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# Bioequivalence Study of Toriem® Tablet to Motilium-M® Tablet (Domperidone Maleate 12.72 mg) Evaluated by Liquid Chromatography/Tandem Mass Spectrometry

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**ABSTRACT** – The aim of the present study was to evaluate the bioequivalence of two domperidone maleate tablets, Motilium-M® Tablet (Janssen Korea Ltd., reference product) and Toriem® Tablet (Daewon Pharm. Co., Ltd., test product). Domperidone was extracted by liquid-liquid extraction using *tert*-butyl methyl ether and separated in less than 3 min on $C_{18}$ reverse-phase column using an isocratic elution. A tandem mass spectrometer, as detector, was used for quantitative analysis in positive mode by a multiple reaction monitoring mode to monitor the *m/z* 426.1→119.1 and the *m/z* 837.4→158.2 transitions for domperidone and the internal standard (roxithromycin), respectively. Calibration curves, from 0.05 ~ 50 ng/mL of domperidone, showed correlation coefficients (r) higher than 0.9941. Intra day and inter day precision (C.V. %) for quality control were ranged from 10.04 to 16.09% and from 10.87 to 18.69%, respectively. The lower limit of quantification (LLOQ) of domperidone was 0.05 ng/mL. The method described is precise and sensitive and has been successfully applied to the study of bioequivalence of domperidone in 24 healthy Korean volunteers. Twenty-four healthy male Korean volunteers received a single dose of each medicine (2 × 12.72 mg domperidone maleate) in a 2 × 2 crossover study. There was a one-week washout period between the doses. Plasma concentrations of domperidone were monitored for over a period of 24 hr after the administration. $AUC_{0\text{-}t}$ (the area under the plasma concentration-time curve) was calculated by the linear trapezoidal rule. $C_{max}$ (maximum plasma drug concentration) and $T_{max}$ (time to reach $C_{max}$) were compiled from the plasma concentration-time data. The 90% confidence intervals for the log transformed data were within acceptable range of log 0.8 to log 1.25 (e.g., log 0.92 ~ log 1.05 for $AUC_{0\text{-}t}$, log 0.81 ~ log 1.05 for $C_{max}$). The major parameters, $AUC_{0\text{-}t}$ and $C_{max}$ met the criteria of KFDA for bioequivalence indicating that Toriem® tablet is bioequivalent to Motilium-M® tablet.

**Key words** – Domperidone, Liquid chromatography/tandem mass spectrometry, Liquid-liquid extraction, Human plasma, Bioequivalence

Domperidone, 6-chloro-3-[1-[3-(2-oxo-3H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1H-benzimidazol-2-one, is a dopamine antagonist which does not penetrate fully into the central nervous system. It stimulates gastro-intestinal motility and is used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies, including that associated with cancer therapy including nausea and vomiting associated with levodopa or bromocriptine therapy for parkinsonism.[1] Although domperidone is rapidly absorbed after oral administration, its bioavailability is only 5% resulting in most of the drug being excreted in the feces. The elimination half-life of domperidone in plasma is about 7 ~ 8 hr.[2]

To date, some analytical methods reported for domperidone determination have been performed by using mainly LC[3-8], LC/MS[9,10] or LC/MS/MS[11,12] methods. HPLC methods with fluorescence or UV detection have been described with lower limits of quantification (≥1 ng/mL)[3-8] or in non-human plasma samples.[3,6-8]

In this paper, we described a reliable, rapid, sensitive method for quantifying nanogram levels of domperidone in human plasma using liquid-liquid extraction of domperidone with *tert*-butyl methyl ether by LC-MS/MS. The chromatographic conditions were optimized and the results of the validation in terms of specificity, accuracy, precision and linearity were provided. The applicability of this method in bioequivalence studies was evaluated. Daewon Pharm. Co., Ltd. (Korea) has developed a new formulation of domperidone maleate: Toriem® Tablet. This study assessed, hence, the bioequivalence of this newly developed formulation with a reference formulation, Motilium-M® (Janssen Korea Ltd.) in twenty-four healthy Korean volunteers. Typical bioavailability, including $AUC_{0\text{-}t}$ (the area under the plasma concentration-time curve) and $C_{max}$ (the maximum plasma concentration) parameters were compared.

