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ORIGINAL RESEARCH

# Quantitative determination of domperidone in human plasma by ultraperformance liquid chromatography with electrospray ionization tandem mass spectrometry

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ABSTRACT: A simple and sensitive liquid chromatography–tandem mass spectrometry method was developed and validated for determining domperidone in human plasma. The analyte and internal standard (IS; mosapride) were isolated from plasma samples by protein precipitation with methanol (containing 0.1% formic acid). The chromatographic separation was performed on an Xterra MS $C_{18}$ Column (2.1 × 150 mm, 5.0 μm) with a gradient programme mobile phase consisting of 0.1% formic acid and acetonitrile at a flow rate of 0.30 mL/min. The total run time was 4.0 min. The analyses were carried out by multiple reaction monitoring using the parent-to-daughter combinations $m/z$ 426 → 175 and $m/z$ 422 → 198 (IS). The areas of peaks from the analyte and IS were used for quantification of domperidone. The method was validated according to the FDA guidelines on bioanalytical method validation. Validation results indicated that the lower limit of quantification was 0.2 ng/mL, and the assay exhibited a linear range of 0.2–60.0 ng/mL and gave a correlation coefficient ($r^2$) of 0.999 or better. Quality control samples (0.4, 0.8, 15 and 50 ng/mL) in six replicates from three different analytical runs demonstrated an intra-assay precision (RSD) 4.43–6.26%, an inter-assay precision 5.25–7.45% and an overall accuracy (relative error) of <6.92%. The method can be applied to pharmacokinetic and bioequivalence studies of domperidone. 

KEYWORDS: domperidone; electrospray ionization; ultraperformance liquid chromatography/tandem mass spectrometry; human plasma

## INTRODUCTION

Domperidone (DOM, 5-chloro-1-{1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)propyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazol-2-one, Fig. 1) is a selective dopamine antagonist of the D2 receptor which does not penetrate fully into the central nervous system, therefore it is apparently devoid of central sedative and extrapyramidal effects. The drug is principally widely used in many countries for the treatment of motility disorders as well as for its antiemetic properties (Brogden *et al.*, 1982). Domperidone was for a long time a second choice to cisapride, but the removal of the latter from the market has increased its clinical use.

Although it is a potent gastrokinetic and antinauseant drug, very little information regarding the pharmacokinetics and bioequivalence of domperidone is available, owing to the lack of sensitive quantitation methods (Smit *et al.*, 2002). Several methods have been investigated for the determination of domperidone in human plasma. Huang *et al.* (1986) measured domperidone levels by a radioimmunoassay (RIA) method using antibodies raised against domperidone. However, antibodies raised in rabbits against domperidone are not commercially available. Recently, some authors developed non-RIA methods to determine domperidone concentration in human plasma.

Kobylinska and Kobylinska (2000) described an HPLC method using solid-phase extraction (SPE). Yamamoto *et al.* (1998) developed a HPLC method with fluorescence detection using a liquid–liquid extraction. Zavitsanos *et al.* (1999) and Smit *et al.* (2002) proposed an LC-MS and LC tandem MS method using a liquid–liquid and back-extraction, respectively. However, most of these methods required time-consuming laborious extraction procedures of two steps or more, a relatively large sample volume (1 mL), and also long chromatographic run times, which lowers sample throughput. It was therefore decided to develop a faster and simpler method using a ultraperformance liquid chromatograph/tandem mass spectrometry with direct injection after simple protein precipitation. The method was relatively fast as

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**Abbreviations used:** DOM, domperidone; RIA, radioimmunoassay.

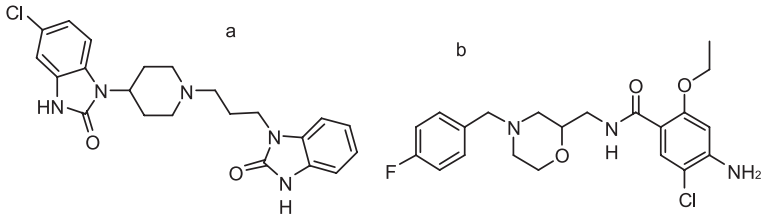


**Figure 1.** Chemical structures of (a) domperidone and (b) mosapride.

compared with existing methods (a total chromatography time of 4 min), allowing the assay of up to 300 samples per day. The method was sensitive (lower limit of quantitation, LLOQ = 0.2 ng/mL), sufficient to determine concentrations of up to 24 h following a 10 mg dose of domperidone, and it required a relatively small sample volume (0.1 mL).

