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Measurement of paclitaxel and its metabolites in human plasma using liquid chromatography/ion trap mass spectrometry with a sonic spray ionization interface

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A quantitative liquid chromatography/ion trap mass spectrometry method for the simultaneous determination of paclitaxel, 6α-hydroxypaclitaxel and *p*-3′-hydroxypaclitaxel in human plasma has been developed and validated. 6α-,*p*-3′-Dihydroxypaclitaxel was also quantified using paclitaxel as a reference and docetaxel as an internal standard. The substances were extracted from 0.500 mL plasma using solid-phase extraction. The elution was performed with acetonitrile and the samples were reconstituted in the mobile phase. Isocratic high-performance liquid chromatography analysis was performed by injecting 50 μL of reconstituted material onto a 100 × 3.00 mm C12 column with a methanol:1% trifluoroacetic acid/ammonium trifluoroacetate in H_2O 70:30 mobile phase at 350 μL/min. The $[M+H]^+$ ions generated in the sonic spray ionization interface were isolated and fragmented using two serial mass spectrometric methods: one for paclitaxel (transition 854 → 569 & 551) and the dihydroxymetabolite (transition 886 → 585 & 567) and one for the hydroxy metabolites (transition 870 → 585 & 567; transition 870 → 569 & 551) and docetaxel ($[M+Na]^+$, transition 830 → 550). Calibration curves were created ranging between 0.5 and 7500 ng/mL for paclitaxel, 0.5 and 750 ng/mL for 6α-hydroxypaclitaxel, and 0.5 and 400 ng/mL for *p*-3′-hydroxypaclitaxel. Adduct ion formation was noted and investigated during method development and controlled by mobile phase optimization. In conclusion, a sensitive method for simultaneous quantification of paclitaxel and its metabolites suitable for analysis in clinical studies was obtained. Copyright © 2006 John Wiley & Sons, Ltd.

Paclitaxel (Taxol®) is an anticancer drug with a broad spectrum of antitumor activity, including breast, ovarian, skin and lung cancer.[1] It was originally isolated from the Pacific yew tree, *Taxus brevifolia*,[2] and, together with the drug docetaxel, represents the antineoplastic taxanes. The taxanes have a unique mechanism of action among chemotherapeutic agents in that the drugs facilitate the formation and suppress the depolymerization of microtubules. Exposed cells are blocked in the G2/M phase in the cell cycle and eventually undergo apoptosis.[3,4] Paclitaxel also induces apoptosis directly, but this may be a result of different mechanisms at different drug concentrations.[5]

Paclitaxel is primarily metabolized in the liver by the cytochrome P450 (CYP) enzymes, CYP3A4 and CYP2C8. CYP3A4 metabolizes paclitaxel to *p*-3′-hydroxypaclitaxel and CYP2C8 converts the drug into 6α-hydroxypaclitaxel and these metabolites can be further oxidized to 6α-,*p*-3′-dihydroxypaclitaxel.[6] Other metabolites have been identified in smaller quantities.[7] Studies have shown that the major portion of unchanged paclitaxel and its metabolites are excreted in the feces, indicating extensive nonrenal clearance.[8] However, only paclitaxel has been shown to be toxic and to have an antitumor activity while its metabolites are considered to be inactive.[9]

Since the beginning of the 1990s, when Taxol was introduced as an anticancer drug,[10] an extensive number of pharmacokinetic studies have been done on the substance. These studies have resulted in the development of several different methods for quantification of paclitaxel in biological samples. The concentrations of paclitaxel and its metabolites in human plasma are measured preferably by high-performance liquid chromatography (HPLC) or liquid chromatography/mass spectrometry (LC/MS),[11] although other techniques have also been reported. Immunological methods such as enzyme-linked immunosorbent assay (ELISA)[12] and radioimmunoassay[13] have been used to screen human plasma, but these methods have a major drawback of cross reactions. Most frequently used are HPLC systems with UV-detection, although other chromatography techniques, e.g. capillary electrophoresis[14] and methods

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using other detectors, e.g. fluorescence detectors,[15] have also been reported.