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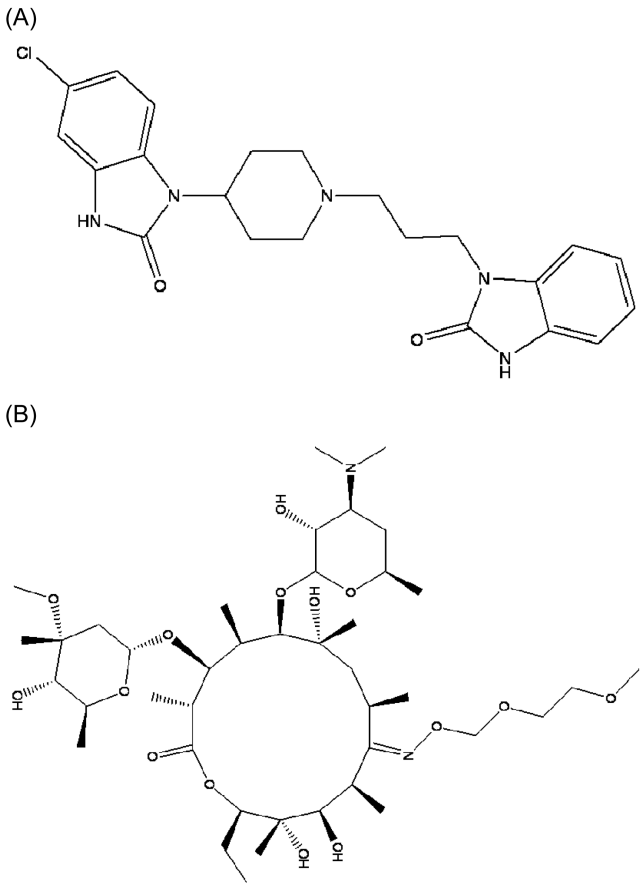


**Figure 1**—Chemical structures of (A) domperidone and (B) roxithromycin.

## Materials and Methods

### Chemicals and reagents

Domperidone maleate (98.6% purity) was supplied from Daewon Pharm. Co., Ltd., (Kyunggi-Do, Korea) and roxithromycin was purchased Sigma-Aldrich (St. Louis, MO, USA), respectively. The structural formulas of domperidone (Figure 1A) and roxithromycin (IS) (Figure 1B) are shown. *tert*-Butyl methyl ether and methanol were obtained from J.T. Baker (Pillipsburg, NJ, USA); sodium bicarbonate from Sigma-Aldrich (St. Louis, MO, USA). Purified water was obtained from a Milli-Q water purification system (Millipore Corp., Bedford, MA, USA). All other chemicals were of analytical grade. The test product, Toriem® (12.72 mg domperidone maleate, Daewon Pharm. Co., Ltd., Korea) and the reference product, Motilium-M® (12.72 mg domperidone maleate, Janssen Korea Ltd.) were supplied in the form of tablets.

### Preparation of calibration standard

Stock solution of domperidone maleate (1 mg/mL calculated as free base) and internal standard roxithromycin (1 mg/mL) were prepared in methanol. The stock solution of domperidone was further diluted with methanol to give a series of standard solution with concentrations of 0.5, 1, 5, 10, 50, 100, 500 ng/mL. A solution of containing 500 ng/mL of IS was prepared with methanol. Calibration curves were prepared by spiking pooled blank plasma with working solutions to final domperidone concentrations of 0.05, 0.1, 0.5, 1, 5, 10, and 50 ng/mL. All the solutions were stored at −20°C.

### Sample preparation

To 500 μL human plasma were added 50 μL of 1M sodium bicarbonate, 20 μL of IS (500 ng/mL) and 1.2 mL of *tert*-butyl methyl ether. The mixture was vortex-mixed for 10 min and then centrifuged at 10000 rpm (10621 rcf) for 10 min at 4°C. The organic phase was decanted into a clean microtube and was evaporated to dryness using a nitrogen flow in a TurboVap LV (Caliper Life Sciences, Mountain View, CA, USA) evaporation system at 45°C. The residue was reconstituted in 100 μL of mobile phase and aliquot of this solution (10 μL) was injected onto the LC-MS/MS system for analysis.

### Chromatographic conditions

LC separation was performed on YMC Hydrosphere $C_{18}$ analytical column (50 × 2.0 mm i.d., S-3 μm, 12 nm; Kyoto, Japan) at 40°C with a mobile phase consisting of acetonitrile-ammonium acetate buffer (80:20, v/v%; adjusted to pH 3.9 with acetic acid) at a flow rate of 0.2 mL/min. The solution was filtered using 0.22 μm membranes and ultrasonically degassed prior to use.