## EXPERIMENT

**Chemical and reagents.** Domperidone was provided by Hangzhou Conba Pharmaceutical Co. (Hangzhou, China). Mosapride, obtained from Jiangsu Hansoh Pharmaceutical Co. Ltd. (China), assigned strength 94.3%, was used as the internal standard (IS; Fig. 1). Acetonitrile and methanol were of HPLC grade and were purchased from Merck Company Inc. (Darmstadt, Germany). Formic acid (96%) was of HPLC grade, purchased from Tedia Company Inc. (Fairfield, OH, USA). All other reagents were of analytical grade. Blank human plasma was obtained from healthy volunteers who had not taken any medications for one month, at the Blood Center of Hangzhou (Hangzhou, China). Ultrapure water was obtained from a Milli-Q Plus water purification system (Millipore, Bedford, MA, USA).

**Preparation of standards and quality control samples.** The stock solutions of domperidone and IS were prepared by dissolving the accurately weighed reference compound in methanol to give a final concentration of 1.0 mg/mL and stored at –20°C for up to 1 month. A working solution of IS 20 ng/mL was prepared by appropriate dilution of the stock solution in methanol and stored at –20°C until use.

An aliquot of the stock solution of domperidone was dried and reconstituted in blank human plasma to obtain the nominal plasma concentration of 1 μg/mL and used to dilute to the other standard concentrations. The nominal plasma concentrations of calibration standards were 0.2, 0.5, 1.0, 5.0, 10.0, 20.0, 40.0 and 60.0 ng/mL. Quality control (QC) samples were prepared at concentrations of 0.4, 0.8, 15.0 and 50.0 ng/mL, respectively, and were prepared daily using the same blank plasma. All of the standard solutions were stored at –20°C until used.

**Sample preparation.** A 100 μL volume of plasma was transferred to a microcentrifuge tube (Eppendorf, 1.0 mL), and then 100 μL of IS working solution (20 ng/mL) was spiked and vortex-mixed for 10 s. A 500 μL aliquot of methanol (contained 0.1% formic acid) was added and vortex-mixed again for 30 s. After centrifugation for 10 min at 20,664***g*** (Allegra™ 22R centrifuge, Beckman Coulter, USA) at 10°C. The clear supernatant was transferred to vials on the rack of the autosampler and a 10 μL aliquot was injected into the UPLC/MS/MS system for analysis.

**Ultraperformance liquid chromatography conditions.** Separation, identification and quantification of domperidone were performed with a coupled liquid chromatography/tandem mass spectrometry system consisting of an Acquity Ultraperformance™ liquid chromatography (Waters, USA) and a Quattro Ultima Pt (Micromass, UK) tandem mass spectrometer. Chromatographic separations of domperidone were performed on an XTerra® MS $C_{18}$ column (5 μm, 150 × 2.1 mm i.d., Waters, Ireland). The analytical column was protected by a Waters $C_{18}$ guard column (4 × 3.0 mm, i.d.) with a Waters in-line filter unit. A gradient program was used with the mobile phase, combining solvent A (0.1% formic acid, v/v), and solvent B (acetontrile) as follows: 35% B (initial), 35–55% B (1.4 min), 55–100% B (0.1 min), 100% B (0.4 min) and 100–35% B (0.1 min). A subsequent re-equilibration time (2 min) was allowed before the next injection. The flow rate was 0.3 mL/min while the injection volume was 10 μL. Separation was conducted under gradient conditions and the total run time was 4 min. Moreover, the column and sample temperature were maintained at 35 and 15°C, respectively.

**MS/MS conditions.** MS/MS was performed on a Micromass Quattro Ultima triple-quadrupole mass spectrometer equipped with an ESI source (Micromass, Manchester, UK). The parameters used for the mass spectrometer under the $ESI^+$ mode are shown in Table 1. The parameters on the *m/z* and collision energy of parent ions and quantitative daughter ions from domerpridone and IS are shown in Table 2. Data acquisition was performed with the MassLynx 4.1 software, while peak integration and calibration were obtained with the QuanLynx 4.1 software.

**Assay validation.** The method was validated for selectivity, accuracy, precision, recovery, calibration curve and reproducibility according to the FDA guidelines for validation of bioanalytical methods (Guidance for Industry, 2001).

Six randomly selected control drug-free human plasma samples were processed by a similar proteins precipitation procedure and injected into the UPLC/MS/MS in order to determine the extent to which endogenous plasma components may interfere at the retention times of domperidone and internal standard.



