Journal of Chromatography B, 877 (2009) 465–470

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Application of a liquid chromatography/tandem mass spectrometry method for the pharmacokinetic study of dihydroartemisinin injectable powder in healthy Chinese subjects

Yiming Liu [a], Xing Zeng [a,*], Yuanhui Deng [a], Lu Wang [b], Yi Feng [a], Liu Yang [a], Dan Zhou [a]

[a] Department of Clinical Pharmacology, Guangdong Provincial Hospital of TCM Affiliated to Guangzhou University of TCM, 111 Dade Road, Guangzhou 510120, China
[b] Beijing Huali Ketai Pharmaceutical Co. Ltd., Beijing 100089, China

ARTICLE INFO

Article history:
Received 8 April 2008
Accepted 19 November 2008
Available online 3 December 2008

Keywords:
Dihydroartemisinin
Injectable powder
LC/MS/MS
Pharmacokinetics
Human plasma

ABSTRACT

A simple, rapid and accurate liquid chromatography–electrospray ionization-tandem mass spectrometry method was developed and validated for quantification of dihydroartemisinin (DHA) in human plasma. Following a simple single-step liquid–liquid extraction with ethyl acetate, the analyte was separated on a C_{18} column by isocratic elution with methanol–water–10 mM ammonium acetate (80:10:10, v/v/v), and analyzed by mass spectrometry in the positive ion MRM mode. Good linearity was achieved over a wide range of 1.01–2020 ng/mL. Intra- and inter-day precisions were less than 9.0%, and accuracy ranged from 93.0 to 98.2%. The pharmacokinetics of DHA injectable powder was studied for the first time in healthy subjects by this method. After single intravenous infusion of DHA injectable powder 40, 80 and 160 mg, the elimination half-life ($t_{1/2\lambda Z}$) was 1.69, 1.88 and 1.92 h, respectively; mean C_{max} and AUC increased in proportion to the doses. The pharmacokinetics of DHA fit the linear dynamic feature over the DHA dose range studied.

1. Introduction

Dihydroartemisinin (DHA, Fig. 1) is the lactol reduction product of artemisinin (ART) and has more potent antimalarial activity than ART [1,2]. The derivatives of ART such as artesunate, artemether and arteether can be rapidly converted to their major active metabolite DHA *in vivo* which is responsible for the antimalarial action [3,4]. DHA is found to be effective against acute malaria and chloroquine resistant strains of falciparum malaria, particularly cerebral malaria. However, DHA is limited to be used directly in clinic for its poor water solubility. Recently, a new formulation of DHA injectable powder, in which DHA–hydroxypropyl-β-cyclodextrin inclusion complex is the main constituent, has been developed to improve the water solubility and stability, and approved to enter clinical trial in China. To further understand and reveal the pharmacokinetics of DHA injectable powder in Chinese volunteers, a rapid, sensitive and specific analytical method for determining DHA in human plasma is urgently required.

Various methods have been developed for the quantification of DHA and its analogues in biological samples, such as high-performance liquid chromatography (HPLC) with electrochemical detection [5–7]. However, there exist some limitations of these methods including long run time, poor reproducibility and inadequate sensitivity.

Currently, liquid chromatography coupled with mass spectrometry (LC/MS) techniques have been widely employed for the analysis of drug compounds in biological fluids because of their excellent specificity, high speed and sensitivity. LC/MS, using different modes of ionization, has been reported for the detection of ART analogues and their metabolite, DHA, in plasma and urine [8–12]. However, these analytical methods for DHA are unsuitable for clinical pharmacokinetic studies because long analytical time and large sample volume are usually required with complicated and labor-costing sample preparation procedures.

To facilitate the pharmacokinetic studies of DHA in humans, a novel liquid chromatography/tandem mass spectrometry (LC/MS/MS) method has been developed and validated to measure DHA concentration in human plasma over the wide range of 1.01–2020 ng/mL. In addition to an improvement in sensitivity, the sample pretreatment was simplified and the analytical time was considerably reduced. This method would be efficient in analyzing large numbers of plasma samples obtained from pharmacokinetic studies after a single intravenous infusion of DHA injectable powder at three dosage levels (40, 80 and 160 mg). The pharmacokinetic profiles of DHA injectable powder were investigated for the first time in healthy subjects.