### Mass spectrometric conditions

Mass spectrometric detection was performed on API 2000 mass spectrometer (Applied Biosystems/MDS SCIEX, Concord, Ontario, Canada) equipped with TurboIonSpray ionization source operating in ESI positive ion mode. Optimization of the MS conditions was carried out using a solution of domperidone and internal standard, delivered at a constant flow-rate of 10 μL/min. The nebulizer and TurboIonSpray gases (nitrogen) were set at a value of 20 and 30 units, respectively. The optimized TurboIonSpray voltage and temperature were set at 5500 V and 350°C, respectively. Nitrogen was also used as curtain gas and collision cell gas, which were set at 10 and 7 instrument unit, respectively. The declustering potential (DP) was set at 41 and 21 V for domperidone and IS, respectively. The optimized collision energy of 85 V was used for domperidone and 51 V for the IS. Quantification was performed using the multiple reaction monitoring (MRM) transition

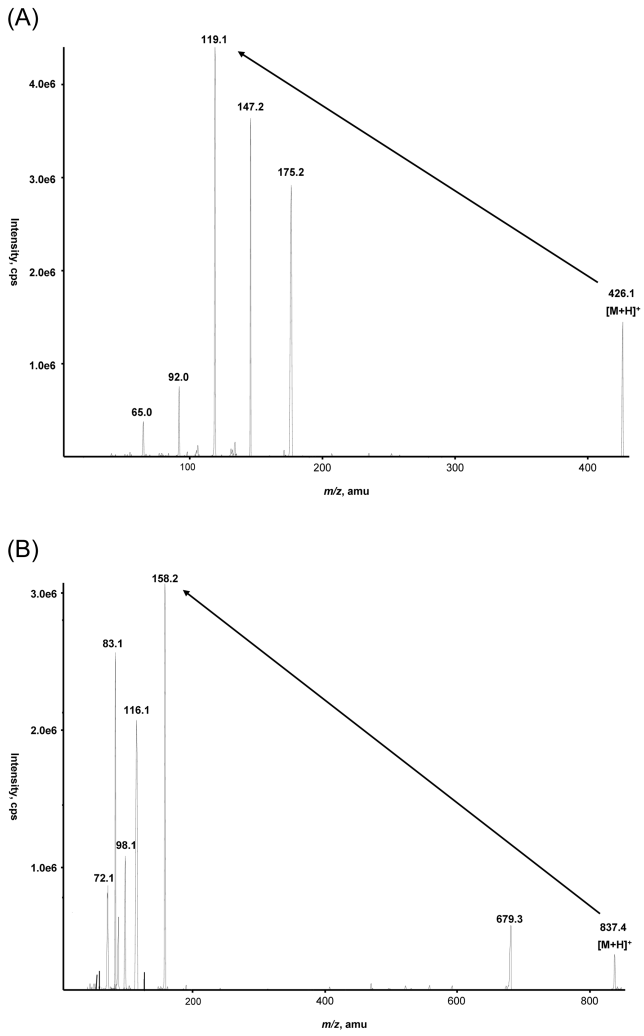


**Figure 2**–Product ion spectra of $[M+H]^+$ ions of (A) domperidone and (B) roxithromycin(IS).

*m/z* 426.1→*m/z* 119.1 for domperidone, *m/z* 837.4→*m/z* 158.2 for the IS, respectively (Figure 2).

### Method validation

The method was validated for specificity, accuracy, precision and linearity according to the FDA guideline[13] for validation of bioanalytical methods. The specificity of the method was measured by analysis of six blank plasma samples of different origin for interference at the retention times of the analyte and IS. Specificity was assessed by comparing the chromatograms obtained from the sample spiked with a concentration of domperidone and IS at LLOQ with those obtained from blank samples.

The linearity of the calibration curves, ranging from 0.05 to 50 ng/mL, was validated with seven different calibration curves. The calibration curves ($y=ax+b$), were constructed using the weighted regression method ($1/x^2$) of peak area ratios of domperidone to IS (y) versus actual concentrations ($x$).

