Journal of Chromatography B 1149 (2020) 122177

Contents lists available at ScienceDirect

Journal of Chromatography B

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

Bioanalytical method for the simultaneous quantification of irinotecan and its active metabolite SN-38 in mouse plasma and tissue homogenates using HPLC-fluorescence

Alejandra Martínez-Chávez[a,b,*], Hilde Rosing[a], Changpei Gan[b], Yaogeng Wang[b], Alfred H. Schinkel[b], Jos H. Beijnen[a,b,c]

[a] Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[b] Division of Pharmacology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[c] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Irinotecan
SN-38
Plasma
Tissue homogenates
HPLC-FL

ABSTRACT

A simple and rapid bioanalytical method was developed for the simultaneous quantification of irinotecan and SN-38 in mouse plasma and tissue homogenates using High-Performance Liquid Chromatography with Fluorescence detection (HPLC-FL). Camptothecin was used as internal standard and protein precipitation with acetonitrile-methanol (1:1, v/v) followed by acidification with 0.5 M hydrochloric acid was used for sample pre-treatment. The analytes and the internal standard were detected using an excitation and emission wavelength of 368 and 515 nm, respectively. The linearity, selectivity, accuracy and precision, carry-over, limit of detection and lower limit of quantification of the method are described. The method was linear from 7.5 to 1500 ng/mL for irinotecan and from 5 to 1000 ng/mL for SN-38. For all matrices, the accuracy bias and precision variation were within ± 15% and ≤15%, respectively. This method was successfully applied to study the pharmacokinetics of irinotecan and SN-38 using *in vivo* mouse models.

1. Introduction

Irinotecan (CPT-11) is an antineoplastic agent indicated to treat metastatic colorectal, pancreatic, ovarian, small and non-small cell lung cancer [1,2]. Irinotecan is the prodrug of SN-38, which binds to topoisomerase I, producing double-strand breaks in DNA and, therefore, causing cell death. Irinotecan is metabolized into SN-38 mainly by Carboxylesterase (CES) enzymes: CES1, which is strongly expressed in lung and liver, and CES2, mostly expressed in small intestine and kidneys [1,3,4]. Since the CES activity is related to irinotecan efficacy, it is important to clarify the role of each isoenzyme in the irinotecan metabolism.

In addition to predicting the efficacy, safety and toxicity, the quantitative analysis of irinotecan and SN-38 in plasma and tissue homogenates is essential to support either clinical or preclinical studies that provide more insights about this metabolic conversion. Some bioanalytical methods using LC-MS/MS or UHPLC-MS/MS have been described to quantify irinotecan and SN-38 in mouse plasma and tissue homogenates [5–7]. However, their major disadvantage is the necessity of a mass spectrometer, which is more expensive and delicate compared to other detectors. Additionally, the use of a stable isotope of the analyte is needed as an internal standard to correct for the variation in the detector. Despite the popularity of MS/MS detection in bioanalysis, fluorescence (FL) also offers a robust, highly selective, and sensitive detection, as well as fewer problems with instrument instability. In the past years, several bioanalytical assays using a fluorescence detection have been described for irinotecan and/or SN-38 in plasma of different species, but not in tissue homogenates [8–10].

The objective of this work is focused on the development and validation of a simple bioanalytical method using HPLC-FL to quantify simultaneously irinotecan and SN-38 in mouse plasma and tissue homogenates, including liver, kidney, lung, spleen, small intestine, and colon. This method was specifically set up to support preclinical pharmacokinetic experiments focused on the study of the metabolism of irinotecan by the CES enzymes and was applied to measure samples from mouse strains with different expression of these enzymes.

* Corresponding author at: Division of Pharmacology, Antoni van Leeuwenhoek – The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: d.martinez@nki.nl (A. Martínez-Chávez).

https://doi.org/10.1016/j.jchromb.2020.122177
Received 25 February 2020; Received in revised form 6 May 2020; Accepted 15 May 2020
Available online 19 May 2020

2. Materials and methods

2.1. Chemicals and reagents

Irinotecan HCl, SN-38 and camptothecin were obtained from Sigma Aldrich (Darmstadt, Germany). Dimethylsulfoxide (DMSO, SeccoSolv), hydrochloric acid, ammonium acetate and acetic acid glacial (all EMSURE® grade) were from Merck (Darmstadt, Germany). Water (LC-MS grade), acetonitrile (MeCN) and methanol (both HPLC supra-gradient) were provided by Biosolve Ltd (Valkenswaard, The Netherlands).