* Corresponding author. Tel.: +86 20 81887233; fax: +86 20 81867705.
E-mail address: zengxing-china@163.com (X. Zeng).

1570-0232/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jchromb.2008.11.039

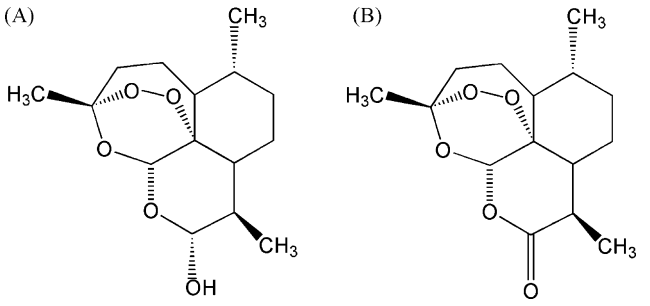

Fig. 1. Chemical structures of (A) dihydroartemisinin (DHA) and (B) artemisinin (ART).

2. Experimental

2.1. Chemicals and reagents

Dihydroartemisinin standard (purity 99.8%) was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Artemisinin as the internal standard (IS) was provided by the Institute of Tropical Medicine of Guangzhou University of TCM (Guangzhou, China). The test drug was DHA injectable powder containing 40 mg of DHA per vial, which was provided by Beijing Huali Ketai Pharmaceutical Co. Ltd. (Beijing, China). Methanol and ammonium acetate were of HPLC grade and purchased from Fisher Scientific (Fairlawn, NJ, USA) and Tedia Company (Fairfield, OH, USA), respectively. The water used in the experiment was doubly distilled in the laboratory. Other chemicals (analytical grade) were purchased from Guangzhou Chemical Reagent Factory (Guangzhou, China).

2.2. LC/MS/MS instrument and conditions

HPLC was performed using an Agilent 1100 series LC system (Agilent Technologies, Palo Alto, CA, USA) equipped with a G1311A quaternary pump, a vacuum degasser unit, and a G1313A autosampler. Room temperature was controlled at 20 °C by air conditioner. Chromatographic separation was achieved on a Pinnacle II C_{18} column (150 mm × 2.1 mm i.d., 5 μm, RESTEK) with a SecurityGuard C_{18} guard column (4 mm × 2.0 mm i.d., Phenomenex, Torrance, CA, USA) at room temperature. An isocratic elution mode was adopted with the mobile phase consisting of methanol–water–10 mM ammonium acetate (80:10:10, v/v/v). The flow rate was 0.2 mL/min.

Mass spectrometric detection was performed on an API 3000 triple–quadrupole mass spectrometer (AB Sciex Instruments, USA). A TurboIonspray interface operating in positive ionization mode was used. The turbo-gas temperature was set at 400 °C and the ionspray voltage (IS) was adjusted at 4000 V. High purity nitrogen served as nebulizer gas (NEB, GAS1, 12), curtain gas (CUR, 6), collision gas (CAD, 3) and auxiliary gas (AUX, GAS2, 7 L/min). The detector was operated at unit resolution in the multiple reaction monitoring (MRM) mode, with a dwell time of 100 ms per MRM channel. The optimized fragmentation transitions for MRM were m/z 302.3 → 163.2 for DHA and m/z 300.3 → 209.1 for IS. The focusing potential (FP), entrance potential (EP), and collision cell exit potential (CXP) were set at 220, 6 and 15 in turn. The declustering potential (DP) and collision energy (CE) were set at 15 and 23 for DHA and 20 and 16 for IS, respectively. Data processing was performed with Analyst software (version 1.4).

2.3. Preparation of standard and quality control (QC) samples

The primary stock solution of 1.01 mg/mL DHA was prepared by dissolving the accurately weighed reference compound in methanol. The solution was then serially diluted with 80% methanol into the standard working solutions at concentrations of 101, 10.1, 1.01 and 0.101 μg/mL. A 505 ng/mL working solution of IS was prepared by further diluting the IS stock solution with 80% methanol. All these solutions were stored at 4 °C and brought to room temperature before use.

