Comparative bioavailability of two different quetiapine doses (50 and 200 mg) in healthy volunteers by using LC/MS method

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ABSTRACT

A selective, sensitive, stable and rugged high performance liquid chromatography tandem mass spectrometric method was developed and validated for determination Quetiapine in human plasma, then successfully applied in pharmacokinetic study for two different tablet doses of quetiapine (50 and 200) mg. The mobile phase consisting of (70% methanol: 30% water), pH=3.0. The method was validated according to European guideline for its linearity, accuracy, precision, selectivity, recovery and various stabilities. The standard curve was linear over a concentration range of (2.25-500.0) ng/ml, $R^2$ was 0.999 and CV\% of intraday accuracy and precision for the validation of QC samples was ranged between (1.82-3.61) \%. A randomized, double-blind, two periods crossover full study was designed to investigate two different tablet doses from Quetiapine (50 and 200) mg. 40 healthy male volunteers were participated in this study, and the oral administration was occurred after overnight fasting. Blood samples were withdrawn from each subject at different time intervals and analyzed for Quetiapine concentrations. The pharmacokinetic parameters were performed and show that the maximum time of absorption ($T_{\text{max}}$) for both doses was the same at 4.5 hr. The maximal plasma concentrations were (49.058 and 262.355) ng/ml and the $K_{el}$ (0.07993 and 0.09207) for the (50 and 200) mg doses, respectively. However, based on these statistical data, quetiapine low and high doses were well tolerated and an obvious significant variation ($p$ value less than 0.05) was found between them in human plasma.

Key words: Quetiapine, bioavailability, LC/MS, human plasma.

INTRODUCTION

Quetiapine (QUE), a derivative of dibenzothiazepine, is an atypical a second-generation of antipsychotic, which indicated for the treatment of many disease such as schizophrenia experiencing an acute exacerbation of their illness, acute mania in bipolar disorders, and bipolar depression especially in adults. Also quetiapine is effective as a monotherapy and as an adjunctive to a mood stabilizer [1-5]. Quetiapine (Figure1) is an antagonist at multiple neurotransmitter receptors in the brain: 5 hydroxytryptophan (5HT1A) or serotonin and 5HT2, dopamine neurotransmitter D1 and D2, histamine H1, and adrenergic α1 and α2 receptors [10].

Therapeutic drug monitoring is an important requirement in antipsychotic treatment to control the compliance and preventive of extrapyramidal side effects [6, 7]. The multiple-dose pharmacokinetics of quetiapine are dose-
proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing.

In addition, pharmacokinetic data suggest quetiapine has a plasma half-life of nearly 6 hours, which is slightly increased with multiple dosing. Thus, in spite of an elimination half-life that averages 6 hours range (5.8 to 6.8) hours [8, 14].

For this reason it is important to perform accurate monitoring and dose adjustment of QUE levels in blood in order to reduce the side effects and to optimize treatment against schizophrenia and depression disease. Among the key pharmacokinetic variables that guide dosing of a drug plasma elimination half-life, the presence or absence of active metabolites, whether the drug exhibits linear pharmacokinetics, and the time taken to achieve steady-state levels of the drug. Therefore, quetiapine, which exhibits a linear pharmacokinetic profile over its therapeutic dosage range (150 to 750 mg daily), which needs 2 days to reach steady-state. For maintain steady-state plasma levels of quetiapine, it would follow that quetiapine needs to be administered 2 or 3 times daily. Quetiapine, is short elimination half-life, so when administrated a single daily dose, it might result in a greater adherence to treatment by patients in the long term.

The current study was conducted to determine the relative bioavailability of two different tablet doses of quetiapine (50 and 200) mg in healthy human volunteers, for this purpose an accurate, sensitive and selective liquid chromatographic mass spectrometer method was developed and validated. Moreover, all pharmacokinetic parameters were calculated in terms of $C_{\text{max}}$, $T_{\text{max}}$, AUC, P value, Rate of elimination ($K_{\text{el}}$) and half-life [15].

![Figure 1: Quetiapine chemical structure](image)

**EXPERIMENTAL SECTION**

2.1. Reagents and chemicals
Nanopure deionized water, methanol, sodium hydroxide, formic acid and acetonitrile advanced gradient grade (Fisher scientific). Human Plasma (harvested from donors), and quetiapine raw materials were kindly obtained from Jordan Pharmaceuticals Manufacturing (JPM) Co., Amman-Jordan.