Control human K_2EDTA plasma originated from BioIVT (Hicksville, NY, USA). Mouse plasma and tissues (liver, kidneys, small intestine, colon, spleen, and lungs) were collected from the animal laboratory of the Netherlands Cancer Institute (Amsterdam, The Netherlands). Tissues were homogenized in the Fast Prep-24™ 5G (MP Biomedicals Inc, Santa Ana, California, USA) using 4% bovine serum albumin (BSA) in water. 3 mL of this solution was added to liver and small intestine, 2 mL to kidneys and lungs, and 1 mL to colon and spleen.

2.2. Stock and working solutions

An independent stock solution from each analyte at 1 mg/mL in DMSO was used for the preparation of working solutions of calibration standards in the concentration range from 150 to 30,000 ng/mL and 100 to 20,000 ng/mL for irinotecan and SN-38, respectively. A second stock solution from each analyte (1 mg/mL in DMSO) was used for the working solutions of quality control samples, which were prepared at 450, 3000 and 20,000 ng/mL for irinotecan, and at 300, 2000 and 15,000 ng/mL for SN-38. All working solutions were prepared in water:MeCN (1:1, v/v).

2.3. Calibration standards and quality control samples

Six non-zero calibration standards were prepared in the range from 7.5 to 1500 ng/mL for irinotecan and from 5 to 1000 ng/mL for SN-38, by diluting working solutions 20-fold with control human plasma. A blank (control matrix spiked with IS) and a double blank (control matrix) were also prepared.

Quality control samples were prepared at three concentration levels: low (QC L), medium (QC M) and high (QC H), by diluting 20-fold the correspondent working solutions in control human plasma, resulting in concentrations of 22.5, 150 and 1000 ng/mL for irinotecan, and 15, 100 and 750 ng/mL for SN-38.

2.4. Internal standard

Camptothecin (CPT), a molecule with an analogue structure, was used as an internal standard (IS) and dissolved in DMSO to prepare a stock solution of 50 μg/mL. It was further diluted up to 100 ng/mL with MeCN:MeOH (1:1 v/v) for the working solution.

2.5. Sample pretreatment

For plasma samples an aliquot of 50 μL was used for the pretreatment, then 100 μL of the working solution of the internal standard was added followed by 100 μL of MeCN:MeOH (1:1 v/v), except for the double blanks to which 200 μL of MeCN:MeOH (1:1 v/v) was added. For tissue homogenate samples (prepared as described in section 2.1) an aliquot of 100 μL was used for the pretreatment and the reagents were added in the same ratio as explained above. After vortex mixing and centrifugation of the samples (23,100 g and 4 °C for 10 min), 100 μL of supernatant was acidified with 10 μL of 0.5 M HCl. Subsequently, samples were vortex mixed again and transferred to a vial. 10 μL of the final extract was injected into the HPLC-FL system for analysis.

2.6. HPLC-FL system

An Agilent 1100 chromatograph (Palo Alto, CA, USA) was used, which consisted of a binary pump, a degasser, an autosampler and a column oven (Models G1312A, G1379A, G1367A, G1316A, respectively). To achieve the chromatographic separation, a Zorbax SB C18 column (150 × 2.1 mm ID, 5 μm) protected by a C18 (4 × 2 mm) guard column (Phenomenex, Torrance, CA, USA) was used. Analytes were eluted using 20 mM ammonium acetate in water pH 3.5 (eluent A) and acetonitrile (eluent B) at a flow rate of 0.3 mL/min. A modified gradient program from Guo *et al.* was used for the elution of the analytes: initially eluent B was kept at 25% for 2.7 min, in 2.3 min B increased to 29%, in 2 min B increased to 66%, in 1 min B increased to 90%, and it was kept for 0.5 min. At 8.5 min, B decreased from 90% to the initial conditions (25%) in 0.5 min, and it was maintained for 3 min to condition the analytical column [11]. The temperatures of the autosampler and oven were set at 6 and 35 °C, respectively. The Jasco FP-920 E fluorescence detector (Easton, Maryland, USA) with a 16 μL flow cell was used to monitor the analytes and the internal standard with the following settings: the emission band width was set at 40 nm, for the filter response settings a CR (analog) filter was selected with a slow (SLW) response, and a gain of 100 was selected. The excitation and emission wavelengths were, respectively, 368 and 515 nm to detect irinotecan, SN-38 and CPT.

