Development and validation of a sensitive HPLC-HESI-MS/MS method for quantitative determination of bitopertin in rat and marmoset plasma [version 1; peer review: awaiting peer review]

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\textbf{Abstract}

Bitopertin is a potent glycine transporter 1 (GlyT1) inhibitor that has undergone clinical trials for diverse disorders and has a well-documented pharmacokinetic (PK) profile in humans. Even though pre-clinical studies have demonstrated potential therapeutic effects on cognition and neuropathic pain, the PK profile of bitopertin in the rat has been partly disclosed and no study reporting its PK profile in the common marmoset has been published. The aim of this study was to develop and validate a sensitive and selective high-performance liquid chromatography coupled with heat assisted electrospray ionisation tandem mass spectrometry (HPLC-HESI-MS/MS) assay to quantify bitopertin in the rat (Sprague-Dawley) and the common marmoset (\textit{Callithrix jacchus}) plasma after administration of 1.0 mg/kg subcutaneously. The analytical method consisted of protein precipitation followed by HPLC-HESI-MS/MS. Chromatographic separation was carried out on a Thermo Scientific Aquasil C18 analytical column (100 x 2.1 mm I.D., 5.0 µm) kept at 50°C using acetonitrile and water both fortified at 0.1% (v/v) with formic acid at a ratio 55:45 as mobile phase with a constant flow rate of 250 µL/min.
The calibration function was linear in the range of 0.3-200.0 ng/mL in rat plasma. The intra-day and inter-day precision and accuracy were within ± 15% at all concentrations. The limit of detection (LOD) and quantitation (LOQ) in rat plasma were 0.08 and 0.3 ng/mL, respectively. This method has demonstrated high sensitivity and specificity and was successfully applied to measure bitopertin in rat and marmoset plasma, allowing the investigation of its PK properties in both species.

**Keywords**
Bitopertin, rat plasma, marmoset plasma, bioanalysis, HPLC-HESI-MS/MS
Introduction
In the last decade, glycine transporter 1 (GlyT1) inhibition has been strongly pursued as a therapeutic strategy in numerous neuro-psychiatric disorders (Bugarski-Kirola et al., 2017; D’Souza et al., 2018; Dunayevich et al., 2017; Lane et al., 2010; Nations et al., 2012; Wu et al., 2011). Also referred to as RG1678 or RO-4917838, bitopertin, by blocking GlyT1, increases levels of synaptic glycine, and since glycine acts as a co-agonist to the N-methyl-D-aspartate (NMDA) receptor, promotes the potentiation of the receptor’s activity (Gabernet et al., 2004; Kinney et al., 2003; Lim et al., 2004; Sur & Kinney, 2007). Bitopertin is a highly selective GlyT1 inhibitor that underwent several clinical trials, notably for the treatment of negative symptoms associated with schizophrenia (Bugarski-Kirola et al., 2017; Hirayasu et al., 2016; Kantrowitz et al., 2018; Rofaii et al., 2016), obsessive-compulsive disorder (Roche, 2012) and β-thalassaemia (Roche, 2017; Taher et al., 2018). Moreover, recent pre-clinical studies suggested that bitopertin could have a therapeutic potential at managing neuropathic pain and improving cognition (Armbruster et al., 2018; Castner et al., 2014).

The known pharmacokinetic (PK) profile of bitopertin in animals is limited, with published PK studies reporting parameters following administration of few doses in rat (2 mg/kg, intravenously [i.v.]; 3 mg/kg, orally [p.o.]) or cynomolgus macaque (0.5 mg/kg i.v.; 3 mg/kg p.o.), limiting dose-concentration response relationship needed in pre-clinical evaluations (Parrott et al., 2013; Pinard et al., 2010). To the best of our knowledge, there are no published validated assays to quantify bitopertin in the common marmoset (Callithrix jacchus).

Most of the published PK studies employed high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) to measure bitopertin in plasma, urine or cerebro-spinal fluid samples (Hofmann et al., 2016; Parrott et al., 2013; Pinard et al., 2010). Although, HPLC-MS/MS is an attractive method to characterise the PK profile of drugs as lower limits of quantitation (LLOQ) can be achieved, there are no published assays that could detect trace concentrations of bitopertin in animals. The LLOQs reached in plasma were 0.300 – 200 ng/mL. Quality control samples were prepared in both rat and marmoset plasma. The internal standard working solution (ISWS) consisted of 5.00 ng/mL of glibenclamide in methanol.