Several developments in the use of paclitaxel have led to lower plasma concentrations of the drug and the need for more sensitive assays. First of all, clinicians have begun to investigate weekly therapy as an alternative to the every-three-week administration schedule, with a reduction of dose as a result.[16] In the development of new chemotherapeutic regimens where paclitaxel is used in combination with other drugs, the dose is often less than the recommended phase II dose. In addition, the investigation of individualization of chemotherapy has also led to the need for more accurate techniques. The relative lack of sensitivity and specificity of the HPLC methods with UV-detection[17] has led to the development of methods using mass spectrometry and multiple MS for detection of the substances.[17–31] Recent reports have described paclitaxel quantifications based on LC/MS/MS instrumentation. Several different extraction methods, mobile phases, columns, interfaces and MS instruments have been used. However, most of these methods were developed for paclitaxel only and not for the metabolites. For our purposes of trying to predict individual elimination of paclitaxel in cancer patients by investigating factors affecting the extent of conversion by each metabolic enzyme, we needed an accurate and sensitive method for quantification of paclitaxel and its metabolites in human plasma.

The aim of our study was to develop an LC/MS method for simultaneous quantification of paclitaxel and its metabolites in human plasma. To our knowledge, this is the first method for quantification of paclitaxel, 6α-hydroxypaclitaxel, *p*-3′-hydroxypaclitaxel and *p*-3′-,6α-dihydroxypaclitaxel in human plasma using ion trap mass spectrometry (ITMS) with a sonic spray ionization (SSI) interface.

EXPERIMENTAL

Materials

Paclitaxel ($C_{47}H_{51}NO_{14}$) was kindly supplied by Bristol-Myers Squibb (Wallingford, CT, USA). *p*-3′- Hydroxypaclitaxel ($C_{47}H_{51}NO_{15}$) and 6α-hydroxypaclitaxel ($C_{47}H_{51}NO_{15}$) were purchased from Gentest (Woburn, MA, USA) through BD Biosciences. Docetaxel ($C_{43}H_{53}NO_{14}$) was kindly supplied by Aventis Pharma (Vitry Alforville, France) and used as an internal standard. HPLC-grade methanol, acetonitrile and hexane were from LabScan Analytical Sciences (Dublin, Ireland). Ethanol was from Kemetyl (Stockholm, Sweden). Water was obtained from a Milli-Q Biocell station (Millipore AB, Stockholm, Sweden). Trifluoroacetic acid (TFA) was from Sigma (Stockholm, Sweden). Human plasma was delivered from the blood bank of Linköping University Hospital.

Instrumentation

The LC/MS system consisted of a LaChrome chromatograph (pump model L-7100, autosampler L-7200, UV detector L-7400 and an interface model D-7000) with a Merck-Hitachi M-8000 LC/MS^n (ion trap) equipped with a SSI interface from Merck KgaA (Darmstadt, Germany). The system was controlled using a computer equipped with the Chromatography Data Station software LC/3DQ MS System Manager from Merck (Darmstadt, Germany) and Hitachi Instruments Inc. (San Jose, CA, USA). An infusion pump (model 11; Harvard Apparatus, Holliston, MA, USA) was connected to the system during some steps in the optimization. The analytical column was a Synergi 4 μ Max-RP 80A (100 × 3.00 mm; Phenomenex, CA, USA) and a guard column (4 × 3.0 mm) with the same stationary phase was used.