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**Table 1. MS/MS conditions for the determination of domperidone**

| MRM mode | $ESI^+$ |
|---|---|
| Capillary voltage (kV) | 3.5 |
| Cone voltage (V) | 50 |
| Source block temperature (°C) | 120 |
| RF lens 1 | 40 |
| Aperture | 0.6 |
| RF lens 2 | 0.7 |
| Cone gas ($l\,h^{-1}$) | 50 |
| Desolvation temperature (°C) | 350 |
| Desolvation gas ($l\,h^{-1}$) | 500 |
| Argon collision gas pressure (mbar) | $3 \times 10^{-3}$ |
| LM lens 1 (V) | 12.5 |
| HM lens 1 (V) | 12.5 |
| Ion energy 1 (eV) | 1 |
| Entrance lens voltage (V) | –2 |
| Collision gradient | 0 |
| Exit lens voltage (V) | 0 |
| LM lens 2 (V) | 12.5 |
| HM lens 2 (V) | 12.5 |
| Ion energy 2 (eV) | 1 |

**Table 2. MS/MS parameters on the parent and quantitative daughter ion (*m/z*) and collision energy of domperidone and mosapride**

| Compound | Parent ion (*m/z*) | Daughter ion (*m/z*) | Collision energy (eV) |
|---|---|---|---|
| Domperidone | 426 | 175 | 25 |
| Mosapride | 422 | 198 | 20 |

A calibration curve was constructed from a blank sample (a plasma sample processed without an IS) and eight non-zero samples covering the total range (0.2–60.0 ng/mL), including the LLOQ. Such calibration curves were generated on six consecutive days. Linearity was assessed by a weighted ($1/x^2$) least squares regression analysis. The calibration curve had to have a correlation coefficient ($r^2$) of 0.99 or better. The acceptance criterion for each back-calculated standard concentration was 15% deviation from the nominal value except for the LLOQ, which was set at 20%.

The within-batch precision and accuracy were determined by analyzing six sets of quality control samples in a batch. The between-batch precision and accuracy were determined by analyzing six sets of quality control samples on three different batches. The quality control samples were randomized daily, processed and analyzed in position either (a) immediately following the standard curve, (b) in the middle of the batch or (c) at the end of the batch. The acceptance criteria of within- and between-batch precision were 20% or better for the LLOQ and 15% or better for the rest of the concentrations, and the accuracy was 100 ± 20% or better for LLOQ and 100 ± 15% or better for the rest of concentrations. The precision of the method was expressed as relative standard deviation and accuracy of the method was expressed in terms of bias (percentage deviation from true value). The recovery of domperidone from human plasma matrix was evaluated by comparing the mean detector responses of six processed QC samples of low, medium and high concentrations with mean detector responses for six standard solutions of equivalent concentration. Similarly, the recovery of the IS was evaluated by comparing the mean detector responses of six-processed plasma samples to mean detector responses of six standard solutions of same concentration.

Six aliquots each of low and high QC samples were kept in deep freezer at –70 ± 5°C for 35 days. The samples were processed and analyzed and the concentrations obtained were compared with the actual value of QC samples to determine the long-term stability of domperidone in human plasma. Six aliquots each of the low- and high-concentration unprocessed QC samples were kept at ambient temperature (20–30°C) for 4.0 h in order to establish the short-term stability of domperidone in human plasma. Thereafter, the samples were analyzed and the concentrations obtained were compared with the actual values of QC samples. Samples were to be concluded to be stable if the bias of the stability samples was not more than ±15% of the actual value. In order to establish the autosampler stability of domperidone in human plasma matrix, six aliquots each of low- and high-concentration QC samples were stored at 15°C in the autosampler for 24.0 h. Thereafter, samples were reanalyzed and concentrations compared with the actual values. The percentage bias was calculated and the sample was concluded to be stable if it was within ±15% of the actual value. The effect of freeze–thaw cycles on the stability of plasma samples containing domperidone was determined by subjecting six aliquots of low- and high-concentration unprocessed QC samples stored at –20 ± 1°C to three freeze–thaw cycles. After the completion of the third cycle, the samples were analyzed. The samples were concluded to be stable if the percentage change in concentration of the stability samples was within ±15% of the actual value.

**Application of the method.** The method was applied to a bioequivalence study of 10 mg domperidone tablets in Chinese volunteers. Twenty healthy adult volunteers participated in this study. The volunteers were selected after a thorough assessment of medical history, physical examination and laboratory biochemical examination. Informed consent was obtained from all the subjects after explaining to them the aim and risks of the study. The study protocol was approved by the Independence Ethical Committee of Second Affiliated Hospital at School of Medicine, Zhejiang University, Hangzhou, China. After overnight fasting (10 h), the volunteers were orally administered a single dose of the assigned tablet with 250 mL of water. Regular standardized low-fat meals were provided 4 h after dose administration, and water intake was allowed at 2 h following drug administration. Following drug administration, venous blood samples (2.5 mL) were collected into tubes containing EDTA anticoagulant (BD, NJ, USA) at the following times: immediately before administration, at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h after dosing. Blood samples were centrifuged at 735*g* (Allegra™ 6R centrifuge, Beckman Coulter, USA) for 10 min, and the plasma was separated. The plasma samples were labeled and stored at –70°C until assay.