In order to assess the intra-day precision and accuracy were performed by repeating the analysis five times in a single day, and inter-day precision and accuracy were performed by repeating this analysis on five consecutive days. Precision is expressed as coefficient of variance (C.V. %), at each level. The accuracy of the assay was defined as a percentage of the measured concentration over the nominal concentration. The acceptance criterion for each back-calculated standard concentration was 15% deviation from the nominal value, except for LLOQ, which was set at 20%. The LLOQ was determined as the concentrations with a signal to noise ratio of 10.

### Bioequivalence study

The method described in this paper was applied to a bioequivalence study of two oral formulations of domperidone maleate (test product: Toriem®; reference product: Motilium-M®). The study population consisted of twenty-four healthy male volunteers with an average age of 29.46 ± 5.90 years and an average weight of 71.13 ± 8.60 kg. Subjects were enrolled in this study after performing a medical history assessment, a physical examination and standard laboratory (blood analysis; hemoglobin, hematocrit, RBC, WBC, platelet, differential counting of WBC, total protein, albumin, sGOT, sGPT, alkaline phosphatase, total bilirubin, cholesterol, creatinine, blood urea nitrogen and glucose fasting and urine analysis; specific gravity, color, pH, sugar, albumin, bilirubin, RBC, WBC and cast) testing. All of the participants signed a written consent form after they had been informed of the nature and details of the study in accordance with the Korean Guidelines for Bioequivalence Test.[14] After an overnight fast (12 hr), each volunteer was given an oral dose (two domeperidone maleate tablets; domperdione maleate 25.44 mg) with 240 mL of water. The subjects were hospitalized (Kyunghee Medical Center, Seoul, Korea) at 10:00 p.m. on the eve of the study and fasted overnight and 4 hr after each drug administration. About 7.0 mL of blood samples were collected from each volunteer using a catheter inserted into the median cubital vein into heparinized tubes before (0 hr) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, 12 and 24 hr after dosing. Plasma was separated by centrifugation at 3,000 rpm for 7 min and kept frozen at −70°C until analysis.

### Pharmacokinetics and statistical analysis

Pharmacokinetics parameters were calculated from plasma levels applying a non-compartmental statistic using BA calc 2002 software. Plasma samples were drawn up to a period of

three to five times the terminal elimination half-life ($t_{1/2}$) and it was considered as the area under the concentration time curve (AUC) ratio higher than 80%. The $C_{max}$ and $T_{max}$ values were determined by visual inspection of the plasma domperidone concentration-time curve ($AUC_{0-t}$) that were obtained by the trapezoidal method in 0~24 hr. Their ratios (test/reference) using log-transformed data, together with their means and 90% confidence intervals, were analyzed with analysis of variance (ANOVA) that was performed with the K-BE Test program® at a significant level of 0.05.[15] Results are indicated as mean ± standard deviation.