2.2. Instrumentation
An API 3200 Mass Spectrometer was used which was composed of a constant auto Sampler (Agilent 1200), ACE 5, C18 (50 x 2.1 mm), 5µm. Solvent delivery system (Agilent 1200), a 100 µL fixed volume injector (Agilent 1200), on-line vacuum. Degasser (Agilent 1200).
2.3. Bioequivalence study protocol

According to declaration of Helsinki, this study was conducted with good clinical practice [11]. The protocol was approved by the local institutional review board. Before the study participation, a written informed consent and consent form were obtained from all volunteers. In this study 40 male healthy adult subjects participated in the clinical study, in order to investigate and correlate pharmacokinetic parameters of Cmax, Tmax, half-life, AUC, and rate of elimination (Kel) for quetiapine 50 mg and 200 mg in plasma. Safety examinations were applied to all subjects at Pre- and post-study, and they were between 18 and 50 years of age and within body mass index range of 17.1–28.6 kg/m2, and they were selected upon inclusion/exclusion criteria. Blood samples for quetiapine analysis were drawn (5 ml for each) pre-dose and at 1.00, 2.00, 3.00, 4.00, 4.5, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 11.00, 12.00, 16.00, 24.00, 36.00, and 48 hours post dose. Blood samples were collected from venous by direct venipuncture of an antecubital vein into tubes containing lithium heparin as antiocoagulant to prevent coagulation process, and then tubes with blood were immediately centrifuged at 5000 rpm (2683 × g), under room temperature for 10.0 min. The separated plasma was transferred into polypropylene tubes, and then immediately stored frozen under –40°C.

2.4. Preparation of solutions

2.4.1 Preparation of stock solution of Quetiapine

10.0 mg of quetiapine working standard dissolved in 10 ml methanol to get concentration 1.0 mg/ml stock solution.

2.4.2 Preparation of working solution of Quetiapine

1.0 ml of quetiapine stock solution was taken and diluted in 10 ml of Methanol to get 100 µg/ml of quetiapine.

2.4.3 Preparation of internal standard solution of Propranolol

A known quantity of Propranolol (10 mg) working standard dissolved in 10 ml Methanol, to get concentration 1.0 mg/ml stock solution. 100 µl of stock Propranolol solution was diluted in 2500 ml of (5% T.C.A), which considered being working solution that contain 0.04 µg/ml of Propranolol.

2.4.4 Preparation of Quetiapine standard serial dilution and quality control samples.

Samples of standard curve in plasma were prepared using seven concentrations, not including zero and these concentrations are: (2.25, 4.5, 10, 30, 70, 150, 300 and 500) ng/ml. Each concentration of the plasma sample was divided to 0.05 ml in an Eppendorf and kept at (-40°C), standard samples were given daily together with the quality control samples Low, Mid1, Mid2 and High (6.75, 40, 250 and 400) ng/ml, respectively.

2.5 Sample preparation

Protein direct precipitation is the drug extraction procedure for plasma sample by adding A 500 µl of (0.04 µg/ml of Propranolol (I.S.) in 5%T.C.A) to 0.05 ml of Plasma in an Eppendorf tube; the mixture was vortex and mixed for 30 seconds by using a Vibrax Type VX-Z, VXR BasicVortexer (IKA-Werke GmbH & Co., Staufen, Germany) and then centrifuged using Multitude Sigma1-15 (Sigma, Germany) for 10 minutes 10,000 rpm (14,680 × g). The supernatant was transferred to an autosampler micro-vial, and then 15 µl was injected into the analytical column.

| Table 1: Chromatographic Conditions and Mass Spectrometric Conditions |
| Column | ACE 5 C18 Column (50 X 2.1 mm), 5µ |
| Solvent system (isocratic elution) | 70% (A) Methanol |
|  | 30% (B) Deionised water adjust pH to 3.00 by T.C.A and ammonia |
| Detection | MRM Mode, Quetiapine : At m/z 384.029 → 253.2 |
|  | Propranolol (IS): At m/z 260.075 →116.2 |
| Injection Volume | 5 microliters |
| Retention Times* | Quetiapine 0.25 minutes |
|  | Propranolol 0.28 minutes (Internal Standard), |
| Flow Rate | 1.0 ml/min. |

2.6. Chromatographic Conditions

The mobile phase composition was a prepared by pump mixing of Methanol (70%) and deionized water (30%), pH adjustment of deionized water by the following: Decrease pH value to 3.0 by T.C.A. An analytical column (ACE, C18, with dimensions of 50 mm × 2.1 mm, 5 m was used at a flow rate of 1.0 ml/min under column oven temperature
maintained at 50°C. The auto sampler tray temperature was set at 4°C and the injection volume was 5 µl. The chromatographic conditions are indicated in table 1.