The calibration samples at concentrations of 1.01, 3.03, 10.1, 30.3, 101, 303, 1010, and 2020 ng/mL for DHA were prepared by spiking appropriate amounts of the working solutions in blank human plasma. The calibration curves were prepared and assayed along with QC samples and each batch of clinical plasma samples. The QC samples were prepared at three different concentration levels of 3.03 (low), 101 (mid), and 1616 ng/mL (high) together with the dilution QC (5050 ng/mL) samples. QC samples were prepared in drug-free human plasma from a second set of DHA stock and working solutions. These solutions were prepared using an independent weighing of the analyte standard. All calibration and QC samples were divided into aliquots in eppendorf tubes (2 mL) and stored at −75 °C until analysis.

2.4. Sample preparation

To each 300 μL plasma sample, 50 μL of IS solution (505 ng/mL) was added. After vortex mixing for 10 s, 3 mL of ethyl acetate was added, then, the mixture was vortexed for 2 min. Following centrifugation and separation, the organic phase was transferred to another tube and evaporated to dryness at 35 °C under a nitrogen stream. The residue was dissolved in 400 μL of mobile phase, and vortex-mixed for 1 min. A 10-μL aliquot of the solution was injected into the LC/MS/MS for analysis.

2.5. Method validation

The selectivity of the method was checked by comparing the chromatograms of six different batches of blank human plasma with the corresponding spiked plasma. Each blank plasma sample was tested using the extraction procedure and chromatographic conditions described above to ensure no interference of DHA and IS from plasma.

Linearity was assessed by assaying calibration curves in human plasma on three consecutive days. And the curves were fitted by a weighted $(1/x^2)$ least-squares linear regression method through the measurement of the peak-area ratio of the analyte to IS. The acceptance criterion for a calibration curve was a correlation coefficient (r) of 0.99 or better, and that each back-calculated standard concentration must be within 15% deviation from the nominal value except at the lower limit of quantitation (LLOQ), for which the maximum acceptable deviation was set at 20%. The LLOQ was defined as the lowest concentration in the standard curve at which the standard deviation was within 20% and accuracy was within 100 ± 20%, and it was established using five samples independent of standards.

To evaluate the accuracy and precision of the method, QC samples at three concentration levels (3.03, 101 and 1616 ng/mL) were analyzed in five replicates on three validation days. The assay accuracy was expressed as (observed concentration/nominal concentration) × 100%. Intra- and inter-day precision was obtained by one-way analysis of variance (ANOVA) testing and was expressed as relative standard deviation (R.S.D.). The accuracy was required to be within 85–115%, and the precisions not to exceed 15%. Dilution QC samples (5050 ng/mL) were assayed to ensure that dilution of study samples did not affect accuracy and precision. The dilution QC samples were diluted at ratio of 1:10 with blank human plasma prior to analysis and processed as other QC samples.

The extraction recoveries of DHA and IS were determined at three QC levels (five samples each) by comparing the peak area

of each analyte in spiked plasma samples with those of samples to which the analytes had been added after extraction.

As far as the stability of DHA in plasma was concerned, there was no significant degradation observed under the storage conditions described in the previous reports [6,11]. In this study we just investigated the bench stability, freeze/thaw stability and the stability of DHA in reconstituted samples. Bench stability was assessed by leaving the QC samples at room temperature for 6 h. QC samples after three freeze–thaw cycles were analyzed for evaluating the freeze/thaw stability. The processed ready-to-inject samples were left in the autosampler vials at ambient temperature for 6 h to evaluate the stability of DHA in reconstituted samples. All the stability studies were conducted at three QC levels with five replicates for each.

2.6. Pharmacokinetic study

The single-dose pharmacokinetics of DHA injectable powder was studied in healthy Chinese subjects in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Medical Ethical Committee of Guangdong Provincial Hospital of TCM.