Preparation of stock solutions and plasma samples

Paclitaxel was dissolved in methanol to a concentration of 20 mg/mL, and further diluted in methanol to give stock solutions in the range of 0.2–200 μg/mL using glass pipettes. The internal standard docetaxel was dissolved in ethanol to a concentration of 20 mg/mL and diluted to 20 μg/mL. *p*-3′-Hydroxypaclitaxel and 6α-hydroxypaclitaxel were dissolved in acetonitrile and methanol, respectively, to give approximate concentrations of 20 μg/mL. Due to the high inaccuracy of the manufacturer's quantity determination, the concentrations were determined using absorption spectroscopy. The absorbance was measured at 227 nm for paclitaxel and 230 nm for the other substances. The following molar extinction coefficients were used: 29.8 $mM^{-1}\,cm^{-1}$ for paclitaxel, 14.8 $mM^{-1}\,cm^{-1}$ for docetaxel, 35.8 $mM^{-1}\,cm^{-1}$ for *p*-3′-hydroxypaclitaxel, and 26.2 $mM^{-1}\,cm^{-1}$ for 6α-hydroxypaclitaxel (according to the manufacturer's documentation).

Standards were prepared by diluting the stock solutions in human drug-free plasma. Nine different standards (denoted STD1–STD9) were prepared with the following concentrations 0.5, 2, 5, 10, 50, 250, 1000, 4000, and 7500 ng/mL of paclitaxel; 0.5, 2, 5, 10, 25, 50, 100, 250, and 750 ng/mL of 6α-hydroxypaclitaxel; and 0.5, 2, 5, 10, 25, 50, 100, 200, and 400 ng/mL of *p*-3′-hydroxypaclitaxel. The standard concentrations were based on the concentrations found in human plasma after a dose of 175 mg/m^2 paclitaxel infused during 3 h.

Five different quality control (QC) samples (denoted QC1–QC5) were prepared with the following concentrations: 8, 100, 300, 1500, and 5000 ng/mL of paclitaxel; 8, 20, 40, 80, and 400 ng/mL of 6α-hydroxypaclitaxel; and 8, 20, 40, 80, and 300 ng/mL of *p*-3′-hydroxypaclitaxel.

Solid-phase extraction

The solid-phase extraction (SPE) procedure was adopted from Huizing *et al.*,[32] with modifications. Prior to extraction, the tips in the vacuum box were washed in acetonitrile to minimize crossover. The CN solid phase (100 mg, 1 mL; Isolute, IST UK) columns were conditioned with 2 mL methanol and 2 mL 10 mM ammonium acetate buffer, pH 5.0. Then, 500 μL of spiked plasma were mixed with an equal volume of 0.2 M ammonium acetate, pH 5.0, and 50 μL of internal standard (20 μg/mL) and applied to the column. The columns were washed with 2 mL of 10 mM ammonium acetate and 1 mL of methanol/10 mM ammonium acetate, 20:80, and finally with 1 mL of hexane. Prior to and after the hexane wash, the columns were dried for a minimum of 2 min. The samples were eluted in 2 mL of acetonitrile and evaporated under a stream of nitrogen at 35°C. The analytes were reconstituted in 200 μL mobile phase and sonicated for 5 min to ensure that the compounds dissolved completely.

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The samples were then placed in the autosampler and 50 μL were injected twice from each vial.

LC/MS optimization and settings

Several mobile phases were tested to yield a sensitive and stable chromatography and MS detection. The mobile phase finally used for chromatographic separation was methanol: 1% TFA/ammonium trifluoroacetate in H_2O, pH 7, 70:30, at a flow rate of 350 μL/min and the chromatography ran for 9 min.

The SSI settings were as follows: plate temperature 200°C, aperture 1 temperature 150°C, aperture 2 temperature 120°C, chamber voltage 0.6 kV, drift voltage 35 V, and focus voltage 34 V.