Extraction procedure
Five hundred μL of ISWS was used as the precipitating agent and was added to an aliquot of 25 μL of plasma sample (rat or marmoset) in a conical polypropylene tube. The sample was vortexed for 5 sec and let stand for 10 min, after which it was centrifuged at 16,000 × g for 10 min. To diminish sample dilution to a minimum, the supernatant was pipetted into a clean 13 × 100 mm borosilicate tube and evaporated to dryness under a gentle nitrogen stream at 40°C. The dried extract was reconstituted with 100 μL of 40:60 methanol: 0.1% (v/v) formic acid in water, after which it was placed into an injection vial for analysis.

Chromatography and mass spectrometry
A Thermo Scientific TSQ Quantiva Triple Quadrupole mass spectrometer (San Jose, CA, USA) was interfaced with a Thermo Scientific UltiMate 3000 XRS UHPLC system (San Jose, CA, USA) using a pneumatic assisted heated electrospray ion source. Positive ion mode was used to conduct MS detection, employing multiple reaction monitoring (MRM). Standard solutions of bitopertin and glibenclamide were used to tune the mass spectrometer to obtain optimum analyte detection. The resulting parameters were nitrogen, used for the sheath, and auxiliary gases set to 50 and 15 arbitrary units, HESI electrode was set to 3,500 V, capillary temperature was set to 300°C, while vaporiser temperature was set to 300°C. The collision gas was argon, at a pressure of 2.5 mTorr. The MRM transitions were set to 544.1 → [199.0 + 295.1] for bitopertin and 494.2 → 169.0 for glibenclamide. The collision energies (E<sub>coll</sub>) were set to 40, 26 and 34 eV for product ions 199.0, 295.1 and 169.0, respectively. Total cycle time was 0.25 sec. The mass spectrometer was calibrated utilising an automated Thermo Scientific algorithm; peak widths of Q1 and Q3 were set to 0.7 full width half mass (FWHM). The separation was achieved with isocratic elution consisting of acetonitrile and water fortified at 0.1% (v/v) formic acid at a
55:45 ratio on a Thermo Scientific Aquasil C18 analytical column (100 × 2.1 mm I.D., 5.0 μm) kept at 50°C. The flow rate was 250 μL/min, bitopertin and glibenclamide were eluted at 5.3 and 2.9 min. Five μL of the extracted sample was injected. Acquisition and analysis of data were conducted using the Xcalibur 4.0 software (San Jose, CA, USA). Each calibration curve was comprised of a double blank (matrix without analyte or internal standard), zero standard and 8 calibration points. Calibration curves were computed from the equation y = ax + b, based on the weight of the calibration lines created from the peak-area ratios of drug relative to the internal standard.

Stability evaluation
For freeze/thaw stability, quality control samples underwent three freeze and thaw cycles. In each of these cycles, the samples were let thaw at room temperature, after which they were refrozen for 24 h at -80°C. For short-term stability, stability samples remained at room temperature for a duration greater than the maximum time expected to conduct the sample preparation (5 h). For auto sampler stability, quality control samples were left in the auto sampler for 148 h. The stability sample concentrations were obtained against a freshly prepared rat plasma calibration curve.

Bioanalytical method validation
The method was validated according to the FDA regulatory guidelines (Bioanalytical Method Validation Guidance for Industry, 2018) for the following parameters: selectivity, sensitivity, linearity, precision and accuracy, stability, matrix effect and recovery. The method selectivity was evaluated by processing rat and marmoset plasma from six individual sources as detailed above in the extraction procedures. The peak area response at the retention time of the analyte was compared to the peak area response of the rat plasma standard spiked at the LLOQ. As per the FDA recommendations, the analyte levels in the blank sample should be less than 20% of the LLOQ. For sensitivity, the LLOQ was set to the concentration of the lowest calibration standard resulting in an analyte response greater than 5 times the blank response with acceptable precision and accuracy (within 20%). To assess linearity, the calibration curve using the simplest model to adequately describe the concentration-response relationship was analysed. The best fit was achieved with least-squares linear regression analysis of the peak area ratio (analyte/IS) versus theoretical concentration of the calibration standard with a weighing factor of (1/x). The calibration curve encompassed a blank (no analyte, no IS), a zero standard (no analyte with IS), as well as eight non-zero standards. The precision and accuracy across the analytical range were evaluated by detecting bitopertin at the LLOQ, low, medium and high quality control (QC) concentrations for rat plasma. Because of matrix limitations, precision and accuracy in marmoset plasma were evaluated at low, medium and high QC concentrations in six replicates per QC level in three independent runs. The intra- and inter-run precision was determined as relative standard deviation (RSD) and must be less than 15%, except at the LLOQ (within 20%, as mentioned above). The intra- and inter-run accuracy was expressed as relative error (RE) and should be smaller than 15%, or 20% at the LLOQ. The chemical stability of bitopertin was measured under several conditions. The effects of freeze and thaw, short-term and auto-sampler were assessed by back-calculation the stability at low, medium and high concentrations in both rat and marmoset plasma, against a freshly generated rat calibration curve. The recovery was determined by extracting replicates (n=5) at low, medium and high concentrations in both rat and marmoset plasma and comparing the intensities of the extracted samples with those garnered from blank extracts reconstituted with pure reference solution at the same corresponding amount, which corresponded to 100% recovery.