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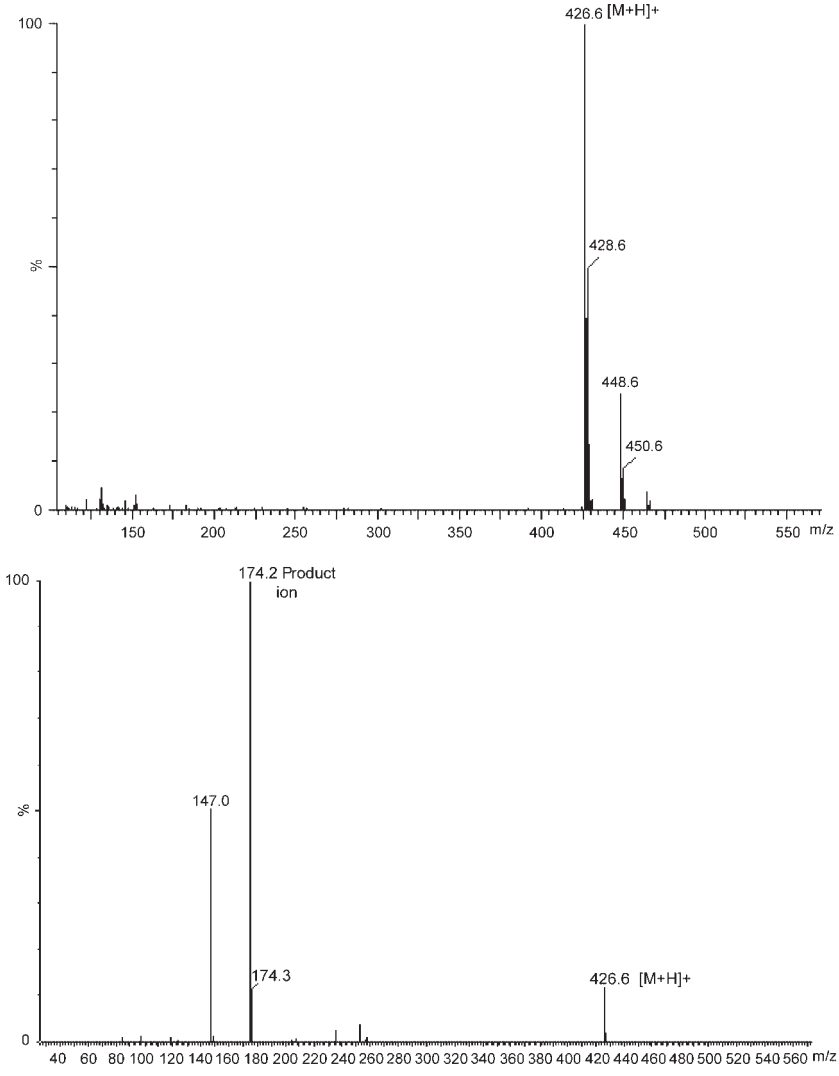


**Figure 2.** Full-scan positive ion MRM mass spectra of domperidone (top), and its product ion (bottom).

## RESULTS AND DISCUSSION

### Method development

The positive product ion scan spectra for the protonated molecules $[M + H]^+$ of domperidone at *m/z* 426 and IS at *m/z* 422 are shown in Figs 2 and 3. The mass spectra resulting from these fragmentations were acquired in the MRM mode at *m/z* 175 for domperidone and *m/z* 198 for IS; the collision energy was 25 eV for domperidone and 20 eV for IS. We applied the ionization of each moleculele to the use of the following channels for quantitative determination: *m/z* 426 → 175 for domperidone and *m/z* 422 → 198 for IS. These fragment ions were the most sensitive ions detected and are specific to domperidone. IS was the most appropriate choice for a specific and sensitive method. The parameters presented are the result of this optimization.

We changed the mobile phase from organic to more aqueous phase with an acid dopant to get a fast-run UPLC method to enhance the throughput capability without being detrimental to the chromatographic separation. Better signals were obtained for 0.1% formic acid:acetontrile as a gradient program mobile-phase.