2.7. Method validation

A partial validation of the method was performed, where the linearity, limit of detection (LOD), lower limit of quantification (LLOQ), selectivity, carry-over, accuracy and precision were evaluated.

Linearity was determined using the 6 non-zero calibration standards prepared as described in 2.4, which were prepared and analyzed in duplicate in at least three analytical runs. The concentration–response correlation for both analytes was described using a linear regression with a 1/x weighting factor (x = analyte concentration).

To determine the selectivity, at least one batch from each blank matrix was evaluated for interferences at the analytes and IS retention times. LOD and LLOQ were determined based on the signal-to-noise ratio.

Carry-over was tested in at least three analytical runs, where two double blank samples were injected after the upper limit of quantification (ULOQ). The response obtained at the retention time of each analyte in the double blanks was compared to the LLOQ response of each analyte.

Intra- and inter-assay accuracy and precision were evaluated in control human plasma at three concentration levels (QC L, QC M and QC H). For mouse matrices, accuracy and precision was tested in one day at one concentration level 300 and 200 ng/mL for irinotecan and SN-38, respectively. These spiked samples were quantified using calibration standards in human plasma. The bias between the nominal and measured concentrations within- and between-run was determined to evaluate the accuracy. ANOVA was used to determine the within- and between-run precision of the method at each concentration level according to the following formulas:

$$\textit{Within-run precision} = \frac{\sqrt{MS_W}}{M} x100\%$$

$$\textit{Between-run precision} = \frac{\sqrt{\frac{MS_B - MS_W}{n}}}{M} x100\%$$

where, MS_W is the within-run mean square, MS_B is the between-run mean square, M is the mean of all measured concentrations, and n is the number of determinations per group [12].

2.8. Applicability of the method

This method was developed to support preclinical investigation of the irinotecan conversion into SN-38 by CES enzymes in mouse models (unpublished data). Animal housing and mouse studies were conducted according to institutional guidelines complying with Dutch and European Union legislation. All experiments were approved by the institutional board for the care and use of laboratory animals. Irinotecan HCl trihydrate was intravenously or orally administered at a dose of 20 mg/kg. After intravenous administration of irinotecan, blood was collected from the tip of the tail at several time points (0.125, 0.25, 0.5, 1 and 2 h) in heparin-coated tubes. Prior the last time point at 4 h, mice were anaesthetized with isoflurane, and blood was collected by cardiac puncture. In a separate experiment, irinotecan was orally administered to mice; prior to organ collection, mice were sacrificed by cervical dislocation and the tissues (liver, kidneys, small intestine, colon, spleen and lungs) were collected and weighed. Tissues were homogenized as described in 2.1. Blood samples were centrifuged (9000g, 4 ˚C, for 6 min) to obtain plasma. To complete the volume needed for the sample pretreatment, 10 µL of mouse plasma was diluted with 40 µL of control human plasma, when necessary.

3. Results and discussion

3.1. HPLC-FL method development

Irinotecan and SN-38 are determined in this bioanalytical method after acidifying the final extract with 0.5 M HCl to favor the conversion to the lactone ring. Irinotecan and SN-38 molecules have a lactone ring which can be reversible hydrolyzed into a carboxylate form (Fig. 1). This hydrolysis depends mainly on pH: at pH less than 5 the lactone form is favored, while at pH > 9 the carboxylate form is formed [2,13,14]. Only the lactone form can bind the topoisomerase I, however, it has been previously described that the quantification of the lactone and carboxylate forms (total irinotecan and SN-38), is as clinically relevant as the quantification of the lactone form, since the pharmacokinetics of both forms is correlated [2,15,16].

3.2. Method validation

The typical chromatograms obtained after spiking the analytes and internal standard in human plasma at the lower and upper limit of quantification are shown in Fig. 2 (A and B, respectively). The resolution between the peaks was always > 2.5 between irinotecan and SN-38 and > 1.5 between SN-38 and camptothecin.