Thirty healthy male and female subjects (aged 19–28, body weight 45–79 kg) were enrolled in this study. They had no history of cardiovascular, hepatic, renal, gastrointestinal, hematologic, nervous or any acute or chronic diseases or drug allergy, and had stopped using any drugs 2 weeks before the study. Physical examination and laboratory tests showed no abnormal findings. All subjects were randomized into 40-, 80- and 160-mg dose groups (five males and five females in each group). A single dose of DHA injectable powder was dissolved in 50 mL natural saline as the intravenous infusion solution before administration. After overnight fasted, each subject was administered with the solution via drip infusion for 30 min. Water intake was allowed 2 h post-dose and standard meals were provided at 4 h and 10 h post-dose. The subjects were required to refrain from smoking, alcohol, caffeine and strenuous exercise during the study and were under direct medical supervision at the study site. Blood samples (3 mL) were collected in heparinized tubes at 0 h (pre-dose) and 10, 20, 30, 35, 45 min, 1, 1.5, 2, 2.5, 3.5, 4.5, 6.5, 8.5, 12.5, 16.5 and 24.5 h post-dose (drip infusion was started at time 0 h and completed at time 30 min). Following centrifugation, plasma was separated and stored at −75 °C for analysis. The plasma DHA concentrations were determined by LC/MS/MS method developed in this study.

The plasma concentrations of DHA versus time profiles were acquired for each subject. The peak plasma concentration (C_{max}) and time to C_{max} (t_{max}) were obtained directly from the data. The other major pharmacokinetic parameters were calculated with WinNonlin software by noncompartmental methods. The terminal elimination rate constant (k) was calculated by linear regression of the final log-linear part of the drug concentration–time curve. Apparent elimination half-life ($t_{1/2}$) was obtained as 0.693/k. The area under the plasma concentration–time curve (AUC_{0-t}) was calculated following the linear trapezoidal rule. The AUC extrapolated to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + C_t/k$, where C_t is the last detectable concentration. The mean residence time (MRT) was obtained by dividing the area under the first moment–time curve ($AUMC_{0-\infty}$) by the area under the curve ($AUC_{0-\infty}$).

3. Results and discussion

3.1. Method development

In order to develop ESI conditions for DHA and IS, quadrupole full scans were carried out in positive ion detection mode. A solution containing DHA and IS was injected directly into the mass spectrometer with the mobile phase. Under these conditions, the analytes yielded major $[M+NH_4]^+$ ions at m/z 302.3 for DHA and at m/z 300.3 for IS. Each of the precursor ions was subjected to collision-induced dissociation to determine the resulting product ions. The product ion mass spectra for DHA and IS are shown in Fig. 2. The most abundant fragment ion at m/z 267.1 for DHA was generated and used as product ion to measure DHA in human plasma at first, but high chemical background noise was observed. The chromatographic peak of DHA at LLOQ concentration was interfered by endogenous compounds and submerged in the baseline noise, which led to poor sensitivity. Therefore the second abundant fragment ion at m/z 163.2 was taken into consideration. As far as we observed, very low background was obtained when monitoring the ion at m/z 163.2. So the mass transitions chosen for quantitation were m/z 302.3 → 163.2 for DHA and m/z 300.3 → 209.1 for IS.

The MRM mode was chosen in this study for the assay development, which provided higher sensitivity and selectivity than the reported methods [8,9]. The MRM state file parameters were optimized to maximize the response for the analyte. The parameters described in Section 2.2 are the result of this optimization.

The chromatographic conditions, especially the composition of the mobile phase, were optimized through several trials to achieve good resolution, sensitivity and symmetric peak shapes for DHA and IS. Considering that the ammonium acetate buffer solution in the mobile phase could be helpful for ionizing the analytes,