2.7 Method validation
According to the European FDA guideline and United States FDA guideline requirements, the method was validated in human plasma [12, 13]. Both guidelines were considered as protocols for all validation sections. The validation was performed in order to evaluate the method in terms of specificity, accuracy, precision, dilution integrity, matrix effect carryover, sensitivity, calibration curve (linearity of response), recovery and stability.

2.7.1 Specificity
By monitoring 6 individual sources of the appropriate blank matrix, the specificity of the method was been evaluated, which were individually analyzed as replicates and evaluated for interference with comparison to LLOQ. Carryover effect was evaluated to ensure that the rinsing solution used to clean the injection needle is able to avoid any carry forward of injected sample in the subsequent runs. Also specificity test was applied on 6 individual sources of the appropriate plasma blank (figure 3). Normally the absence of interfering components is accepted where the response is less than 20% of the lower limit of quantification for the analyte and 5% for the internal standard in the plasma.

2.7.2 Linearity, accuracy and precision
The accuracy and precision of done evaluations has been determined by running analytical batch with 6 replications from LLOQ, every level of QC had a calibration curve included blank and zero, separately for plasma. During three separated days, three sets of within run batches were used to determine linearity, accuracy and precision, each precession run was from freshly spiked eight levels constructing standard calibration curve, QC samples at five levels (LLOQ, low, medium1 medium2 and high, n = 6 for each level), in addition to blank and zero samples. Results evaluation acceptance criteria for linear calibration curve and QC samples were based on European guideline on bio-analytical method validation [12]. The linearity assessment was done by a weighted (1/x) least squares regression analysis.

2.7.3 Stability
A triplicate from both of QC low and high samples were estimated stability validation sections, and calculated upon freshly spiked calibration curve. The stock solution and spiked plasma has been kept under room temperature for 20 h in order to examine short term stability, after 6 months further examination of long term storage was done under −40°C. Freeze–thaw cycles stability of the samples has been obtained over five freeze-thaw cycles by thawing from frozen state at room temperature for 1 h and refrozen for 24 h. In order to evaluate the stability of the injectable processed samples, they were kept for 48 h under autosampler cooling condition (4°C) before being injected. Acceptance criteria of the outcome evaluation for stability section-related QC samples were based on European guideline on bioanalytical method validation [12].

RESULTS AND DISCUSSION

3.1 Validation
3.1.1 Precision for Quetiapine
At the intraday one of validation, the variability of errors (precision) in predicted concentration ranged between as low as 2.21% observed with high target concentration (500 ng/ml) to maximum coefficient of variation of (CV%) of 4.44% with the LLOQ target concentration of 2.25 ng/ml, table 2. The precision for low and mid concentrations of target were 2.35%, 3.61% respectively, (table 2) and figures (4, 5).

At the intraday two of validation, the variability of errors (precision) in predicted concentration ranged between as low as 2.25% observed with the QC Mid target concentration of 70 ng/ml to a maximum coefficient of variation of (CV%) of 3.09% at the high target concentration of 400 ng/ml, table 3. The precision for low and LLOQ concentrations of target was 2.63%, 2.71% respectively, (table 3).

At the intraday three of validation, the precision of predicted concentration ranged between as low as 1.82% observed with the mid concentration of target of 70ng/ml to a maximum coefficient of variation of (CV %) of 3.15% at the High target concentration of 400 ng/ml, table 4. The precision for LLOQ and low concentration of target was 2.19%, 2.76% respectively, table 4.
The precision (CV %) was not exceed 20% for LLOQ, and 15% for the other concentrations which prove the closeness of the measurements.

### 3.1.2 Accuracy

At the intraday one of validation, the accuracy of mean predicted value compared to target concentration ranged between a minimum of 98.14% at the Low concentration of target 6.75 ng/ml to a maximum accuracy of 102.66% at the LLOQ concentration for target. Accuracy range for six replicates of LLOQ, QC low, QC mid, QC high samples was (97.84%- 108.48%), (95.73%-101.74%), (94.96%-103.48%), (95.72%-101.74%) respectively, table 2.

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>LLOQ 2.25 ng/ml</th>
<th>QC low 6.75 ng/ml</th>
<th>QC mid1 40 ng/ml</th>
<th>QC mid2 250 ng/ml</th>
<th>QC high 400 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean accuracy %</strong></td>
<td>102.66</td>
<td>98.14</td>
<td>100.83</td>
<td>99.58</td>
<td>99.24</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>4.56</td>
<td>2.30</td>
<td>2.86</td>
<td>3.60</td>
<td>2.19</td>
</tr>
<tr>
<td><strong>CV %</strong></td>
<td>4.44</td>
<td>2.35</td>
<td>2.84</td>
<td>3.61</td>
<td>2.21</td>
</tr>
</tbody>
</table>

#### Table 2: Intra-day one accuracy and precision of quetiapine

At the intraday two of validation, the accuracy of mean predicted value compared to target concentration ranged between a minimum of 96.82% at the Low concentration of target 6.75 ng/ml to a maximum accuracy of 102.07% at the QC mid target concentration of 70 ng/ml. Accuracy range for six replicates of LLOQ, QC low, QC mid, QC high samples was (98.55%-105.76%), (94.07%-100.74%), (96.24%-101.12%), (97.06%-106.21%) respectively, (table 3).