The selectivity of the method was evaluated in all the previously described matrices. In Fig. 2 C-J the chromatograms obtained with blank matrices are shown, where no interferences were observed at the retention times of the analytes. The method was selective for all the matrices tested, since no peaks were detected at the retention times of the analytes.

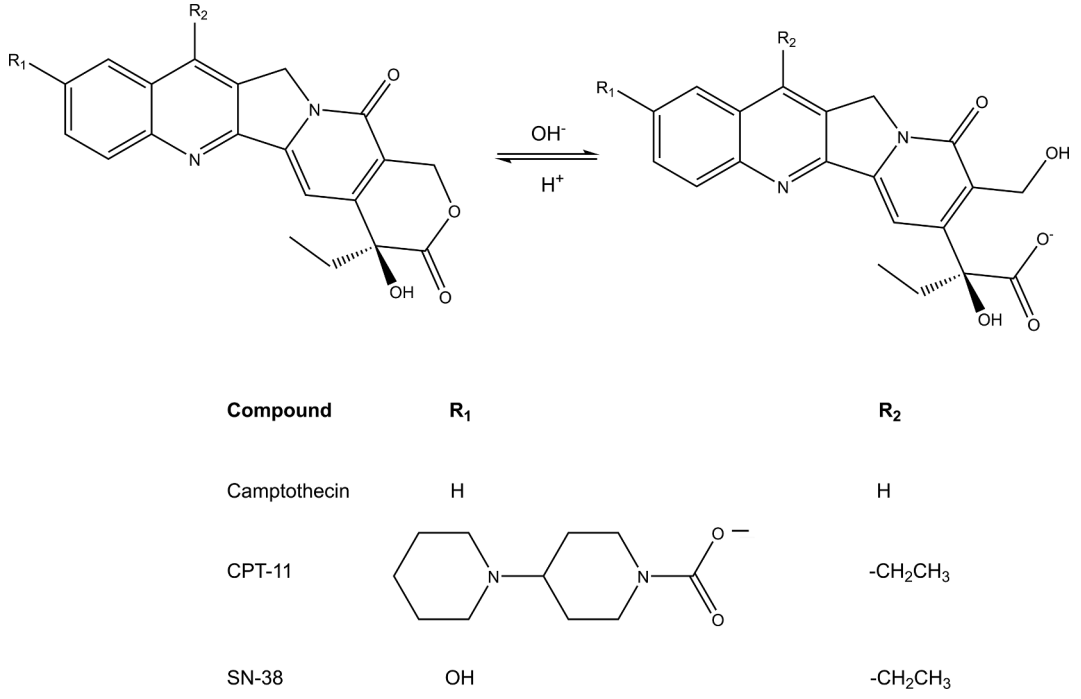
The LOD and the LLOQ for irinotecan were 1.3 and 7.5 ng/mL, respectively, and for SN-38 1.7 and 5 ng/mL, respectively. Both parameters were estimated based on the signal-to-noise ratio (S/N) for each analyte. The LOD was calculated considering a S/N ≥ 3 and the LLOQ was selected considering a S/N of at least ≥ 5; for both analytes the bias of the back-calculated concentration was within ± 20% of the nominal concentrations.

The calibration range for irinotecan and SN-38 was selected as wide as possible due to the high variability in the study samples. It was limited by the capacity of the fluorescence detector, which is based on the S/N ratio for the LLOQ and the signal saturation for the irinotecan ULOQ. The calibration curves for both analytes were linear using a weighting factor of 1/x in the range of 7.5–1500 ng/mL for irinotecan and 5–1000 ng/mL for SN-38. The correlation coefficient of the calibration model was 0.9988 for irinotecan and 0.9993 for SN-38.

No peak was detected in the double blank samples injected after the ULOQ, neither for irinotecan nor for SN-38, therefore there was not carry-over for the established concentration ranges.

The intra- and inter-assay accuracy and precision of this method is shown in Table 1, where the bias and the coefficient of variation were within ± 15% and ≤ 15%, respectively for both analytes. The accuracy and precision obtained for the mouse matrices are summarized in Table 2, where all the results met the criteria previously mentioned.

Prior experiments indicate that approximately 85.8% of irinotecan and 102% of SN-38 are recovered after processing human plasma



Compound	R_1	R_2
Camptothecin	H	H
CPT-11		$-CH_2CH_3$
SN-38	OH	$-CH_2CH_3$

Fig. 1. Chemical structures (lactone and carboxylate forms) of irinotecan (CPT-11), SN-38 and camptothecin.