Animals
Animal experiments were approved by the Montreal Neurological Institute Animal Care Committee and McGill University Animal Care and Use Committee and performed in agreement with the regulations defined by the Canadian Council on Animal Care. All efforts were made to avoid causing any suffering to animals; we worked in close collaboration with the Animal Care Committees and veterinary teams to improve animal’s conditions. All experiments were conducted in specific experimental rooms around 09:00 am.

Six female Sprague-Dawley rats (225–250 g; Charles River, Saint-Constant, QC, Canada) were group-housed (3 per cage) under controlled settings of temperature (21 ± 1°C), humidity (55%), light (12-h light/dark cycle, lights on at 07:00 a.m.), with unlimited access to food and water. After arrival, rats were left undisturbed for one week to adapt to the new environment. The number of animals was determined based on previous studies (Maiti et al., 2007; Park et al., 2019).

Six (5 males and 1 female) common marmosets (McGill University breeding colony; 340-530g and aged between 3 and 6 years old at the time of experiments) were group-housed (2 per cage) under controlled conditions of temperature (24 ± 1°C), humidity (50 ± 5%) and a 12 h light/ dark cycle (07:15 a.m. lights on). Animals had unrestricted access to food, fresh fruits and water. The home cages were enhanced with nestboxes, primate toys and perches. The number of animals is in agreement with previous PK studies in the marmoset (Fernandez et al., 2019; Toda et al., 2018).

Application of the method
Bitopertin was dissolved in sterile 0.9% NaCl containing 0.3% (v/v) Tween 80 and injected s.c. to drug naïve Sprague Dawley rats or common marmosets at a dose of 1.0 mg/kg body weight (BW). Two min were allowed ibetween each administration between rat subjects and five min between marmoset subjects. Blood samples (150 μL) were collected by jugular vein puncture in rats and tail vein puncture in marmosets at the following time points: predose, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 24 h, 48 h, 72 h, 96 h, 144 h and 216 h, as previously described (Gaudette et al., 2017; Gaudette et al., 2018; Hamadjida et al., 2018). A sparse sampling technique was utilised in marmoset (n=3 per time point), to limit the number of animals used, as previously reported (Frouni et al., 2019; Gaudette et al., 2018). Samples were transferred into K_EDTA-coated tubes, delicately inverted, centrifuged at 1,500 × g for 10 min at 4°C, then stored at -80 °C until analysis.
Results and discussion

Method development

Appropriate sample preparation is a critical element of quantitative bioanalysis. Protein precipitation technique (PPT) is abundantly employed since it offers a quick, generic and simple way to prepare samples. We evaluated different organic solvents, e.g. acetonitrile, acetone and methanol to precipitate proteins. Methanol was selected as it was the least expensive and provided the best recovery. The overall average recoveries were higher than 94.2% and 91.7% in rat and marmoset plasma, respectively (Table 1). The analysis of supernatant from plasma PPT samples may at times result in matrix effects, a decrease or increase in ion signal caused by the presence of salts and/or endogenous material within the sample (Gosetti et al., 2010; Zhou et al., 2017). To assess possible matrix effect, we utilized a post extraction addition protocol (Zhou et al., 2017) at low, medium and high concentrations in six different donors in rat and, because of matrix limitations, five different donors in marmoset. The matrix effect was determined quantitatively by comparing the response of the analyte at low, medium and high levels in neat solution to the response of a post extract spiked with the analyte at the same concentration. No significant difference was encountered between the different plasma lots tested in each species (Table 2).