## Results and Discussion

### Method validation

Figure 3 shows the typical chromatograms of a drug-free

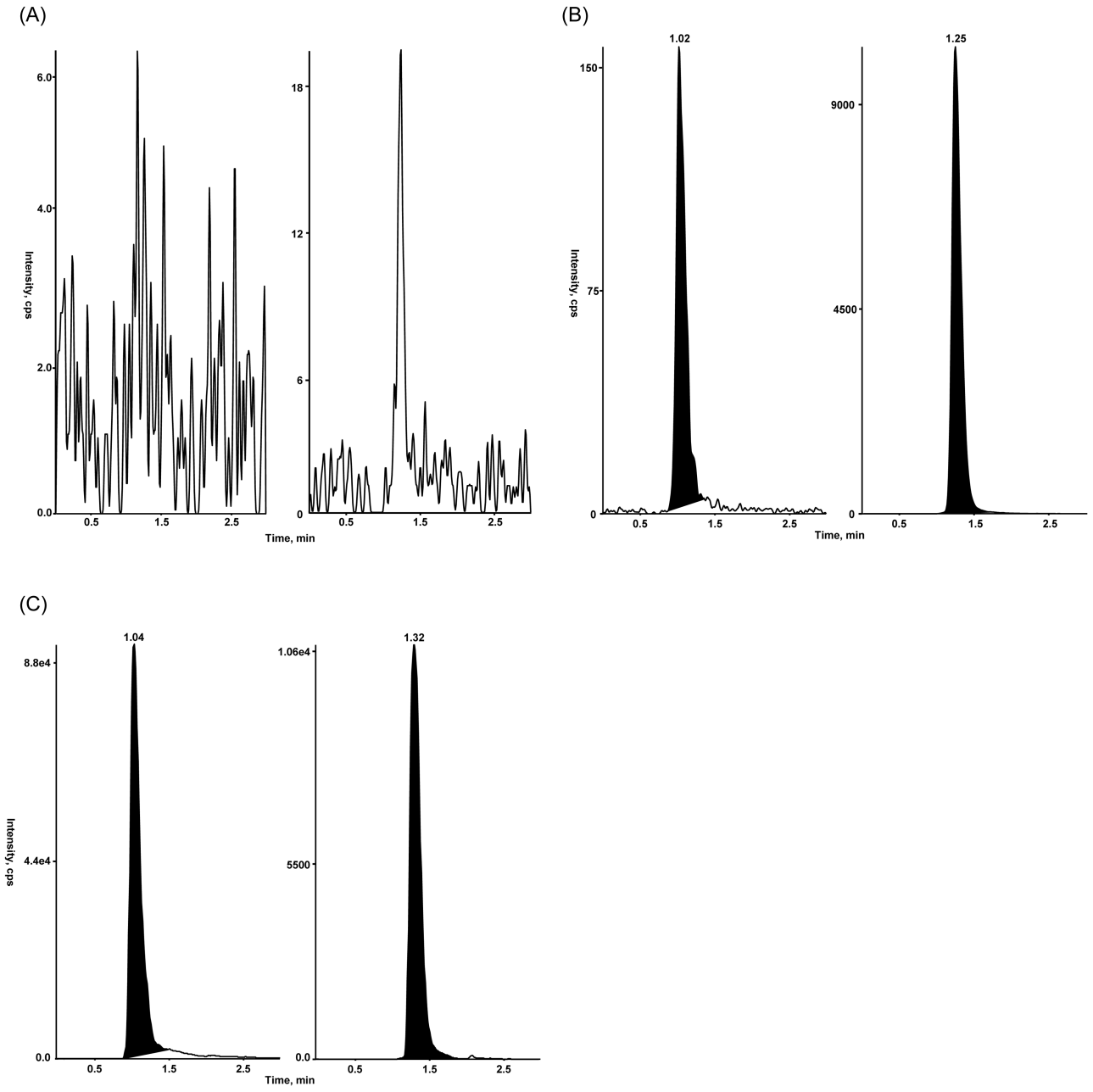


**Figure 3**–Multiple reaction monitoring chromatogram of (A) blank human plasma, (B) plasma spiked with domperidone (0.05 ng/mL) and IS (500 ng/mL) and (C) plasma (44.4 ng/mL) from a volunteer 0.5 hr after the oral administration of 2 Toriem® tablets (domperidone maleate 25.44 mg).

**Table I**–*Precision and Accuracy for the Determination of Domperidone in Human Plasma (n = 5)*

| Concentration (ng/mL) | Precision (C.V. %) | | Accuracy (%) | |
|---|---|---|---|---|
| | Intra-day | Inter-day | Intra-day | Inter-day |
| 0.05 | 16.09 | 18.69 | 93.84 | 96.81 |
| 0.50 | 12.89 | 14.23 | 97.48 | 101.66 |
| 5.00 | 10.04 | 10.87 | 98.20 | 91.76 |
| 10.00 | 11.00 | 14.64 | 89.40 | 93.00 |

plasma sample, a blank plasma spiked with (0.05 ng/mL) and IS, and a plasma sample collected at 1 hr after drug administration. There is no significant interference from the plasma found at the retention time. Domperidone and IS were separated from the biological background at 1.0 and 1.3 min,

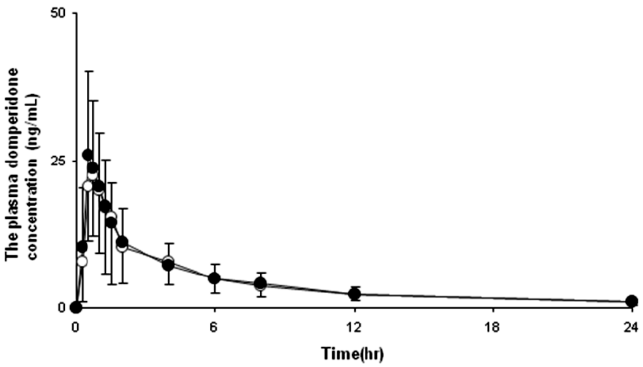


**Figure 4**–Mean (±S.D., n=24) plasma concentration-time curves of domperidone following oral administration of Toriem® (○) and Motilium-M® (●) tablets at the dose of 25.44 mg of domperidone maleate.

