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ORIGINAL RESEARCH PAPER

LC-MS/MS determination of glimepiride in human plasma with a high recovery at picogram scale: Pharmacokinetic study after oral administration

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ABSTRACT

Although glimepiride (GLM) is the first-line treatment of Type II diabetes, low extraction recovery is still a significant limitation in previous plasma analysis methods. An optimized solid-phase extraction method of GLM in human plasma with excellent extraction recovery, $100 \pm 0.06\%$, was achieved using liquid chromatography-electrospray ionization tandem mass spectrometry and Gliclazide (GLZ) as an internal standard. GLM was extracted from 100 μ L plasma sample using Sep-Pak[®] vac 1cc (100 mg) C18 column and methylene chloride: methanol (2: 1, v/v) as eluant. Both GLM and GLZ were monitored by a triple quad mass spectrometer applying positive multiple reaction monitoring mode (+MRM). The protonated precursor ions and product ions of GLM and GLZ were m/z 491(352), and m/z 324 (127), respectively. The detection and measurement of low levels of GLM in human plasma reached to picogram range (limit of detection (LOD) = 60 pg/mL, limit of quantification (LOQ) = 200 pg/mL). The method was validated in terms of selectivity, linearity, recovery, accuracy, and precision. The method was successfully applied to the pharmacokinetic study of GLM following oral administration of 1 mg GLM tablets to 12 healthy volunteers.

KEYWORDS

glimepiride, plasma, SPE C18 extraction, excellent extraction recovery, pharmacokinetic

INTRODUCTION

The sulfonylurea glimepiride (GLM) (1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea) is used as first-line treatment of non-insulin-dependent type II diabetes mellitus [1, 2]. Many generic products have been produced and distributed in Egypt and many other countries. We need to ensure that all these generic products have similar quality and efficacy as the brand product. So, there is still an urgent need to optimize a simple, highly sensitive, and efficient method for the extraction of GLM from biological fluids.

The maximum recommended GLM dose is 8 mg once daily [3]. It has been reported that about 40% of a GLM oral dose is eliminated in feces as metabolites, and about 60% is eliminated in the urine [3, 4]. Besides, it was found that the serum concentration of GLM

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measured 30 min after a single dose of 0.25–1.5 mg to healthy volunteers was 54–247 ng/mL and after 180 min, 17–72 ng/mL [5]. However, a lower limit of quantification is required to cover the 24 h after administration as the drug is administered once daily. In addition, several generic formulations have been introduced with the possibility of lower plasma concentrations.

Many quantitative methods have been developed for the determination of GLM in biological fluids, such as high-performance liquid chromatography with ultraviolet detection (HPLC-UV) which showed, relatively, very high quantitative limits, that are far from the actual amount of non-metabolized GLM [6–9]. Also, liquid chromatography-tandem mass spectrometry (LC-MS) has been developed for its determination [10–13]. Generally, two extraction procedures were used for the recovery of GLM from plasma, including liquid-liquid extraction (LLE) [9] and solid-phase extraction (SPE) [8, 10]. The major limitation of LLE that it consumes a large quantity of organic solvent and leads to environmental pollution. The previously reported LLE methods showed a percent recovery of GLM from plasma ranged from 70 to 84%. SPE has been widely used to extract drugs from complex biological fluids due to its low consumption of organic solvents. Musmade et al. developed an LC-UV method for the determination of GLM in rat plasma using SPE with a % recovery of $76.8 \pm 2.8\%$ [8]. An LC-MS method was developed for measuring GLM in human plasma within a concentration range of 2.0–650 ng/mL using acetonitrile: methanol (1:1, v/v) as eluant, showed a % recovery of 81.9–83.4% [10]. It is noticeable that the reported methods handled a volume of 1 mL plasma adjusted at pH around 3.0 for LLE or SPE methods, using different solvent mixtures. Recently, a magnetic SPE using Fe_3O_4 @PDA nanomaterials followed with LC-MS/MS to determine GLM in beagle dog plasma showed extraction recovery (71.2–85.7%) [13]. Also, protein precipitation with acetonitrile has been used for the extraction of GLM from plasma with lower sensitivity (limit of quantification (LOQ) 3.3 $\mu\text{g mL}^{-1}$) [12]. The United States Pharmacopoeia 2013 [14] reported the use of acetonitrile: methanol (1:1, v/v) as a diluent for dissolving GLM bulk material. Glimepiride is known to have a high affinity to conjugate with plasma protein (>99.5%), as cited by Clarke's textbook [4]. This factor has not yet been considered by any reported method for the efficient extraction of GLM from the plasma of humans or rats.