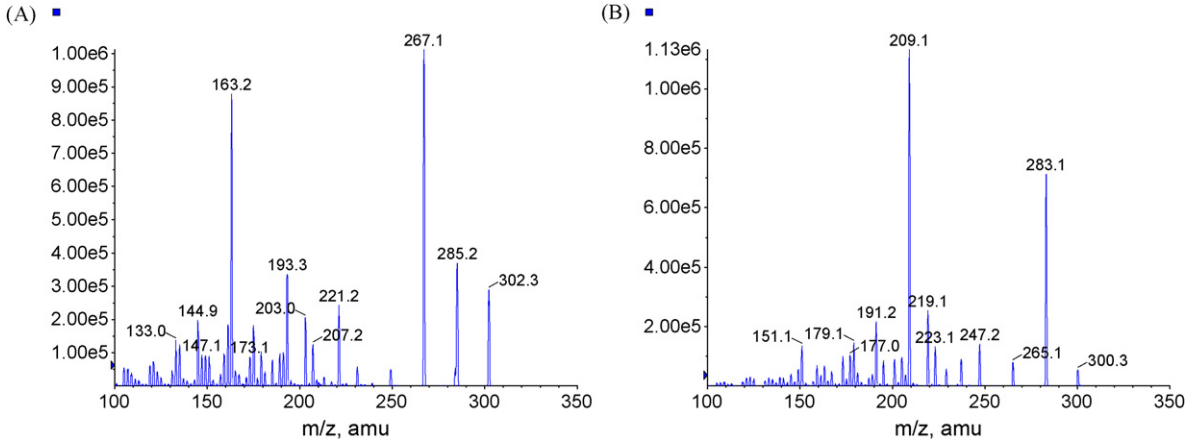

Fig. 2. Product ion mass spectra of the $[M+NH_4]^+$ ions of (A) DHA and (B) IS.