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>LLOQ 2.25 ng/ml</th>
<th>QC low 6.75 ng/ml</th>
<th>QC mid1 40 ng/ml</th>
<th>QC mid2 250 ng/ml</th>
<th>QC high 400 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean accuracy %</strong></td>
<td>101.37</td>
<td>98.62</td>
<td>101.29</td>
<td>99.64</td>
<td>102.07</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>2.75</td>
<td>2.54</td>
<td>2.91</td>
<td>2.24</td>
<td>3.16</td>
</tr>
<tr>
<td><strong>CV %</strong></td>
<td>2.71</td>
<td>2.63</td>
<td>2.87</td>
<td>2.25</td>
<td>3.09</td>
</tr>
</tbody>
</table>

#### Table 3: Intra-day two accuracy and precision of quetiapine

At the third day validation, the accuracy of mean predicted value compared to target concentration ranged between a minimum of 98.40% at the low concentration of target 6.75 ng/ml to a maximum accuracy of 101.84% at the LLOQ target concentration of 2.25 ng/ml.

<table>
<thead>
<tr>
<th>Accuracy</th>
<th>LLOQ 2.25 ng/ml</th>
<th>QC low 6.75 ng/ml</th>
<th>QC mid1 40 ng/ml</th>
<th>QC mid2 250 ng/ml</th>
<th>QC high 400 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean accuracy %</strong></td>
<td>101.84</td>
<td>98.40</td>
<td>99.45</td>
<td>99.13</td>
<td>100.37</td>
</tr>
<tr>
<td><strong>STD</strong></td>
<td>2.24</td>
<td>2.71</td>
<td>1.56</td>
<td>1.81</td>
<td>3.16</td>
</tr>
<tr>
<td><strong>CV %</strong></td>
<td>2.19</td>
<td>2.76</td>
<td>1.57</td>
<td>1.82</td>
<td>3.15</td>
</tr>
</tbody>
</table>

#### Table 4: Intra-day three accuracy and precision of quetiapine

At the intraday two of validation, the accuracy of mean predicted value compared to target concentration ranged between a minimum of 96.82% at the Low concentration of target 6.75 ng/ml to a maximum accuracy of 102.07% at the QC mid target concentration of 70 ng/ml. Accuracy range for six replicates of LLOQ, QC low, QC mid, QC high samples was (98.55%-105.76%), (94.07%-100.74%), (96.24%-102.54%), (98.69%-107.92%) respectively, (table 3).

At the third day validation, the accuracy of mean predicted value compared to target concentration ranged between a minimum of 98.40% at the low concentration of target 6.75 ng/ml to a maximum accuracy of 101.84% at the LLOQ target concentration of 2.25 ng/ml.

Accuracy range for six replicates of LLOQ, QC low, QC mid, QC high samples was (98.10%-104.86%), (95.69%-103.32%), (96.24%-101.12%), (97.06%-106.21%) respectively, table 4. Comparing with the accepted criteria which
is 85-115% for all concentration except for LLOQ which is 80-120%, the accuracy obtained was within the required criteria in terms of accuracy.

3.1.3 Stability
The spiked plasma and stock solutions kept under room temperature on bench top were stable for 20 h. Tables 5, 6, and 7 illustrates freeze–thaw cycles, auto-sampler and long term stability test results with their storage condition.

<table>
<thead>
<tr>
<th>Time</th>
<th>Accuracy % Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 hours</td>
<td>99.50 103.69 101.08</td>
</tr>
<tr>
<td>24.0 hours</td>
<td>99.52 99.04 99.22</td>
</tr>
</tbody>
</table>

Table 6: Quetiapine QC low samples stability at 10°C (auto sampler stability). QC high (400 ng/ml)

<table>
<thead>
<tr>
<th>Time</th>
<th>Accuracy % Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 hours</td>
<td>103.51 100.89 102.14</td>
</tr>
<tr>
<td>24.0 hours</td>
<td>99.09 97.88 100.16</td>
</tr>
</tbody>
</table>