As the previous methods failed in the efficient extraction of GLM from plasma with high % recovery and good sensitivity, the aim of this work is to optimize the extraction method and to highlight the influential extraction variables by applying a sensitive LC-MS/MS analytical method with the highest and precise percentage recovery. All the factors that can affect the efficiency of extraction were studied, including selecting proper extraction solvent, displacement of drug conjugated to plasma protein, and type of solid support.

EXPERIMENTAL

Chemicals and reagents

Glimepiride (>99%, GLM), gliclazide (>97%, GLZ), trifluoroacetic acid (99%, TFA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other materials were of HPLC grade. Sep-Pak[®] vac 1cc (100 mg) solid-phase extraction (SPE) columns were purchased from Waters, Ireland. The extraction manifold with 12 ports and membrane vacuum pump was from Waters, USA.

Plasma samples were collected from 12 healthy volunteers with a mean age of 41 years. Plasma samples were analyzed either immediately or kept at -80°C until the time of analysis. The bioethical and research committee of King Abdulaziz University Hospital approved the handling of the plasma samples and volunteers.

LC-MS/MS conditions

The HPLC system consisted of an Agilent 1,200 system, a solvent delivery module, a quaternary pump, an autosampler, and a column compartment (Agilent Technologies, Germany). The detector used was an Agilent 6420 triple quadrupole mass spectrometer (QQQ-MS), equipped with electrospray ionization (ESI) source, which was controlled by MassHunter software (version B.03.01, Build 3.1.346.0). The QQQ-MS conditions were as follows: gas temperature, 330°C ; gas flow rate, 11 L/min; capillary voltage, 4000 V; and nebulizer pressure, 35 psi. The MS conditions were optimized for each compound separately, including the dwell voltage, fragmentor voltage, collision energy (CE) electro volt, and a positive multiple reaction-monitoring (+MRM) mode was applied. The separation was performed on an Agilent Zorbax Eclipse Plus C18 column, 3.5 μm , 4.6 $\times$ 100 mm (Agilent Technologies, USA), and maintained at 35°C . The screw-capped (PTFE/silicon) total recovery 1-mL autosampler vial, 12 $\times$ 32 mm, was purchased from Waters (Milford, MA, USA). The analytes were isocratically eluted using a mobile system composed of acetonitrile: 0.1% formic in water (70: 30, v/v) and pumped at a flow rate of 0.4 mL/min.

Standard solutions and calibration standards

The stock solutions of the studied analyte (GLM) and of the internal standard (GLZ) were prepared separately by dissolving 5 mg of each in methanol to obtain a concentration of 0.5 mg/mL. The calibration solutions were prepared by spiking the drug-free plasma with GLM (1:10, v/v) to give a concentration spanning the range of 0.2–1,500 ng/mL and a fixed concentration of GLZ of 0.5 mg/mL. Four quality control (QC) samples were prepared in drug-free plasma to study the accuracy, recovery, and freeze and thaw stability, including a concentration of 0.2, 50.0, 1,000.0, and 1,500.0 ng/mL. All stock solutions, working, and standard solutions were prepared freshly, however, the QC samples were analyzed at zero time and stored at -80°C until analysis for later analysis.

Sample preparation

Sep-Pak[®] vac 1cc (100 mg) solid-phase extraction (SPE) column was fitted to the extraction manifold, washed with 2 mL methanol and 2 mL water containing 0.4% TFA, subsequently. The vacuum tap was closed, a volume of 100 μ L 0.4% TFA in water was added, followed by the addition of 20 μ L GLZ (0.5 mg/mL) and 100 μ L plasma sample and mixed by clicking on the column. The vacuum tape was opened to allow the sample just to pass the surface of solid support, and immediately closed, and stand for 2 min. The vacuum tap was then opened, and a volume of 2 mL water (0.4% TFA) was added to clean up the sample. The SPE column was kept under vacuum for 2 minutes, and a stream of nitrogen gas was forced to flow through the column to remove any residual water. The SPE column was then detached and fixed to another vacuum port with a clean test tube. The sample was extracted with 2 mL elution solvent composed of CH_2Cl_2 : CH_3OH , 2:1, v/v. The received extract was evaporated under a gentle stream of nitrogen gas at room temperature. The residue was reconstituted in 100 μ L CH_2Cl_2 : CH_3OH , 2:1, v/v, with the aid of vortex, and then transferred quantitatively to a total recovery autosampler vial (using Pasteur pipette) and dried with a gentle stream of nitrogen gas (at 50 °C with the aid of heating block). The residue was reconstituted in 20 μ L mobile phase, vortexed, and a volume of 10 μ L was injected for LC-MS/MS analysis. Calibration samples were spiked by 10 μ L GLM standard solutions to 100 μ L plasma, extracted, and analyzed by LC/MS.