**Table II**–*Bioavailability Parameters in Normal and Logarithmic Scales for Each Subject Obtained after Oral Administration of Motilium-M® and Toriem® Tablets at the Domperidone maleate Dose of 25.44 mg*

| Subjects | Motilium-M® | | | | | Toriem® | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $AUC_{0-t}$ (ng·hr/mL) | Log $AUC_{0-t}$ | $C_{max}$ (ng/mL) | Log $C_{max}$ | $T_{max}$ (hr) | $AUC_{0-t}$ (ng·hr/mL) | Log $AUC_{0-t}$ | $C_{max}$ (ng/mL) | Log $C_{max}$ | $T_{max}$ (hr) |
| A1 | 165.31 | 2.22 | 55.00 | 1.74 | 0.50 | 144.64 | 2.16 | 32.90 | 1.52 | 0.75 |
| A2 | 99.32 | 2.00 | 23.70 | 1.37 | 0.75 | 76.90 | 1.89 | 25.50 | 1.41 | 0.50 |
| A3 | 131.85 | 2.12 | 44.40 | 1.65 | 0.50 | 89.49 | 1.95 | 31.80 | 1.50 | 0.75 |
| A4 | 163.11 | 2.21 | 60.10 | 1.78 | 0.50 | 146.63 | 2.17 | 53.50 | 1.73 | 0.75 |
| A5 | 77.27 | 1.89 | 31.00 | 1.49 | 0.50 | 93.38 | 1.97 | 38.00 | 1.58 | 0.75 |
| A6 | 152.12 | 2.18 | 32.80 | 1.52 | 0.75 | 140.19 | 2.15 | 17.20 | 1.24 | 1.25 |
| A7 | 89.70 | 1.95 | 40.60 | 1.61 | 0.25 | 104.31 | 2.02 | 27.50 | 1.44 | 0.50 |
| A8 | 151.53 | 2.18 | 42.30 | 1.63 | 0.50 | 155.44 | 2.19 | 31.30 | 1.50 | 0.75 |
| A9 | 61.66 | 1.79 | 19.50 | 1.29 | 0.50 | 65.73 | 1.82 | 24.00 | 1.38 | 0.75 |
| A10 | 132.88 | 2.12 | 40.60 | 1.61 | 0.50 | 203.80 | 2.31 | 63.70 | 1.80 | 1.25 |
| A11 | 117.76 | 2.07 | 47.80 | 1.68 | 0.75 | 98.74 | 1.99 | 30.90 | 1.49 | 0.50 |
| A12 | 88.61 | 1.95 | 23.50 | 1.37 | 0.50 | 71.86 | 1.86 | 20.60 | 1.31 | 0.75 |
| B1 | 110.42 | 2.04 | 24.50 | 1.39 | 1.00 | 96.52 | 1.98 | 22.60 | 1.35 | 0.50 |
| B2 | 97.14 | 1.99 | 21.00 | 1.32 | 0.75 | 107.67 | 2.03 | 25.00 | 1.40 | 0.50 |
| B3 | 69.08 | 1.84 | 21.70 | 1.34 | 0.50 | 78.03 | 1.89 | 11.90 | 1.08 | 0.75 |
| B4 | 74.29 | 1.87 | 20.40 | 1.31 | 0.50 | 58.02 | 1.76 | 18.80 | 1.27 | 0.25 |
| B5 | 185.90 | 2.27 | 31.40 | 1.50 | 1.25 | 158.65 | 2.20 | 32.60 | 1.51 | 0.50 |
| B6 | 170.55 | 2.23 | 27.90 | 1.45 | 1.25 | 162.39 | 2.21 | 33.00 | 1.52 | 0.50 |
| B7 | 44.57 | 1.65 | 20.90 | 1.32 | 0.50 | 45.25 | 1.66 | 10.90 | 1.04 | 1.00 |
| B8 | 58.01 | 1.76 | 17.10 | 1.23 | 0.75 | 73.07 | 1.86 | 23.40 | 1.37 | 0.75 |
| B9 | 47.44 | 1.68 | 7.83 | 0.89 | 1.25 | 44.34 | 1.65 | 13.80 | 1.14 | 0.50 |
| B10 | 64.91 | 1.81 | 25.30 | 1.40 | 0.50 | 57.80 | 1.76 | 18.40 | 1.26 | 0.25 |
| B11 | 48.37 | 1.68 | 10.50 | 1.02 | 0.75 | 58.57 | 1.77 | 19.90 | 1.30 | 0.50 |
| B12 | 96.70 | 1.99 | 23.50 | 1.37 | 0.50 | 112.63 | 2.05 | 21.80 | 1.34 | 1.50 |
| Mean | 104.10 | 2.02 | 29.72 | 1.47 | 0.67 | 101.83 | 2.01 | 27.04 | 1.39 | 0.70 |
| (S.D.) | 43.46 | 1.64 | 13.34 | 1.13 | 0.27 | 42.91 | 0.18 | 12.15 | 0.18 | 0.30 |