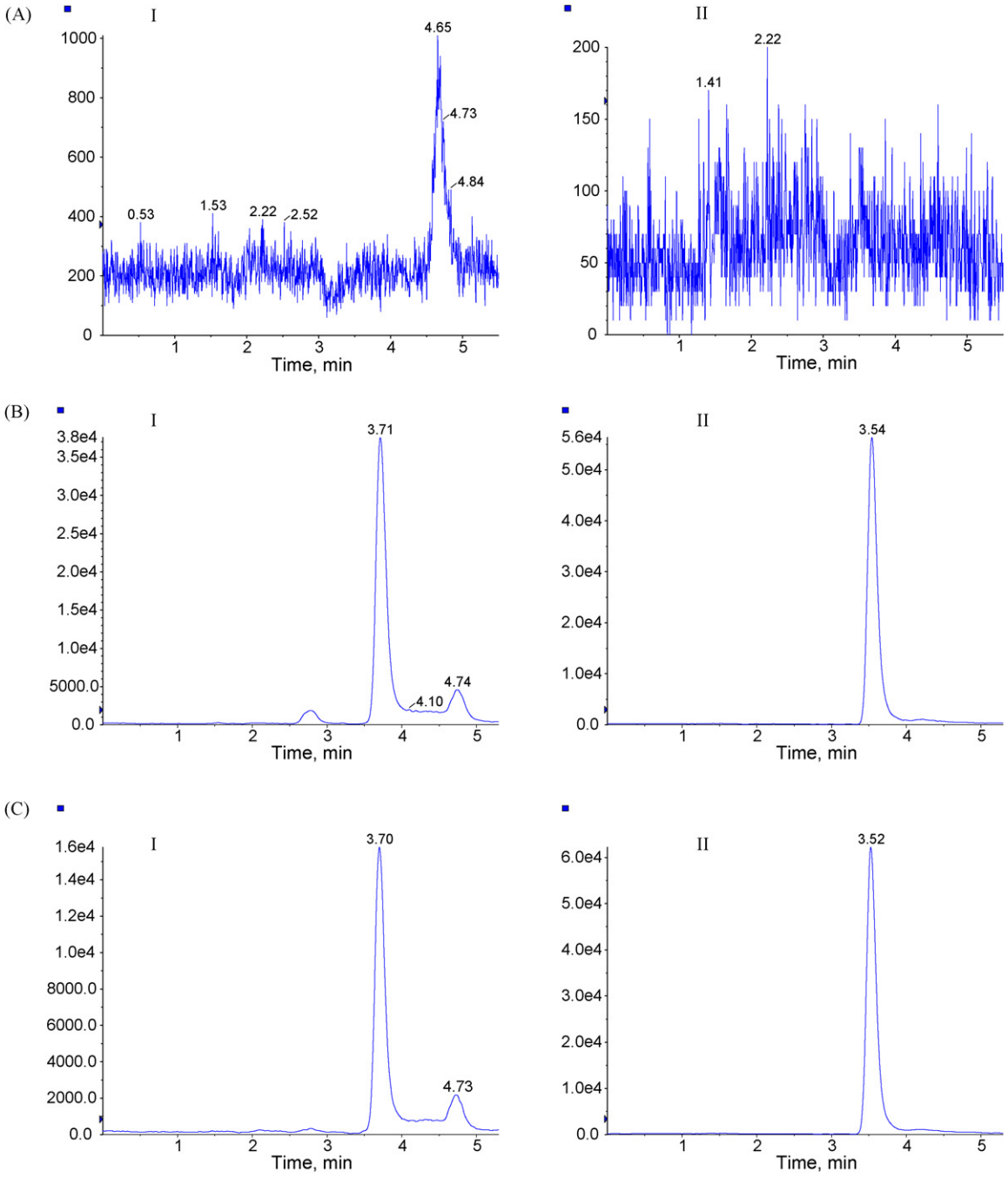

Fig. 3. Representative MRM chromatograms of (A) blank human plasma; (B) blank plasma spiked with DHA (101 ng/mL) and IS; (C) plasma obtained from a subject 3.5 h after an intravenous infusion of 40 mg DHA. (I) DHA (m/z 302.3 → 163.3) and (II) IS (m/z 300.3 → 209.3).

enhancing the ion response and modifying the peak shape, different percentages of methanol–10 mM ammonium acetate were attempted. Finally, methanol–water–10 mM ammonium acetate (80:10:10, v/v/v) was adopted as the mobile phase, due to the better separation, higher sensitivity and more stable MS signal. Under the optimized LC/MS/MS conditions, DHA and IS were detected at retention times of 3.71 and 3.52 min, respectively, and were not interfered by endogenous compounds. Matrix effects were also evaluated by comparing the peak areas of DHA from the spike-after-extraction samples (the blank plasma samples were from six different sources) to those obtained for the standards in mobile phase at equivalent concentrations. The ratios were 91.6 ± 4.2% at low concentration and 95.6 ± 5.8% at high concentration. The same assay was preformed for the IS and the ratio was 96.9 ± 4.8%. These observations indicated that the matrix effect should not have a significant impact on assay performance.

Choosing the appropriate IS is important to get high accuracy and deal with sample matrix effects when LC/MS/MS is used for assay. Artemether and artemisinin were selected as the IS for the determination of DHA [11,13]. Based on our trials, artemether was eluted late and the retention time was 8.43 min under this chromatographic condition. Meanwhile, artemether can be converted to DHA *in vivo*, suggesting that it is not suitable to use artemether as IS. Therefore artemisinin was adopted as the IS since its chromatographic behavior and ionization properties are similar to DHA.

Table 1
Accuracy and precision for the analysis of DHA in QC samples (n = 3 days, five replicates per day).

Added concentration (ng/mL)	Found concentration (mean ± S.D.) (ng/mL)	Accuracy (%)	Precision (%)	
			Intra-day R.S.D.	Inter-day R.S.D.
3.03	2.93 ± 0.17	96.7	5.3	9.0
101	99.2 ± 6.4	98.2	6.5	6.4
1616	1502 ± 39	93.0	2.6	2.3

3.2. Method validation

3.2.1. Specificity

The specificity of the method was evaluated by analyzing individual blank plasma samples from six different sources. All samples were found to have no interferences from endogenous substances at the retention time of either the analyte or the IS. Typical chromatograms of a blank plasma, a spiked plasma sample with DHA and IS, and a plasma sample from a subject are shown in Fig. 3.

3.2.2. Calibration curve, linearity and LLOQ

The calibration curve was constructed by plotting the peak area ratios (y) of DHA to IS versus the plasma concentrations (x) of DHA. Good linearity was exhibited over the concentration range of 1.01–2020 ng/mL with correlation coefficients $r > 0.996$. A typical equation of the calibration curve was $y = (6.17 \times 10^{-3})x - (6.79 \times 10^{-4})$, $r = 0.9976$.

The LLOQ was established at 1.01 ng/mL, which was sensitive enough for pharmacokinetic study of DHA in human. The precision and accuracy at this concentration level was acceptable, with 7.2% of the R.S.D. and 99.2% of the accuracy.