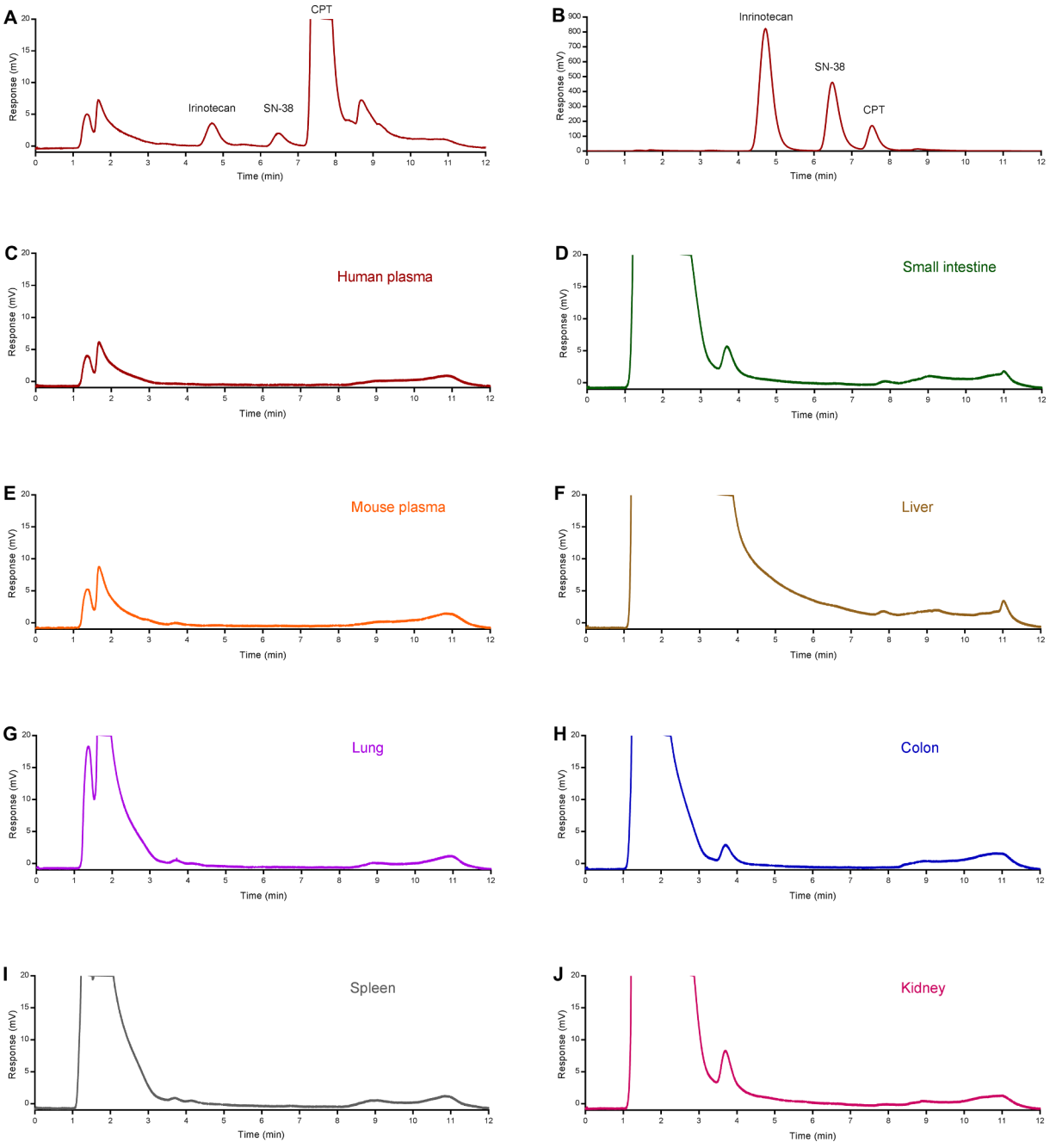


Fig. 2. Representative chromatograms of human plasma spiked with irinotecan, SN-38 and the internal standard at the LLOQ (A) and ULOQ (B). Chromatograms obtained after processing blank samples from different matrices (C-J).

Table 1
Intra- and inter-assay precision and accuracy for irinotecan and SN-38 in human plasma.