In the ion trap mass spectrometer positive ion polarity was used, the multiplier voltage being set to 400 V, and the peak threshold to 10. The automatic sensitivity control (ASC) was turned on and for each run three microscans were centroided and averaged. The mass spectrometer was run in MS^2 mode using two alternating methods. The first MS^2 method was used for detection of paclitaxel and dihydroxypaclitaxel (a reference substance was not available for this metabolite so paclitaxel was used as reference). In the ion accumulation step for this method, the low mass cutoff (LMC) was set to 80, the accumulation mass range was set to 750–940 *m/z*, the accumulation voltage was set to 0.03 V, and the sensitivity was 200. The settings for the isolation step were as follows: isolation mass range 849–859 and 881–891, LMC 750, isolation voltage 0.15 V, and isolation time 10 ms. During the collision-induced dissociation (CID) step, the following settings were used: CID resonance 849–863 and 876–896, LMC 420 V, CID time 50 ms, and CID voltage 0.15 V. The second MS^2 method was used for the detection of both hydroxypaclitaxel metabolites and docetaxel. The settings for the ion accumulation step were as follows: the accumulation mass range was set to 766–940 *m/z*, the accumulation voltage was set to 0.03 V, and the sensitivity was 200. During the isolation step, the following settings were used: isolation mass range 825–835 and 865–875, LMC 770, isolation voltage 0.12 V, and isolation time 10 ms. In the CID step, LMC was set to 420, CID resonance to 825–835 and 865–881 *m/z*, CID time to 50 ms, and CID voltage to 0.2 V. During both methods the MS spectra were scanned for a mass-to-charge ratio between 500 and 600 *m/z*. Chromatograms for each substance were extracted from the MS chromatograms using the product ions as indicated in Table 1.

Validation procedure

The precision and accuracy of the method were evaluated by analyzing paclitaxel, *p*-3′-hydroxypaclitaxel and 6α-hydroxypaclitaxel at five different concentrations (QC1–QC5) on three different days. Six QC samples at each concentration were used to evaluate within-day variation and six were used for between-day variation. To determine the concentration of the analytes in the QC samples one calibration curve consisting of nine different concentrations (STD1–STD9) were analyzed each day. Calibration was performed using the area of the corresponding peak in the chromatogram and the calibration curve was created using a cubic-fit regression model forced through zero.

The precision of the assay was expressed as a coefficient of variation (CV) at each concentration by calculating the standard deviation as a percentage of the mean calculated concentrations, while accuracy of the method was evaluated by expressing the mean calculated concentration as a percentage of the nominal concentration. The percentage extraction recoveries of paclitaxel, *p*-3′-hydroxypaclitaxel and 6α-hydroxypaclitaxel for the QC samples were determined by comparing extracted blank samples in which the SPE eluate had been spiked with a corresponding amount of substance to those obtained by injections of extracted spiked plasma samples. The stability of paclitaxel, *p*-3′-hydroxypaclitaxel and 6α-hydroxypaclitaxel in the samples was checked in three different experiments; one for room temperature stability, one for stability after reconstitution in the mobile phase, and one experiment for freeze/thaw stability. The stability at room temperature was evaluated by letting eight samples of spiked plasma at two different concentrations (paclitaxel 50 and 1000 ng/mL, *p*-3′-hydroxypaclitaxel 50 and 200 ng/mL, and 6α-hydroxypaclitaxel 50 and 200 ng/mL) stand at room temperature for 24 h and another set of eight samples for 48 h. The concentrations were then compared with the QC samples with corresponding concentrations. To check the stability after reconstitution, ten QC samples were left on the bench after injection and re-injected 4 days later. The areas of the peaks were then compared to the first injection. Eight plasma samples, at the same two concentrations as for the room temperature stability test, were frozen to −70°C and thawed for three cycles and then extracted and analyzed. The areas of the peaks were compared to the QC samples spiked at the same concentrations.