3.2.3. Accuracy and precision

The intra- and inter-day precision and accuracy of the assay were investigated by analyzing QC samples (3.03, 101 and 1616 ng/mL). All the values are shown in Table 1. Intra-day R.S.D. was below 6.5% and inter-day R.S.D. was below 9.0%. The accuracy was within 93.0–98.2%. The method was proved to be highly accurate and precise.

Since samples may be diluted when the measured concentration of a sample is above the standard curve, the accuracy and precision of dilution were assessed using five replicates dilution QC samples prepared at a concentration of 5050 ng/mL and diluted 10-fold. The precision (R.S.D.) was 3.9% and the accuracy was 106.0%, demonstrating good reproducibility of results when sample dilutions are needed.

3.2.4. Recovery and stability

The clean-up of the plasma samples was achieved through a simple single-step liquid–liquid extraction (LLE) with ethyl acetate. Solid-phase extraction (SPE) was used in previous methods [5,11], but it was limited by the expensive cost of the apparatus and instrumentation. Many different mixtures of organic solvents including n-butyl chloride–ethyl acetate (9:1, v/v), l-chlorobutane–isooctane (55:45, v/v), hexane–ethyl acetate (8:2, v/v) have been reported for extracting DHA and ART from plasma [6,7,9]. Recently, Van Quekelberghe et al. [12] used ethyl acetate as the extraction solvent, but the extracting procedure was very complicated and labor-intensive. In this method, the plasma sample was only extracted one time (single-step extraction), which can significantly simplify the sample preparation procedure and also meet the requirement of recovery for the assay. The extraction recoveries of DHA were 70.3 ± 4.2, 70.9 ± 3.4 and 79.4 ± 2.9% at three concentrations of 3.03, 101 and 1616 ng/mL, respectively. While the recovery of the IS was 80.8 ± 2.5%. These results suggested that the recovery of DHA and the IS was consistent and was not concentration-dependent.

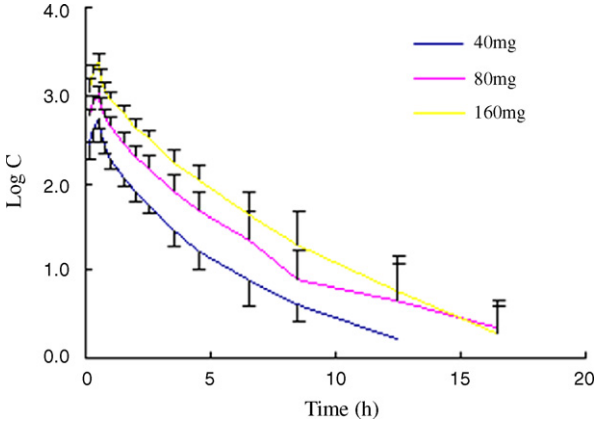

Fig. 4. Mean log(plasma concentration)–time curves of DHA in Chinese healthy subjects following single dose of DHA injectable powder 40 (n = 8), 80 and 160 mg (n = 10, mean ± S.D.).

It was previously reported that DHA in plasma appeared to be stable when stored at −80 °C for at least 60 days [11] and −20 °C for 4 months [13]. The mean recoveries of QC samples were 101.3, 93.7 and 89.9% for the low, mid and high concentrations, which indicated that DHA was stable in plasma samples at room temperature for at least 6 h. Plasma samples were also stable over three freeze–thaw cycles in terms of mean recoveries (88.1, 91.4 and 94.7%). DHA in the ready-to-inject samples was stable at room temperature for 6 h at least with no significant loss (the mean recoveries were 101.0, 102.7 and 91.9%, respectively). Take all the points into consideration, DHA can be stored and extracted under routine laboratory conditions without special attention.

3.3. Pharmacokinetic study

Following single intravenous infusion of DHA injectable powder 40, 80 and 160 mg, the plasma DHA concentrations were successfully determined by using the LC/MS/MS method described above. The mean plasma concentration–time curves of DHA are shown in Fig. 4. The major pharmacokinetic parameters are reported in Table 2.

Over the DHA dose range studied, mean C_{max} and AUC increased in proportion to the doses. Mean values of $t_{1/2\lambda Z}$ seemed to be dose-independent and ranged from 1.69 to 1.92 h, which showed that

Table 2
Main pharmacokinetic parameters of DHA in Chinese healthy subjects following single dose of DHA injectable powder 40 (n = 8), 80 and 160 mg (n = 10, mean ± S.D.).