Analyte	Nominal concentration (ng/mL)	Intra-assay (n = 3)		Inter-assay (n = 25 in 10 analytical batches)	
		Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)
Irinotecan	22.5	−3.2	3.3	−8.3	4.5
	150	4.6	2.8	−7.7	6.3
	1000	2.0	2.8	−0.8	2.2
SN-38	15	−4.0	5.0	−4.8	1.8
	100	0.9	1.4	−5.7	3.8
	750	2.8	1.5	−0.4	2.6

Table 2
Accuracy and precision in mouse matrices (n = 3, one analytical batch).

Matrix	Irinotecan (nominal concentration 300 ng/mL)		SN-38 (nominal concentration 200 ng/mL)	
	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)
Mouse plasma	13.5	1.5	3.7	0.7
Liver homogenate	−1.5	2.5	3.6	0.7
Kidney homogenate	0.2	0.3	4.1	0.9
Spleen homogenate	8.6	0.9	6.8	2.3
Small intestine homogenate	7.5	3.1	2.6	1.4
Colon homogenate	10.5	5.0	5.2	5.8
Lung homogenate	10.6	1.4	4.3	0.6

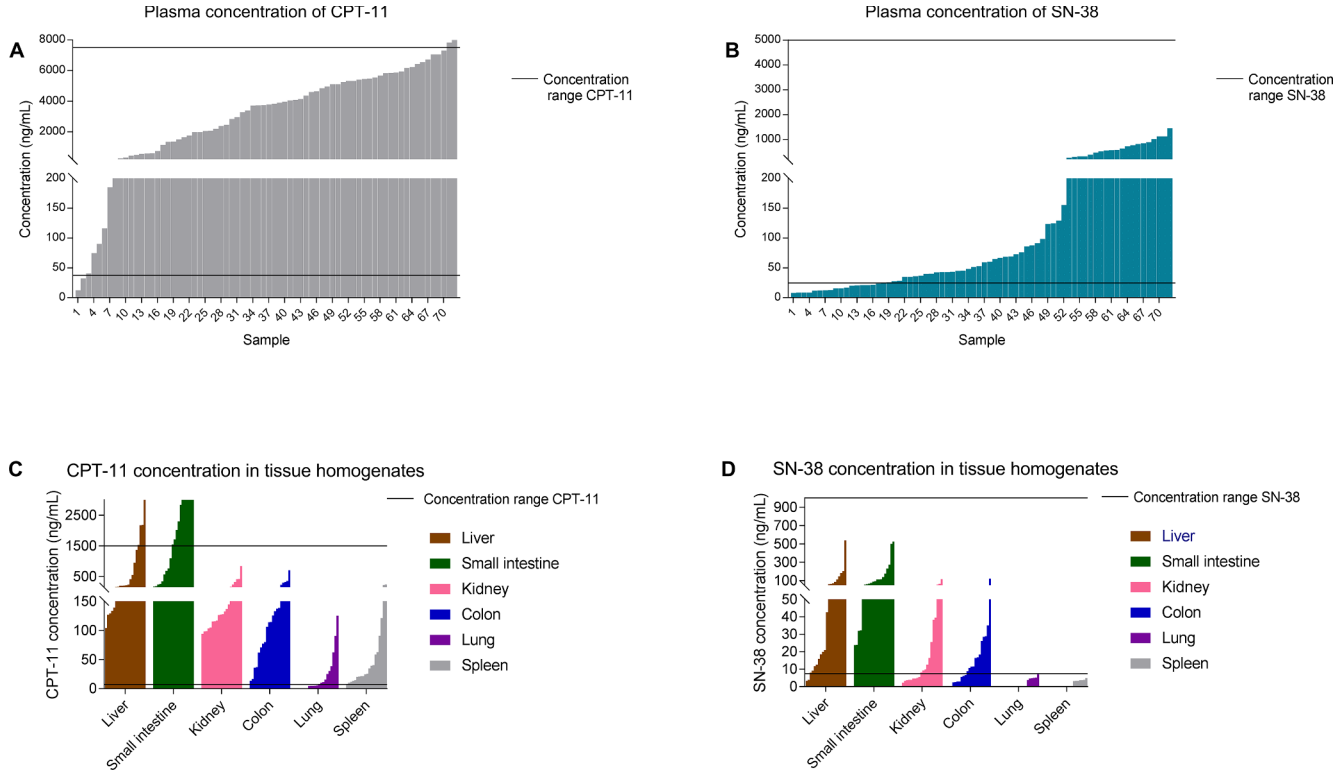


Fig. 3. Measured concentrations of irinotecan (CPT-11) and SN-38 (ng/mL) in mouse plasma samples (A-B), and tissue homogenates (C-D).The concentration range of the bioanalytical method is indicated in the graphs with a black line; for plasma samples the dilution factor (5x) is considered in the indicated range.

samples with the described sample pre-treatment at concentrations within the calibration range.