RESULTS AND DISCUSSION

Method development

The major goal in the development of this assay was to quantify low concentrations of both paclitaxel and its hydroxy metabolites in human plasma. Due to the fact that we only had access to small amounts of the metabolites, the method was first developed for paclitaxel and then the

Table 1. Product ions and isolation *m/z* values in MS and retention times (Rt) for the analytes

Substance	Rt (min)	Isolation *m/z*	Product ions	Method #
Paclitaxel	6.1	849–859	550+551+568+569	1
p-3′-Hydroxypaclitaxel	3.6	865–875	550+551+568+569	2
6α-Hydroxypaclitaxel	5.1	865–875	566+567+583-586	2
6α-,*p*-3′-Dihydroxypaclitaxel	3	881–891	566+567+583-586	1
Docetaxel	7	825–835	548–551	2

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settings were adopted to fit the quantification of the available metabolites and thereafter fine-tuned for the best performance.

In most instruments and previously reported methods, paclitaxel either forms the $[M+H]^+$ ion or the $[M+Na]^+$ molecular ion. To suppress the formation of the Na^+ adduct in favor of the $[M+H]^+$ ion an acidic mobile phase would be required. However, in our system we could not get a reproducible formation of the $[M+H]^+$ ion between different batches of acidic mobile phase due to the formation of a lower or higher amount of $[M+Na]^+$. To stabilize the system the mobile phase was changed to push paclitaxel to form other ions instead of $[M+H]^+$. By adding positive or negative ions to the mobile phase, the following adducts could be detected in the LC/MS: $[M+K]^+$ (2 mM KCl/MeOH 30:70), $[M+Na]^+$ (2 mM NaCl/MeOH 30:70), and $[M+Acetate]^-$ (20 mM ammonium acetate(pH 5.0)/MeOH 30:70). The highest sensitivity of these adducts was reached with the $[M+K]^+$ ion. However, the $[M+H]^+$ ion showed a higher sensitivity, although unstable, than any of the other ions, probably due to fragmentation of the latter in the ion source. We then tried to stabilize the formation of the $[M+H]^+$ ion by suppressing the $[M+Na]^+$ ion. This was done using crown ethers or TFA, the latter giving the highest sensitivity and the lowest amount of $[M+Na]^+$adducts. Although TFA caused a suppression of the absolute signal, the signal-to-noise (S/N) ratio for paclitaxel was increased and a stable $[M+H]^+$ ion formation was achieved. The mobile phase was then optimized for TFA concentration and pH. Optimum MS^2 conditions for the analyte response were established using a continuous infusion of a stock solution containing paclitaxel while running the chosen mobile phase components. Note that docetaxel forms the $[M+Na]^+$ adduct using this mobile phase and instrument.

Several interfaces were also tested to evaluate the response. The M-8000 LC/MS^n ion trap was equipped with both an SSI interface as well as an electrospray ionization (ESI) interface. The SSI interface was about four times more efficient in ionizing paclitaxel than the ESI one. We also had the opportunity to test the ionization on a Perkin Elmer SCIEX equipped with both an ESI and an atmospheric pressure chemical ionization (APCI) interface. In this system, the ESI interface was more efficient in ionizing paclitaxel than the APCI interface. The SSI interface was then considered the best choice.

The HPLC column was chosen to retain the analytes sufficiently to avoid ion suppression by early eluting substances in the sample extract and separate the analytes since some of them have identical mass-to-charge ratios for some fragments. The monohydroxy metabolites have the same molecular mass but they fragment into ions with a different *m/z*. However, *p*-3′-hydroxypaclitaxel dissociates into fragments with the same *m/z* as fragments from paclitaxel and 6α-hydroxypaclitaxel dissociates into fragments with the same *m/z* as dihydroxypaclitaxel (Fig. 1). To achieve single-peak mass chromatograms two methods were run in parallel, one for paclitaxel and dihydroxypaclitaxel and one for the monohydroxy metabolites (Table 1). By making sure that the HPLC conditions yielded peak separation, interference between the analytes was minimized. Typical retention times were 6.05 min for paclitaxel, 3.65 min for *p*-3′-hydroxypaclitaxel, 5.0 min for 6α-hydroxypaclitaxel, 3.3 min for dihydroxypaclitaxel, and 6.8 min for docetaxel. After each injection the chromatography was run for 9 min. Figure 2 shows typical chromatograms for paclitaxel and its hydroxylated metabolites generated from the product ions formed in MS^2 (*m/z* values shown in Table 1). Docetaxel was used as an internal standard; however, it did not increase the precision or accuracy of the method and was therefore only used to control the SPE and autosampler.