The XTerra $C_{18}$ HPLC column was chosen based on its good separation. UPLC/MS/MS chromatograms showed that domperidone and IS were separated with no interference from each other. Furthermore, proteins precipitation produced clean extracts with no matrix effects presented on the chromatograms.



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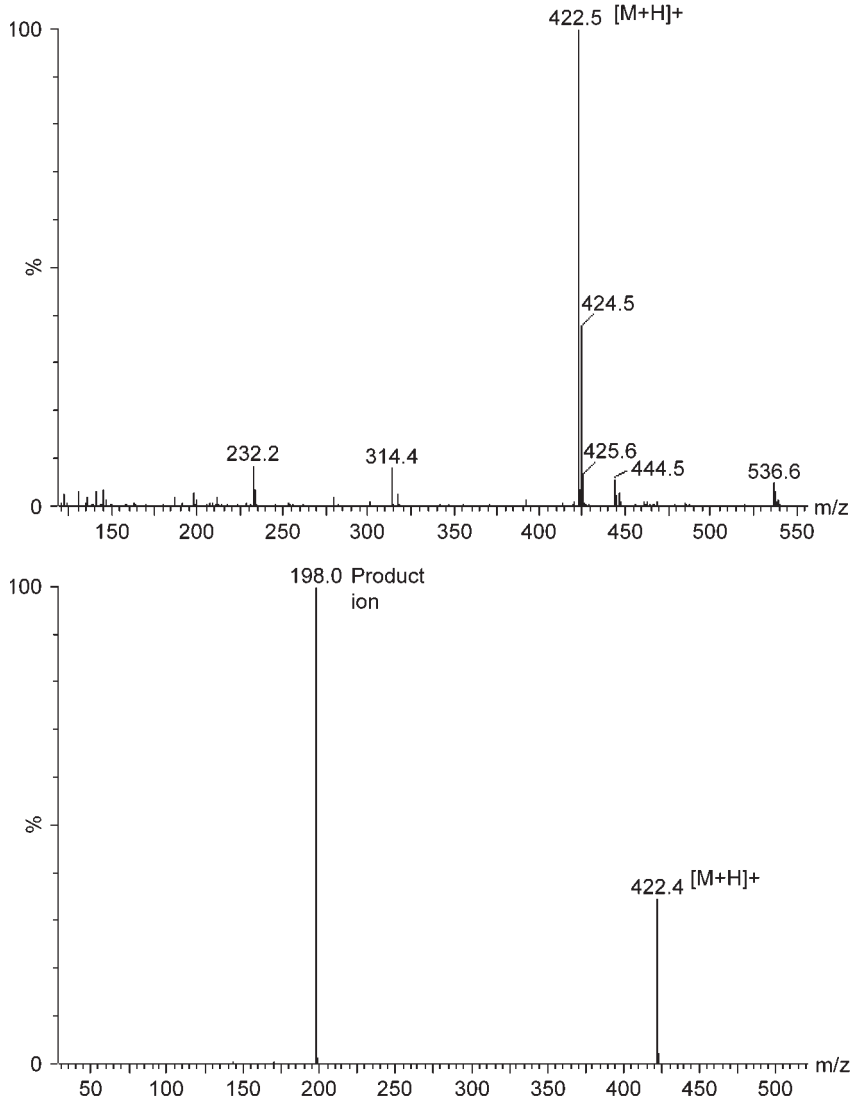


**Figure 3.** Full-scan positive ion MRM mass spectra of internal standard, mosapride (top), and its product ion (bottom).

## Method validation

**Specificity.** The specificity of the method was determined by analyzing six different lots of blank control both with and without the internal standard. The chromatograms indicate that protein precipitation produced clean extracts with no interference from endogenous compounds at the retention times for domperidone and the internal standard. Representative chromatograms of plasma with and without the analytes and internal standard are shown in Figs 4 and 5.

**Sensitivity and linearity.** Sensitivity was determined by the lowest of reliable quantification for the compounds. The LLOQ was 0.2 ng/mL. The linear range was from the LLOQ to 60 ng/mL. A linear fit using a weighting factor of the inverse squared concentration ($1/x^2$) appeared to fit the data. Correlation coefficients of 0.9993 or higher were obtained. The calibration standards were back-calculated from the responses. The deviations from the nominal concentrations were between –13.0 and 14.7% for all concentrations. CV values were <13.38% for all concentrations.

