foundation of Guangdong Province (grant numbers 2018A0303130074, 2021A1515011325); Guangzhou Municipal Science and Technology Project for Medicine and Healthcare (grant numbers 20201A011047, 20202A011016); Science and Technology Plan Project of Guangdong Province (grant number 2019B030316001); Guangzhou Municipal Key Discipline in Medicine (stage 2021–2023); and Guangzhou Municipal Clinical Characteristic Technology Projects (grant number 2023C-TS22).

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