Paclitaxel adheres strongly to most surfaces; carry-over effects and ghost peaks were major problems during early method development. The problems were traced to the SPE procedure and solved by replacing the nylon tips in the SPE vacuum box with steel needles, which were washed between all extractions.

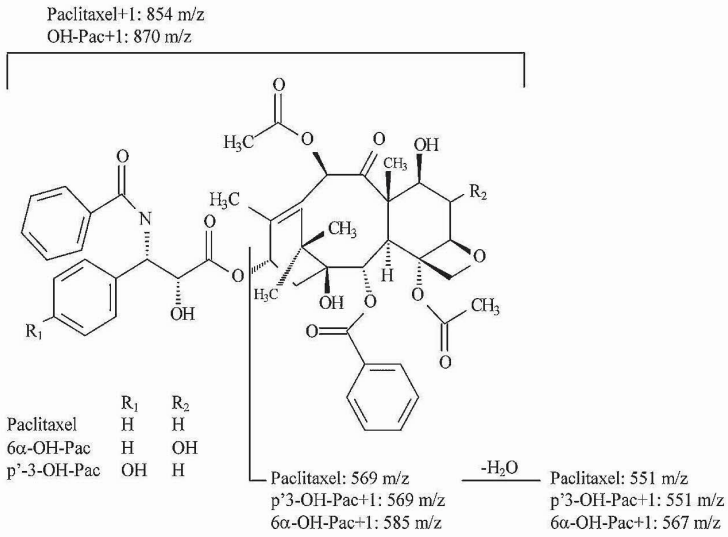

Figure 1. Molecular structure and fragmentation of paclitaxel and its monohydroxy metabolites.

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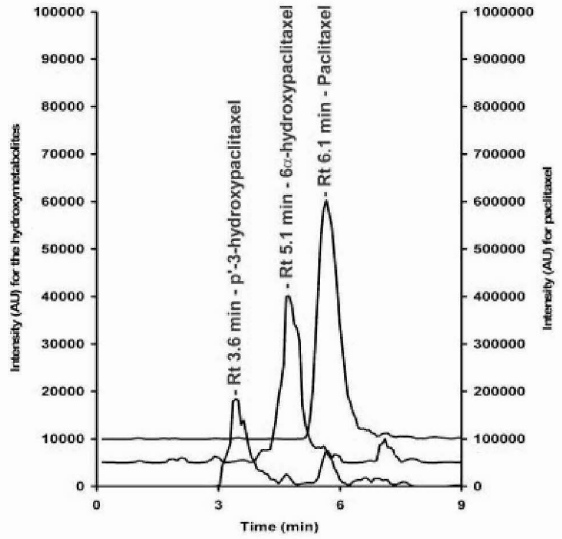

Figure 2. Typical chromatograms for paclitaxel and its hydroxy metabolites isolated from plasma (15 min post end of infusion) from a patient with ovarian cancer receiving 175 mg/m^2 of paclitaxel (Taxol®). The chromatograms were generated using the sum of the product ions formed in MS^2 (550+551+568+569 *m/z* for paclitaxel, 550+551+568+569 *m/z* for *p*-3′-hydroxypaclitaxel, and 566+567+583-586 *m/z* for 6α-hydroxypaclitaxel). In the chromatogram the baseline for 6α-hydroxypaclitaxel is elevated with 5000 AU and that for paclitaxel with 100 000 AU for illustrative purposes. In this method the ion trap works with two serial methods: one generating the paclitaxel (and the dihydroxymetabolite) chromatogram and one the hydroxyl metabolites (and the internal standard). Note that the peak at 6.1 min in the *p*-3′-hydroxypaclitaxel chromatogram is from paclitaxel (more than 100-fold intensity in the correct method) and that the peak at 7 min in the 6α-hydroxypaclitaxel chromatogram is from the internal standard, which has a ^{13}C fragment with the same *m/z* as the metabolite.