**Accuracy and precision.** Precision and accuracy of the assay were determined by replicate analytes ($n = 6$) of QC samples at three concentrations, by performing the complete analytical runs on the same day and also on four consecutive days. The precision and accuracy of QC samples were assessed by the determination of the mean calculated concentrations as compared with nominal concentrations. The intra- and inter-day precisions were less than 6.92% for each QC level of domperidone. The accuracy, assessed by calculating the percentage deviation observed in the analysis of QC samples and expressed as the coefficient of variation



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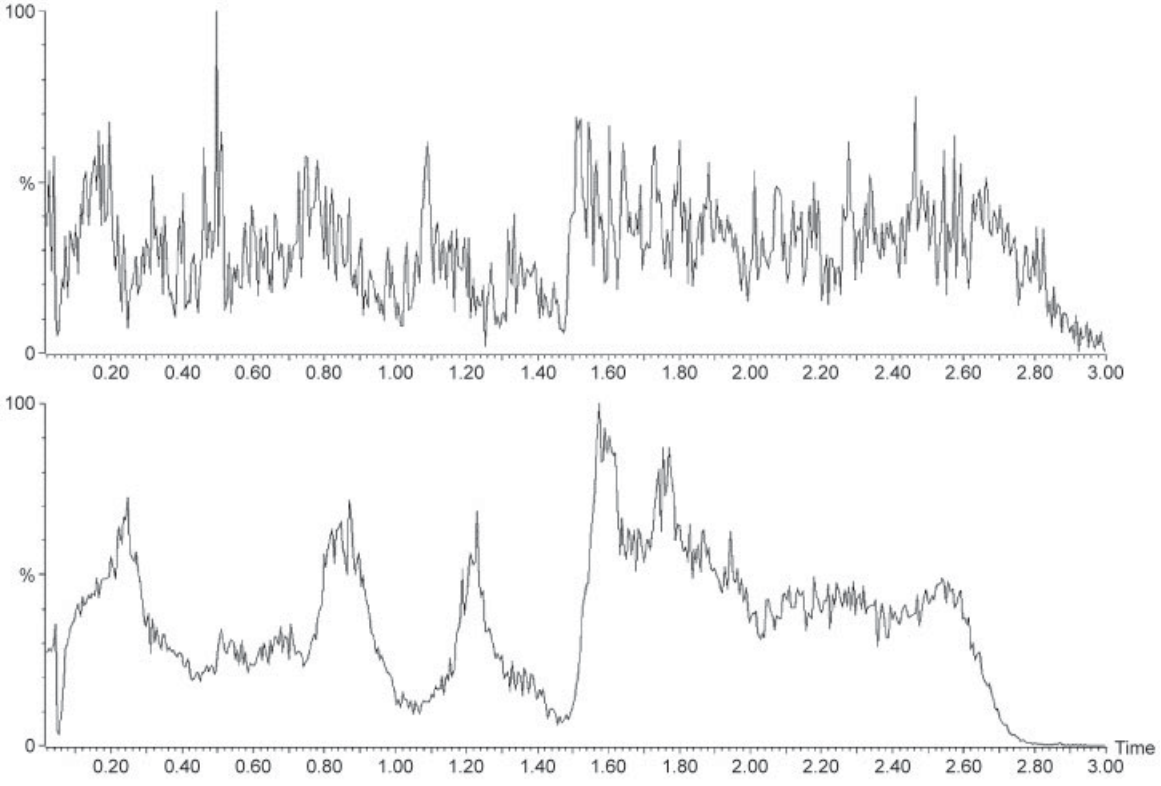