3.3. Application of the method

This bioanalytical method developed was used to support *in vivo* studies of the conversion of irinotecan into SN-38 by CES enzymes. Fig. 3 shows the measured concentrations in each matrix. Plasma samples were diluted 1:5 (v/v) to complete the sample volume required for the pre-treatment. The calibration ranges included for mouse plasma are corrected for this dilution factor (Fig. 3A, B). Fig. 3C and D show the measured concentrations in each tissue homogenate for irinotecan and SN-38, respectively. Most of the measured samples fit in the calibration range for both compounds. Irinotecan was abundant in liver and small intestine homogenate samples, in some of them the concentration of irinotecan was above the ULOQ, where it was necessary to dilute the samples to properly quantify it. Lung homogenates showed low concentrations for irinotecan, where 30% of the samples were below the LLOQ and above the LOD, and 25% were below the LOD. For SN-38, none of the samples exceeded the ULOQ. For most matrices the concentration of SN-38 was within the calibration range, except for lung and spleen homogenates, where SN-38 had a very low distribution and this was reflected in the negligible measured concentrations (Fig. 3D). For the other matrices there was a high difference in SN-38 concentration among the measured samples (Fig. 3D), showing that this method is useful for either normal or negligible conversion of irinotecan into SN-38.

4. Conclusions

A bioanalytical assay for irinotecan and SN-38 in plasma and tissue homogenates using HPLC-FL is described. We showed that this method is linear, accurate, precise, selective and sensitive to simultaneously measure the total irinotecan and SN-38 in mouse plasma and tissue homogenate samples using human plasma as a surrogate matrix. This method was successfully applied to study the conversion of irinotecan into SN-38 *in vivo*.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors thank the Mexican National Council for Science and Technology (CONACyT) for the scholarship awarded to A. Martínez-Chávez (No. 440476).

References

[1] F.M. de Man, A.K.L. Goey, R.H.N. van Schaik, R.H.J. Mathijssen, S. Bins, Individualization of Irinotecan Treatment: A Review of Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics, Clin. Pharmacokinet. (2018), https://doi.org/10.1007/s40262-018-0644-7.

[2] R. Mullangi, P. Ahlawat, N.R. Srinivas, Irinotecan and its active metabolite, SN-38: Review of bioanalytical methods and recent update from clinical pharmacology perspectives, Biomed. Chromatogr. 24 (2010) 104–123, https://doi.org/10.1002/bmc.1345.

[3] T. Satoh, M. Hosokawa, Carboxylesterases: Structure, function and polymorphism, Biomol. Ther. 17 (2009) 335–347, https://doi.org/10.4062/biomolther.2009.17.4.335.

[4] R. Humerickhouse, K. Lohrbach, L. Li, W.F. Bosron, M.E. Dolan, Characterization of CPT-11 hydrolysis by human liver carboxylesterase isoforms hCE-1 and hCE-2, Cancer Res. 60 (2000) 1189–1192.

[5] S. Bardin, W. Guo, J.L. Johnson, S. Khan, A. Ahmad, J.X. Duggan, J. Ayoub, I. Ahmad, Liquid chromatographic-tandem mass spectrometric assay for the simultaneous quantification of Camptosar® and its metabolite SN-38 in mouse plasma and tissues, J. Chromatogr. A. 1073 (2005) 249–255, https://doi.org/10.1016/j.chroma.2004.08.060.

[6] S. Basu, M. Zeng, T. Yin, S. Gao, M. Hu, Development and validation of an UPLC-MS/MS method for the quantification of irinotecan, SN-38 and SN-38 glucuronide in plasma, urine, feces, liver and kidney: Application to a pharmacokinetic study of irinotecan in rats, J. Chromatogr. B Anal. Technol. Biomed, Life Sci. 1015–1016 (2016) 34–41, https://doi.org/10.1016/j.jchromb.2016.02.012.