Method validation

The method has successfully validated in terms of selectivity, linearity, stability, accuracy, and precision. A selectivity study was confirmed by comparing the chromatograms of blank human plasma with that of the spiked plasma to ensure that no endogenous substances were observed at the retention times of GLM and GLZ. The linearity was determined by plotting the peak area ratio (y) of analytes to internal standard versus the analyte (x) nominal concentration with the least square linear regression. The limit of detection (LOD) and LOQ were calculated depending on the signal to noise ratio of 3:1 and 10:1, respectively, calculated using the MassHunter program. The intra-day precision and accuracy were evaluated by three replicates of QC plasma samples spiked with LOQ, low, medium, and high concentration levels, on the same day. Three replicates of QC samples were analyzed on four consecutive days for evaluation of inter-day precision and accuracy. Both precision and accuracy were expressed by % relative standard deviation (RSD) and % relative error (Er%), respectively. The RSD values of less than 15% and Er% values within a range of –15 to 15% were required to meet the precision and accuracy requirements. The stability studies were performed on three replicates of QC samples at four concentration levels to study the analyte stability during the analysis (autosampler stability, 24 h) and three freeze and thaw cycles of QC samples stored at –80 °C along 30 days.

Pharmacokinetic study

The bioethical and research committee approved the clinical protocol of King Abdulaziz University before the study. The volunteers who agreed to attend the project were medically examined to study the pharmacokinetics of GLM. They were administered a single dose of 1 mg GLM after an overnight, 12 h fast. Blood samples were collected into heparin tubes before medication and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7, 9, 12, 18, and 24 h after oral administration. Blood samples were centrifuged at 3,000 rpm for 10 min and kept frozen at –80 °C until the time of analysis.

RESULTS AND DISCUSSION

This LC-MS method was developed and optimized to enhance the extraction recovery of GLM from plasma with optimal mass spectrometric sensitivity and low ionization suppression at the ESI compartment.

Optimization of LC-MS conditions

A standard solution containing both GLM and GLZ at a concentration of 10 ng/ μ L each was repetitively injected for LC-MS analysis using different mobile system composition at scan positive mode, followed by extracting molar ions of GLM (m/z 491.6) and GLZ (m/z 324.9). The optimal separation was obtained on the Zorbax Eclipse Plus C18 column with a mobile system composed of acetonitrile: 0.1% formic acid in water (70:30, v/v). The mobile system containing methanol (60%, v/v) showed tailed peaks eluted at retention time (t_R) of 2.5 and 2.7 min for GLZ and GLM, respectively. The QQQ-ESI-MS conditions were optimized by applying different and alternative values of capillary voltage, v , fragmentor voltage, dwell time, and CE (eV). The most abundant product ions were selected based on the most suitable fragmentor voltage and CE (eV) for both GLM and GLZ (Fig. 1). The optimal +MRM transitions were m/z 491.6 $\rightarrow$ 352.8 for GLM and m/z 324.9 $\rightarrow$ 127.2 for GLZ as shown in Table 1. The more selective and sensitive analysis was obtained by +MRM monitoring of one compound at the corresponding elution time range (time segment program).

Matrix effect

The matrix effect was evaluated to detect any possible ion suppression or enhancement of the MS response. It was estimated by comparing the peak area ratio of the analyte in the presence of matrix (blank plasma spiked with analyte) with the peak area ratio in absence of matrix (pure analyte solution) at the same concentration level (250 ng/mL). The relative percentage of GLM peak area ratio recovered from plasma sample to that recovered from the pure standard solution was $98.7 \pm 3.1\%$ which was within the acceptable range (Fig. 2). Thus, plasma matrix did not appear to interfere significantly with the method. The matrix effect was also minimized by programming the ESI-nebulizer switch to waste stream from zero to 2.5 min to elute the co-extracted biogenic materials.