**Figure 4.** Ion chromatogram of a double blank extract [domperidone (top), internal standard mosapride (bottom)].

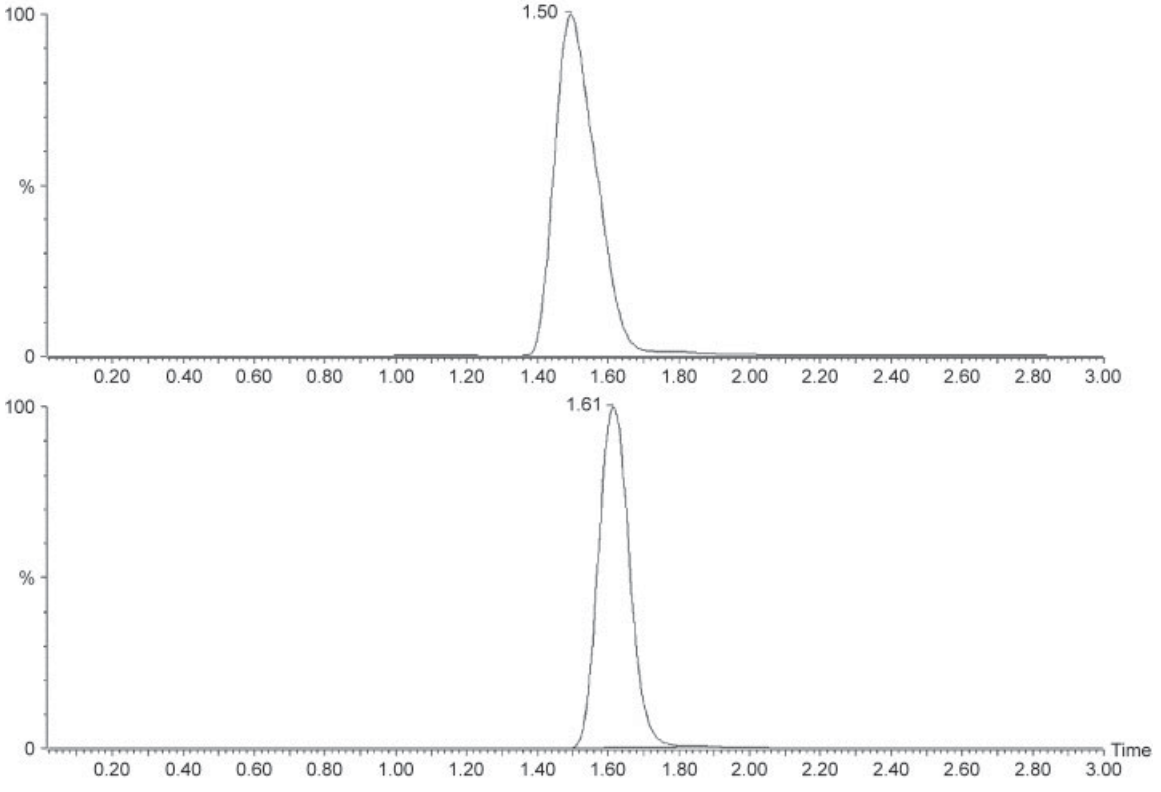


**Figure 5.** Ion chromatogram of 10 ng/mL domperidone (top) and internal standard mosapride (bottom) in human plasma.



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(CV%), was within 8.78% at all four QC levels. Data obtained from the replicate analysis of QC samples indicated that the method was accurate and reliable. The results were summarized in Table 3.

**Recovery.** Recovery was determined by adding domperidone and internal standard to blank human plasma. Three replicates at four concentrations (0.4, 0.8, 15.0 and 50.0 ng/mL) were prepared. The plasma was extracted under the conditions noted above. Neat standards were prepared at the same concentrations. Recovery was determined by comparison of the integrated peak area response for the extracted samples with the response for the neat solutions adjusted by the difference in volume between extracted samples and neat standards. Average recoveries were 103.82, 94.38, 103.99 and 97.92% for 0.4, 0.8, 15.0 and 50.0 ng/mL, respectively.

**Stability.** The storage stability of domperidone and IS was evaluated to determine whether degradation occured during long-term storage. Stability was determined by analyzing QC samples stored at –20°C over a period of 7, 14 and 35 days. The data indicated that domperidone and IS were stable at –20°C for at least 35 days (Table 4).

Owing to the need for occasional delayed injection or re-injection, extract stability was studied. Six replicates of each QC level were extracted. Of the six replicates, three replicates for each level remained at 4°C for 24 h and the other three replicates remained at injection room (15°C) for 24 h prior to analysis. The results showed that all three analytes were stable in the extract solution at both temperatures for 24 h (Table 4).

The analytes were also tested for freeze–thaw stability. Three freeze–thaw cycles were tested where one cycle consisted of thawing replicate ($n$ = 3) QCs at each level at room temperature for 4 h and re-freezing at –20°C. The freeze–thaw samples were assayed and mean concentrations were compared with those values obtained for the QC intra day analysis. The results indicate that domperidone and IS were stable after three freeze–thaw cycles (Table 4).

In the current assay, the mobile phase B (acetonitrile) was used as the autosampler needle wash solution with rinse volume of 50 µL. No significant carryover was observed (Table 4).

**Application of method.** In our study, 20 healthy subjects were randomized to receive a single oral dose of

**Table 3. Inter- and intra-assay accuracy and precision data for assays of domperidone in plasma ($n$ = 6)**

| Nominal concentration (ng/mL) | Inter-assay | | | Intra-assay | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Accuracy (bias, %) | Precision (RSD,[a] %) | Mean ± SD | Accuracy (bias, %) | Precision (RSD,[a] %) |
| 0.4 | 0.40 ± 0.04 | 0.61 | 8.78 | 0.39 ± 0.02 | –3.33 | 4.22 |
| 0.8 | 0.86 ± 0.06 | 6.92 | 7.45 | 0.79 ± 0.05 | –0.83 | 6.26 |
| 15 | 15.16 ± 0.80 | 1.07 | 5.25 | 15.85 ± 0.70 | –5.69 | 4.43 |
| 50 | 49.66 ± 3.64 | –0.69 | 7.34 | 47.32 ± 2.11 | –5.37 | 4.47 |

[a] RSD = relative standard deviation.