[7] S. Khan, A. Ahmad, W. Guo, Y.F. Wang, A. Abu-Qare, I. Ahmad, A simple and sensitive LC/MS/MS assay for 7-ethyl-10-hydroxycamptothecin (SN-38) in mouse plasma and tissues: Application to pharmacokinetic study of liposome entrapped SN-38 (LE-SN38), J. Pharm. Biomed. Anal. 37 (2005) 135–142, https://doi.org/10.1016/j.jpba.2004.09.053.

[8] N. Taneja, V. Gota, M. Gurjar, K.K. Singh, Development and validation of high-performance liquid chromatographic method for quantification of irinotecan and its active metabolite SN-38 in colon tumor bearing NOD/SCID mice plasma samples: Application to pharmacokinetic study, Acta Chromatogr. 31 (2019) 166–172, https://doi.org/10.1556/1326.2018.00370.

[9] F. D'Esposito, B.N. Tattam, I. Ramzan, M. Murray, A liquid chromatography/electrospray ionization mass spectrometry (LC-MS/MS) assay for the determination of irinotecan (CPT-11) and its two major metabolites in human liver microsomal incubations and human plasma samples, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 875 (2008) 522–530, https://doi.org/10.1016/j.jchromb.2008.10.011.

[10] X. Yang, Z. Hu, Y.C. Sui, B.C. Goh, W. Duan, E. Chan, S. Zhou, Simultaneous determination of the lactone and carboxylate forms of irinotecan (CPT-11) and its active metabolite SN-38 by high-performance liquid chromatography: Application to plasma pharmacokinetic studies in the rat, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 821 (2005) 221–228, https://doi.org/10.1016/j.jchromb.2005.05.010.

[11] W. Guo, A. Ahmad, S. Khan, F. Dahhani, Y.F. Wang, I. Ahmad, Determination by liquid chromatography with fluorescence detection of total 7-ethyl-10-hydroxy-camptothecin (SN-38) in beagle dog plasma after intravenous administration of liposome-based SN-38 (LE–SN38), Journal of Chromatography B 791 (1-2) (2003) 85–92, https://doi.org/10.1016/S1570-0232(03)00210-1.

[12] H. Rosing, M.J.X. Hillebrand, J.M. Jimeno, A. Gómez, P. Floriano, G. Faircloth, L. Cameron, R.E.C. Henrar, J.B. Vermorken, A. Bult, J.H. Beijnen, Analysis of ecteinascidin 743, a new potent marine-derived anticancer drug, in human plasma by high-performance liquid chromatography in combination with solid-phase extraction, J. Chromatogr. B Biomed. Appl. 710 (1998) 183–189, https://doi.org/10.1016/S0378-4347(98)00143-1.

[13] J. Fassberg, V.J. Stella, A Kinetic and Mechanistic Study of the Hydrolysis of Camptothecin and Some Analogues, J. Pharm. Sci. 81 (1992) 676–684.

[14] G. Boyd, J.F. Smyth, D.I. Jodrell, J. Cummings, High-Performance Liquid Chromatographic Technique for the Simultaneous Determination of Lactone and Hydroxy Acid Forms of Camptothecin and SN-38 in Tissue Culture Media and Cancer Cells, Anal. Biochem. 297 (2001) 15–24, https://doi.org/10.1006/abio.2001.5317.

[15] L.P. Rivory, E. Chatelut, P. Canal, A. Mathieu-Boué, J. Robert, Kinetics of the in Vivo Interconversion of the Carboxylate and Lactone Forms of Irinotecan (CPT-11) and of Its Metabolite SN-38 in Patients, Cancer Res. 54 (1994) 6330–6333, https://doi.org/10.1016/0959-8049(95)96205-R.

[16] L.P. Rivory, J. Robert, Reversed-phase high-performance liquid chromatographic method for the simultaneous quantitation of the carboxylate and lactone forms of the camptothecin derivative irinotecan, CPT-11, and its metabolite SN-38 in plasma, J. Chromatogr. B Biomed. Sci. Appl. 661 (1994) 133–141, https://doi.org/10.1016/0378-4347(94)00340-8.