Parameter	40 mg	80 mg	160 mg
C_{max} (ng/mL)	561.5 ± 127.4	1080 ± 210	2533 ± 503
$t_{1/2\lambda Z}$ (h)	1.69 ± 0.52	1.88 ± 0.66	1.92 ± 0.53
AUC_{0-t} (ng h/mL)	575.6 ± 98.7	1370 ± 289	2893 ± 649
$AUC_{0-\infty}$ (ng h/mL)	585.3 ± 99.3	1379 ± 290	2903 ± 653
Vz (L)	170.1 ± 54.9	158.0 ± 44.8	154.1 ± 40.8
CL (L/h)	70.6 ± 15.2	60.4 ± 13.1	57.8 ± 13.5
MRT_{0-t} (h)	1.25 ± 0.30	1.60 ± 0.59	1.58 ± 0.32
$MRT_{0-\infty}$ (h)	1.41 ± 0.39	1.69 ± 0.64	1.63 ± 0.33

DHA was rapidly cleared from plasma. CL values were similar and had no significant differences ($P > 0.05$) among the three groups, as well as Vz and MRT. The results indicated that the pharmacokinetics of DHA fit the linear dynamic features in the dose range of 40–160 mg.

4. Conclusions

The optimized LC/MS/MS method was validated to guarantee a reliable determination of DHA in human plasma. Good linearity was observed over the wide range of 1.01–2020 ng/mL, the simplified sample pretreatment, the high sensitivity, selectivity, precision, accuracy and short retention time make the whole method suitable for related pharmacokinetic studies.

The method was successfully applied to determine DHA in human plasma, and the pharmacokinetic profiles of DHA were investigated for the first time in healthy subjects after single intravenous infusion of DHA injectable powder 40, 80 and 160 mg.

Acknowledgement

This study was supported by grants from National (grant number: 2006BAI14B07) "115" Key Technology Research and Development Program of China.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jchromb.2008.11.039.

References

[1] D.L. Klayman, Science 228 (1985) 1049.
[2] K.F. Ilett, B.T. Ethell, J.L. Maggs, T.M.E. Davis, K.T. Batty, B. Burchell, T.Q. Binh, L.T.A. Thu, N.C. Hung, M. Pirmohamed, B.K. Park, G. Edwards, Drug Metab. Dispos. 30 (2002) 1005.
[3] P.M. O'Neill, G.H. Posner, J. Med. Chem. 47 (2004) 2945.
[4] J.M. Grace, A.J. Aguilar, K.M. Trotman, T.G. Brewer, Drug Metab. Dispos. 26 (1998) 313.
[5] C.S. Lai, N.K. Nair, S.M. Mansor, P.L. Olliaro, V. Navaratnam, J. Chromatogr. B 857 (2007) 308.
[6] J. Karbwang, K. NA-Bangchang, P. Molunto, V. Banmairuroi, K. Congpuong, J. Chromatogr. B 690 (1997) 259.
[7] N. Sandrenan, A. Sioufi, J. Godbillon, C. Netter, M. Donker, C. van Valkenburg, J. Chromatogr. B 691 (1997) 145.
[8] C. Souppart, N. Gauducheau, N. Sandrenan, F. Richard, J. Chromatogr. B 774 (2002) 195.
[9] M. Rajanikanth, K.P. Madhusudanan, R.C. Gupta, Biomed. Chromatogr. 17 (2003) 440.
[10] S. Sabarinath, M. Rajanikanth, K.P. Madhusudanan, R.C. Gupta, J. Mass Spectrom. 38 (2003) 732.
[11] H. Naik, D.J. Murry, L.E. Kirsch, L. Fleckenstein, J. Chromatogr. B 816 (2005) 233.
[12] S.A.A. Van Quekelberghe, S.A. Soomro, J.A. Cordonnier, F.H. Jansen, J. Anal. Toxicol. 32 (2008) 133.
[13] X. Hong, T.L. Huang, S.Q. Mi, S.M. Ye, W.P. Ou, N.S. Wang, J. Instrum. Anal. 24 (2005) 46.