**Table 4. Stability of domperidone in human plasma under various storage conditions ($n$ = 3)**

| Storage condition | Nominal concentration (ng/mL) | Calculated Mean ± SD | Conc. (ng/mL) $Er$[a] (%) |
|---|---|---|---|
| 4°C/24 h | 0.8 | 0.92 ± 0.03 | 14.58 |
| (extracted sample) | 15.0 | 13.91 ± 0.18 | –7.24 |
| | 50.0 | 50.66 ± 4.99 | 1.31 |
| Room temperature/4 h | 0.8 | 0.86 ± 0.04 | 7.04 |
| (extracted sample) | 15.0 | 15.69 ± 1.16 | 4.57 |
| | 50.0 | 54.38 ± 1.87 | 8.75 |
| –20°C/three | 0.8 | 0.88 ± 0.09 | 10.42 |
| freeze–thaw cycles | 15.0 | 15.54 ± 1.23 | 3.62 |
| | 50.0 | 48.21 ± 3.39 | –3.58 |
| –20°C /35 days | 0.8 | 0.74 ± 0.02 | –7.00 |
| | 15.0 | 15.41 ± 0.42 | 2.73 |
| | 50.0 | 54.56 ± 0.79 | 9.12 |
| Carry over | 0.8 | 0.81 ± 0.05 | 1.67 |
| | 50.0 | 50.53 ± 1.43 | 1.06 |

[a] relative error = (overall mean assayed concentration) – (added concentration)/(added concentration) × 100%.



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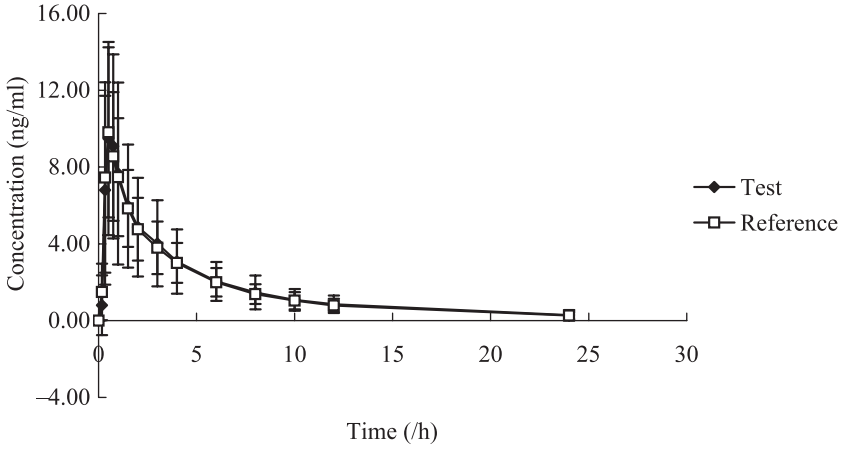


**Figure 6.** Mean concentration vs time profiles of domperidone after oral administration of a 10 mg tablet of the test and reference drug respectively ($n$ = 20, mean value and SD are plotted).

10 mg of test and reference domperidone tablet. Domperidone plasma concentrations were determined up to 24 h by the UPLC/MS/MS method described above. Figure 6 shows mean plasma concentration–time curves of domperidone after administration. The half-life varied from 0.33 to 1 h, similar to the results reported (Brogden *et al.*, 1982; Huang *et al.*, 1986; Kobylinska and Kobylinska, 2000).

## CONCLUSIONS

In summary, UPLC/MS/MS method for the quantification of domperidone in human plasma was developed and fully validated as per USFDA guidelines. This method offers significant advantages over those previously reported, in terms of improved sensitivity and selectivity, shorter run time (4.0 min) and lower sample volume requirements (0.1 mL). The current method has shown acceptable precision and adequate sensitivity for the quantification of domperidone in human plasma samples in pharmacokinetic or bioequivalence study.

Domperidone was shown to be stable in routine analysis conditions and in human plasma for at least 35 days when stored at below –20°C. The simple, inexpensive protein precipitation and high sample turnover rate (4.0 min per sample) makes this method an attractive procedure in high-throughput bioanalysis of domperidone. The validated method allows quantification of chloroquine in the 0.2–60.0 ng/mL range.

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