respectively. The total analysis time for each run was 3 min.

Calibration curves were prepared over the domperidone concentration range of 0.05~50 ng/mL by linear regression using a $1/x^2$ weighting factor. Correlation coefficients ($r$) were greater than 0.9941 (n=7) for all curves and the within- and between-run C.V.s of the response factors for the concentrations assayed were <15%. The limit of detection (LOD) arbitrarily set at a signal to noise ratio (S/N)=3 and the lower limit of quantitation (LLOQ) at an S/N=10. The precision and accuracy of LLOQ was required to be within 20% according to FDA guidelines. Under the validation conditions described, the lower limit of quantification was 0.05 ng/mL for domperidone (S/N ratio >10).

Intra- and inter-day precision and accuracy of the method used for domperidone analysis are presented in Table I. Intra-day precisions were between 10.04 and 16.09%, and inter-day precisions between 10.87 and 18.69%. Intra- and inter-day accuracies ranged from 89.40 to 98.20% and from 91.76 to 101.66%, respectively. All results were within the ranges of precision (%) and accuracy (%) specified by the KFDA for bioanalytical applications.

**Pharmacokinetic analysis**

Figure 4 shows the plasma domperidone concentration time profile after administration of the different tablets. Plasma profiles of the domperidone concentration versus time after the oral administration of a single dose of both formulations exhibited closely similar patterns. All calculated pharmacokinetic parameter values were shown in Table II. The extent of absorption is a key characteristic of drug formulation, and therefore AUC is an important parameter for bioequivalence study. The other two parameters, $C_{max}$ and $T_{max}$, are also important features and could affect the therapeutic behavior of a drug and hence were also considered in the study. The sampling schedule should be planned to provide a reliable estimate of the extent of absorption. This is generally achieved if $AUC_{0-t}$ is at least 80% of $AUC_{0-\infty}$. The $AUC_{0-t}$ value of this test estimated was 89.48% of $AUC_{0-\infty}$ value.

In our study, $AUC_{0-t}$ and $C_{max}$ for domperidone were 104.10 ± 43.36 ng·hr/mL (reference drug) and 101.83±42.91 ng·hr/mL (test drug), 29.72±13.34 ng/mL (reference drug) and 27.04± 12.15 ng/mL (test drug), respectively. The 90% confidence intervals for the ratios of $AUC_{0-24}$ and $C_{max}$ were log 0.92~log 1.05 and log 0.81~log 1.05, respectively, meeting the bioequivalence criteria of log 0.80~log 1.25.[16]

No significant sequence effect was found for all of the bioequivalence parameters indicating that the cross-over design was properly performed. The difference of the test product/ the reference product for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ were −1.86%, −1.60% and −7.38%, respectively.

**Table III**–*Statistical Results of Bioequivalence Evaluation between Two Domperidone maleate Tablets*

| | Parameters | | |
|---|---|---|---|
| | $AUC_{0-t}$ | $AUC_{0-\infty}$ | $C_{max}$ |
| Difference (%) | −1.86 | −1.60 | −7.38 |
| Test/Ref estimate | 0.981 | 0.983 | 0.926 |
| 90% C.I. | 0.9173−1.0499 | 0.9244−1.0474 | 0.8132−1.0548 |

## Conclusions

It was shown that this method is suitable for the analysis of domperidone in human plasma samples for bioequivalence studies. Using this method, the bioequivalence of two different 12.72 mg of domperidone maleate tablet products was examined in twenty-four healthy male volunteers. The statistical analysis results based on comparisons of the two pivotal parameters ($AUC_{0-t}$ and $C_{max}$) demonstrated the bioequivalence of these two tablet products of domperidone maleate.

## Acknowledgements

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