Tandem mass spectrometry

Positive ion mode was employed to acquire bitopertin and glibenclamide precursor and product ion spectra. Bitopertin and glibenclamide precursor ion spectra showed a strong signal for the protonated molecules ([M+H]+) at m/z 544 and 494, respectively (Figure 1A and 1B). The product ion spectra of bitopertin revealed fragment ions at m/z 147, 184, 199, 277, 295 and 524, whereas glibenclamide displayed fragment ions at m/z 169, 288, 352, 369 and 395 (Figure 1C and D). Figure 2 depicts fragment ion structures for the MS/MS transitions of bitopertin and glibenclamide. For bitopertin, the mass spectrometer was set to MRM mode for best sensitivity, MS/MS transition were set to m/z 544→[199+295]. For glibenclamide, the mass spectrometer was programmed for best selectivity and the MS/MS transition inputted was 494→169.

Selectivity, sensitivity and calibration curve analysis

For rat and marmoset matrices, interference was evaluated in each individual blank sample (n=6), and selectivity was assessed at the LLOQ. Absence of interfering components is adequate when the blank sample response is no greater than 20% of LLOQ for the analyte and smaller than 5% for the internal standard. Interference caused by endogenous elements was not observed in any blank plasma evaluated in either species. The limit of detection (LOD), defined as the amount of analyte required to obtain at least 3 times the signal response of the blank response, was evaluated at 100 fg injected on column for both matrices. LLOQ was 0.3 ng/mL in rat plasma. Figure 3 depicts examples of chromatograms of extracted blank plasma in rodent and primate matrices, as well as a LLOQ sample in rat plasma and an overlay of extracted blank sample and a zero standard. A linear regression (1/x) modelled the concentration–detector relationship most accurately. The calculated coefficients of correlation (r) were higher than 0.9975 for an analytical range spanning 0.30 to 200 ng/mL in rat plasma.

Precision and accuracy

The method’s reproducibility was determined by analysing six replicate plasma samples at three bitoperin concentrations 1.20, 4.80 and 60.0 ng/mL in rat and marmoset plasma within an analytical run (intra) and between three individual runs (inter). Precisions better than 13% and accuracies within the 93.2-112.8% range were obtained. Table 3 presents the intra- and inter-batch precision and accuracy of statistical analyses.

Stability

The stability of bitopertin under typical sample storage and analysis in the two species was assessed by conducting

Table 1. Bitopertin recovery in rat and marmoset plasma. Recovery results are presented as percentage of the pure reference sample fortified in the blank extract (mean ± SD; n=5).

<table>
<thead>
<tr>
<th>Species</th>
<th>Bitopertin concentration (ng/mL)</th>
<th>% recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1.20</td>
<td>102.4 ± 10.4</td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>97.2 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>94.2 ± 6.9</td>
</tr>
<tr>
<td>Marmoset</td>
<td>1.20</td>
<td>96.3 ± 10.1</td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>95.3 ± 9.9</td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>91.7 ± 3.7</td>
</tr>
</tbody>
</table>

Table 2. Matrix effect of bitopertin at low, medium and high concentrations in different rat and marmoset plasma lots. (Percent nominal, mean ± SD; n = 3).

<table>
<thead>
<tr>
<th>Species</th>
<th>Bitopertin concentration (ng/mL)</th>
<th>Lot-01</th>
<th>Lot-02</th>
<th>Lot-03</th>
<th>Lot-04</th>
<th>Lot-05</th>
<th>Lot-06</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1.20</td>
<td>107.0 ± 11.5</td>
<td>96.4 ± 4.7</td>
<td>100.1 ± 2.2</td>
<td>110.9 ± 9.0</td>
<td>100.8 ± 1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>106.3 ± 13.0</td>
<td>99.5 ± 4.3</td>
<td>103.1 ± 3.6</td>
<td>101.5 ± 3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>101.1 ± 7.7</td>
<td>95.3 ± 1.2</td>
<td>104.5 ± 1.2</td>
<td>101.3 ± 3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marmoset</td>
<td>1.20</td>
<td>105.5 ± 4.8</td>
<td>152.5 ± 4.8</td>
<td>194.5 ± 2.9</td>
<td>26.7 ± 3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>106.0 ± 3.9</td>
<td>100.1 ± 1.7</td>
<td>99.5 ± 4.5</td>
<td>99.0 ± 2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.00</td>
<td>98.3 ± 0.8</td>
<td>98.3 ± 0.0</td>
<td>99.6 ± 2.4</td>
<td>98.3 ± 3.2</td>
<td></td>
<td></td>
</tr>
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</table>
stability experiments. Stability results were determined by back-calculating the concentration of the stability samples (low, medium and high concentrations) compared to newly generated rat plasma calibration curve. Stability data were considered adequate when the average accuracy value was within ±15% of the nominal value and the %RSD of the replicate (n=5) was less than 15%. Stability was measured for freeze and thaw, short-term and auto sampler. Bitopertin remained stable for at least three freeze/thaw cycles, 5 h short-term and 148 h in the auto sampler. Table 4 reports stability results.
Figure 2. Chemical structures and fragmentation ions for bitopertin (A) and glibenclamide (B).