Fig. 1. The ESI-MS product ions of GLM (m/z 352.8) and GLZ (m/z 127.2) using QQQ-MS

Extraction recovery

The three primary critical conditions that affect the extraction of GLM from plasma were investigated. These factors included a selection of suitable solvent mixture, selection of suitable extraction column and size, and the protein binding affinity of GLM. A solid-phase extraction, using Sep-Pak[®] vac 1cc (100 mg) C18, and a spiked water sample was used to exclude the effect of protein binding factor. A volume of 100 μ L aqueous sample containing 10 ng of GLM was loaded on the SPE column and extracted with different solvent alternatives to include methanol, isopropanol, chloroform, dichloromethane, and diethyl ether. The same experiment has been repeated using spiked plasma with the same concentration of GLM. Table 2 showed that optimal and precise percent extraction recovery of $100 \pm 0.06\%$ was obtained using a 2 mL solvent mixture containing CH_2Cl_2 : methanol at a ratio of 2: 1, v/v. The extraction of spiked plasma showed this optimal result only in case of mixing the sample with 100 μ L 0.4% trifluoroacetic acid (TFA). As we mentioned before, due to the high affinity of GLM to conjugate with plasma protein (>99.5%) [4], it was necessary to mix the plasma sample with 100 μ L water containing 0.4% TFA. Heptafluorobutyric acid and trichloroacetic acid were tried instead of TFA but showed a % recovery of $100 \pm 2.6\%$. Also, acetic acid, formic acid, and phosphoric acid were tried instead of TFA, but the calculated % recovery was $70 \pm 15.9\%$. The % recovery was calculated from the ESI-MS response of the same claimed concentration prepared in methanol (100 ng/mL).

SPE's impact on the extraction recovery was tested by matching the results obtained on using Sep-Pak[®] vac 1cc (100 mg) C8 and C18, 100 mg. Four concentration levels of

Fig. 2. Representative +MRM transitions of GLM (250 ng/mL) and GLZ (500 ng/mL) extracted from pure standard solution and from spiked plasma

GLM in plasma, including LOQ, were tested. The use of Sep-Pak C18 was superior in the % recovery with better precision and accuracy, as shown in Table 3.

Method validation

Linearity and sensitivity. Free-drug-plasma was used as a calibration matrix. The linearity was tested by spiking these blank plasma samples with standard GLM solutions and 20 μ L GLZ (0.5 mg/mL) as internal standard, extracted and

Table 1. Agilent 6420 LC/MS system analysis parameters of GLM and GLZ, cell accelerated voltage is 7 V

Compound	t_R , min	+MRM transition, m/z	Dwell time, ms	Fragmentor voltage, V	Collision energy, eV
Glimepiride	4.22	491.6 $\rightarrow$ 352.8	125	135	8
Gliclazide	5.08	324.9 $\rightarrow$ 127.2	125	135	16

Table 2. The percentage recovery values of GLM spiked in control human plasma using different extraction solvents, $n = 6$

Solvent	Ratio, v/v	% Recovery $\pm$ SD in case of column cleanup with:	
		Deionized water	Water containing 0.4% TFA ^a
Methanol	1	22 $\pm$ 3.1	30 $\pm$ 5.20
Isopropanol	1	32 $\pm$ 3.6	49 $\pm$ 6.50
CH ₂ Cl ₂	1	55 $\pm$ 4.5	65 $\pm$ 7.50
CH ₂ Cl ₂ :isopropanol	2:1	81 $\pm$ 3.4	98 $\pm$ 1.40
CH ₂ Cl ₂ :ethyl acetate	2:1	28 $\pm$ 4.4	78 $\pm$ 2.20
Diethylether:ethyl acetate	1:1	19 $\pm$ 5.4	75 $\pm$ 6.7 0
CH ₂ Cl ₂ :methanol	2:1	82 $\pm$ 3.6	100 $\pm$ 0.06

^aSample added to the SPE column and mixed with 100 μ L of 0.4% TFA in water.

Table 3. Matching the extraction efficiency of Sep-Pak[®] vac 1cc (100 mg) C₈ and C₁₈ in the HPLC–MS/MS analysis of spiked GLM in the plasma

Concentration, pg/mL	C ₁₈ SPE, 100 mg		C ₈ SPE, 100 mg	
	Mean recovery (%) $\pm$ RSD ^a	E_r (%) ^b	Mean recovery (%) $\pm$ RSD ^a	E_r (%) ^b
0.2 (LOQ)	98.66 $\pm$ 3.04	−1.34	74.05 $\pm$ 9.50	−17.95
50.0	99.98 $\pm$ 1.11	−0.02	88.10 $\pm$ 5.05	−11.9
1000.0	100.01 $\pm$ 0.05	0.01	91.87 $\pm$ 4.00	−8.13
1500.0	100.04 $\pm$ 0.02	0.04	94.22 $\pm$ 2.07	−5.78

^a Mean recovery (%) $\pm$ RSD of three determinations.