Each sample was injected twice due to spiking of the chromatograms. We were not able to get rid of the spiking phenomenon by adjusting the MS conditions or cleaning of the mass spectrometer, although improving the water quality in the mobile phase helped some. The spiking was, however, rather infrequent, and readily identified, and if one of the chromatograms contained interference, the other injection was used. With more advanced software, it would be rather easy just to exclude a single data point caused by spiking instead of having to run the samples twice.

Due to the wide range of paclitaxel concentrations found in plasma, the calibration curve for paclitaxel was divided into a low- (0.5–250 ng/mL) and high-range (250–7500 ng/mL) calibration curve. The calibration curve was also created using a cubic-fit regression model due to nonlinearity at high paclitaxel concentrations. The response is linear from 0.5 up to 1000 ng/mL. Proposed causes of nonlinearity at the high end of the calibration curve have been the formation of paclitaxel dimers and trimers at the interface,[33] as well as charge transfer in the trap at high ion concentrations. Others have solved this nonlinearity by diluting the samples.[33] However, we found that in the range presented in this assay, the use of nonlinear calibration curves worked just as well. The calibration curves for the metabolites were linear over the whole calibration range. Figure 3 shows a calibration curve for paclitaxel obtained during one of the validation runs.

The final method conditions were chosen for several reasons. First of all they allow the quantification of low concentrations (<10 ng/mL) of the analytes in human plasma. Second, they allow the determination of paclitaxel and its metabolites simultaneously. The method presented here has some special features, especially the use of TFA as a Na^+-adduct suppressor and the SSI interface, both of which improved the performance of the assay.

Precision and accuracy

The reproducibility of the method was evaluated by analyzing six replicates of five different QC samples on three different days. Extracted standard curves obtained in the range of 0.5–7500 ng/mL showed excellent curve fitting with a coefficient of correlation greater than 0.99. The within-day and between-day variations are reported in Table 2. The method was found to be acceptably precise (CV < 14%) and accurate (range 83–113%, except for the within-day variation of paclitaxel at the lowest concentration). The mean extraction recovery, assessed at the same concentrations as the QC samples, was a bit low: paclitaxel range 63–74%, *p*-3′-hydroxypaclitaxel 65–71%, and 6α-hydroxypaclitaxel 72–85%. The quantification of paclitaxel and its hydroxy metabolites was possible within the range of the standard curves. The lower limit of quantification was set to 0.5 ng/mL for paclitaxel (within-day precision <12%, n = 4, and between-day accuracy 103–122%, n = 3) and to 2 ng/mL for the hydroxy metabolites (within-day variation <20%, n = 4, and between-day accuracy 107–125%, n = 3).

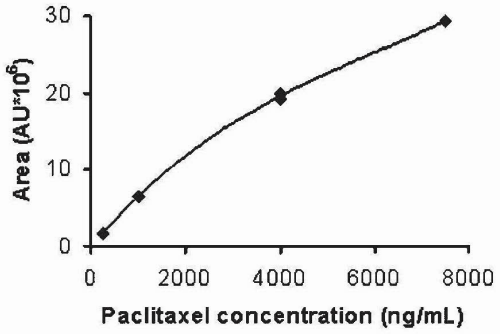

Figure 3. A nonlinear calibration curve for the higher range of paclitaxel concentrations obtained during one of the validation runs. The concentration of paclitaxel in spiked standard samples is shown on the x-axis and the response of the mass spectrometer as the area of the peak is presented on the y-axis. A cubic-fit regression model was used for calibration of the paclitaxel concentrations. The responses of the metabolites were linear within the calibration ranges.

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