Figure 3. Reconstructed ion chromatograms for bitopertin and glibenclamide. (A) MRM transition at m/z 544 → [199 + 295] of an extracted rat blank sample (red line), an extracted marmoset blank sample (black line) and an extracted LLOQ plasma sample (blue line). (B) SRM transition m/z 494 → 169 of an extracted rat blank sample (red line), an extracted marmoset blank sample (black line) and extracted blank with internal standard (blue line).
Sample analysis
The analytical method described here is suitable for pre-clinical PK experiments as demonstrated by the analysis of bitopertin in rat and marmoset plasma after performing a pilot study where s.c. administration of 1.0 mg/kg BW was performed. Figure 4 illustrates the plasma concentration-time profiles in rat and marmoset.

### Table 3. Intra- and inter-batch precision and accuracy data for bitopertin in rat and marmoset plasma. (6 replicates per level (intra) in 3 individual runs (inter)).

<table>
<thead>
<tr>
<th>Species</th>
<th>Bitopertin concentration (ng/mL)</th>
<th>Intra (n=6)</th>
<th>Inter (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (ng/mL)</td>
<td>RSD (%)</td>
<td>RE (%)</td>
</tr>
<tr>
<td>Rat</td>
<td>0.30</td>
<td>0.325 ± 0.008</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>1.20</td>
<td>1.30 ± 0.02</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>5.35 ± 0.09</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>67.7 ± 1.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Marmoset</td>
<td>1.20</td>
<td>1.12 ± 0.10</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>4.57 ± 0.59</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>62.2 ± 6.4</td>
<td>10.4</td>
</tr>
</tbody>
</table>

RSD = relative standard deviation, RE = relative error

### Table 4. Freeze and thaw, short-term and auto sampler stability of bitopertin in rat and marmoset plasma. (Percent nominal ± SD; n = 3).

<table>
<thead>
<tr>
<th>Species</th>
<th>Bitopertin concentration (ng/mL)</th>
<th>Freeze/thaw (3 cycles)</th>
<th>Short-term (5h)</th>
<th>Auto sampler (148h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>1.20</td>
<td>90.6 ± 3.4</td>
<td>110.3 ± 3.1</td>
<td>91.0 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>89.5 ± 6.2</td>
<td>109.9 ± 6.1</td>
<td>86.1 ± 5.5</td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>102.9 ± 6.7</td>
<td>102.9 ± 6.5</td>
<td>107.0 ± 5.1</td>
</tr>
<tr>
<td>Marmoset</td>
<td>1.20</td>
<td>108.0 ± 5.3</td>
<td>108.0 ± 5.3</td>
<td>92.8 ± 4.7</td>
</tr>
<tr>
<td></td>
<td>4.80</td>
<td>106.4 ± 3.0</td>
<td>106.4 ± 3.0</td>
<td>94.1 ± 9.4</td>
</tr>
<tr>
<td></td>
<td>60.0</td>
<td>112.5 ± 6.8</td>
<td>112.4 ± 6.8</td>
<td>104.1 ± 11.9</td>
</tr>
</tbody>
</table>

Figure 4. Concentration-time profile for bitopertin in rat and marmoset plasma. Mean ± SD; n = 6 for rat, n = 3 per timepoint for marmoset.
Conclusion
We developed and validated a sensitive and selective HPLC-HESI-MS/MS method for the quantitation of bitopertin in rat and marmoset plasma. The assay meets all conditions of specificity, sensitivity, linearity, precision, accuracy and stability generally accepted in bioanalytical chemistry. The method was suitable for the determination of PK parameters after a s.c. administration of 1.0 mg/kg BW in rats and marmosets.

Data availability
Underlying data

This project contains the following underlying data:
- Validation raw data
- Chromatography raw data
- Spectrum raw data

References


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