^b Percentage relative error.

analyzed by the developed method (Fig. 2). The peak area ratios of GLM to GLZ were found linear in the concentration range 0.2–1,500 ng/mL. The regression coefficient was close to unity, 0.9992, and the slope value was 0.00151 ± 0.0005 (SD). The linear curve was accurate because the intercept was very small and equal to 0.0023. The LOD and LOQ were calculated as GLM levels that give +MRM responses of at least three or ten times the blank signals, respectively. The LOD and LOQ concentration levels were 0.06 and 0.2 ng/mL, respectively (Fig 3).

Precision and accuracy. The results of the intra- and inter-day precision and accuracy of LOQ, low, medium, and high QC levels of GLM were found to be within the accepted limits. The % RSD values for intra- and inter-day precisions were less than 2.27% for low, medium, and high concentration levels and below 4.22% for LOQ level. Also, the % E_r values for accuracy studies were within the range of −1.22 to 0.50% (Table 4). The obtained data indicated that the method is precise and accurate because it was within the allowed limits for all four concentration levels, including LOQ.

Fig. 3. Representative +MRM transitions of GLM at LOD (0.06 ng/mL), and LOQ (0.20 ng/mL) concentration levels

Table 4. Evaluation of the intraday and interday accuracy and precision for the determination of GLM in plasma

Concentration, ng/mL	Intraday		Interday	
	Mean recovery (%) $\pm$ RSD ^a	E_r (%) ^b	Mean recovery (%) $\pm$ RSD ^a	E_r (%) ^b
0.2 (LOQ)	100.50 $\pm$ 3.60	0.5	99.13 $\pm$ 4.22	−0.87
50.0	98.88 $\pm$ 2.05	−1.12	99.10 $\pm$ 2.27	−0.9
1000.0	99.94 $\pm$ 0.18	−0.06	99.77 $\pm$ 1.05	−0.23
1500.0	100.01 $\pm$ 0.04	0.01	98.91 $\pm$ 1.06	−1.09

^a Mean recovery (%) $\pm$ RSD of three determinations.

^b Percentage relative error.

Stability. The stability studies were performed to ensure that the targeted analyte is stable during the analysis (autosampler stability) and in the plasma matrix stored at -80°C for 30 days. The autosampler stability testing showed an average % recovery of 98.70–100.11% with RSD value of 0.01–1.55% at the four concentration levels (Table 5). However, the average data of % recovery of three freeze-thawed samples, four concentration levels, were within an acceptable range of 99.16–100.30% with % RSD value ranged from 0.02 to 0.39%.

Application of the method in a pharmacokinetic study

The method was applied to measure plasma samples from 12 healthy volunteers after an oral administration of a single dose of 1 mg GLM. The mean plasma concentrations versus time profiles are represented in Fig. 4. A non-compartmental model was applied to calculate the pharmacokinetic parameters of GLM. The drug reached its maximal concentration ($C_{max} = 99$ ng/mL) after 1.5 h and returned to 1 ng/mL after 24 h from dosing. Terminal half-life ($t_{1/2}$) was

Table 5. Stability results of GLM spiked in plasma samples

Stability	Concentration, ng/mL	Average recovery (%) $\pm$ RSD
Autosampler stability (25 °C/24 h)	0.2 (LOQ)	98.70 $\pm$ 1.55
	50.0	98.85 $\pm$ 0.70
	1000.0	100.07 $\pm$ 0.11
	1500.0	100.11 $\pm$ 0.01
Freeze-thaw stability (–20 °C/3 cycles)	0.2 (LOQ)	99.16 $\pm$ 1.00
	50.0	98.87 $\pm$ 0.39
	1000.0	100.30 $\pm$ 0.04
	1500.0	100.04 $\pm$ 0.02

Fig. 4. Mean plasma concentrations of glimepiride in 12 healthy volunteers after a single oral dose of 1.0 mg of glimepiride

3.2 h. The values of the pharmacokinetic parameters were in agreement with the published values [1, 13, 15].

CONCLUSIONS

An efficient LC-ESI-MS/MS quantification method for GLM in plasma was developed and validated. The percentage of extraction recovery was improved to $100 \pm 0.06\%$ by using SPE C18 columns, 100 mg, and pre-mixing the plasma samples with aqueous 0.4% trifluoroacetic acid to release

drug GLM from bound protein. Besides, the use of total recovery vials enables low volume reconstitution and hence more sensitive detection. The method was successfully applied in the pharmacokinetic study of GLM in human plasma.

Conflict of interest: There are no conflicts to declare.

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