Table 7: Quetiapine QC High samples stability at frozen temperature (freeze thaw). QC high 400 ng/ml

<table>
<thead>
<tr>
<th>Time</th>
<th>Accuracy % Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 hours</td>
<td>103.51 100.89 102.14</td>
</tr>
<tr>
<td>72.0 hours</td>
<td>103.25 99.07 98.51</td>
</tr>
</tbody>
</table>

From the table’s data, it was found that the auto sampler stability test was passed according to the accepted criteria where the accuracy% doesn’t exceed ±15%.
Regarding short term stability at room temperature or processing temperature, freshly prepared 0.0 hour two QC’s concentrations were taken as a reference upon calculating stability of quetiapine at room temperature. All the results were within the accepted criteria which were in the range 85%-115%.

3.1.4 Linearity

Linearity was determined by calculating the regression line using a mathematical treatment of the results (i.e. least mean squares) vs. analyte concentration. The determination coefficient (R^2) measures the amount of variation in the response (dependent) variable explained by changes in the explanatory (independent variable).

A value of 1 for R^2 indicates a perfect linear relation between target concentration and predicted concentration. The closer the value of R^2 to 1 the stronger was the linear relation. A strong regression indicates a strong dose-response relationship between predictor and outcome, which in turn supports a stronger validity for predicted concentration of the drug. The R^2 which represents the strength of the correlation coefficient of standard calibration curve was greater than 0.99 during the validation course. Data of the standard curve with regards to correlation, slope, R^2 and intercept are shown in table 8 and figure 2.

Table 8: Standard curves with regards to correlation, slope, R^2, and Intercept for quetiapine

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Slope</th>
<th>R^2</th>
<th>Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.999970</td>
<td>0.000593</td>
<td>0.999928</td>
<td>-0.007665</td>
</tr>
</tbody>
</table>

![Figure 2: The mean plot of linearity for calibration curves mean ratio](image)
Figure 3: Plasma zero concentration (Blank + Propranolol (IS)) of standard calibration curve chromatogram

Figure 4: LLOQ (2.25 ng/ml) chromatogram
Figure 5: QC Mid1 (40.0 ng/ml) chromatogram

Figure 6: Plasma blank chromatogram, taken from participant volunteer in this study before dosing

3.2. Clinical study applications
After oral administration of quetiapine @50 mg and @200 mg tablet dosage forms, investigation and correlation pharmacokinetic parameters of Cmax, Tmax, half-life, AUC, and rate of elimination (Kel) for quetiapine 50 mg and 200 mg in plasma for 40 subjects are illustrated in table 9. The comparative mean plasma concentrations versus time are plotted in figure 7. Table 10 provides the pharmacokinetic parameters for both doses, there is no difference in Tmax values between the two doses, while highly significant difference in the maximum concentrations and AUC were observed. The relative extent of absorption was expressed by the area under the curve of quetiapine concentration versus the time 0-48 hours. The relative agreement between quetiapine two doses is observed.
Fig. 7. Illustrated mean concentration–time profile of 40 subjects for 50 mg Quetiapine over 48 h following oral administration of Quetiapine.

Table 9: Comparative Quetiapine concentrations in each time interval for both doses

<table>
<thead>
<tr>
<th>Time</th>
<th>Quetiapine 50 mg</th>
<th>Quetiapine 200 mg</th>
<th>The Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C(ng/ml) Std. Deviation</td>
<td>C(ng/ml) Std. Deviation</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>1.00</td>
<td>12.266 12.98</td>
<td>52.209 35.29</td>
<td>-51.65</td>
<td>-28.24</td>
</tr>
<tr>
<td>2.00</td>
<td>24.031 19.09</td>
<td>109.393 58.61</td>
<td>-104.54</td>
<td>-66.18</td>
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<tr>
<td>3.00</td>
<td>29.755 19.19</td>
<td>146.822 93.86</td>
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<td>-87.42</td>
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<tr>
<td>4.00</td>
<td>33.571 17.69</td>
<td>168.239 99.86</td>
<td>-166.54</td>
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</tr>
<tr>
<td>5.00</td>
<td>45.171 23.59</td>
<td>221.759 107.05</td>
<td>-169.58</td>
<td>-112.37</td>
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<tr>
<td>6.00</td>
<td>44.964 24.95</td>
<td>212.287 101.36</td>
<td>-199.79</td>
<td>-134.85</td>
</tr>
<tr>
<td>7.00</td>
<td>43.700 22.56</td>
<td>198.638 95.81</td>
<td>-158.93</td>
<td>-104.62</td>
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<tr>
<td>8.00</td>
<td>41.459 19.63</td>
<td>175.151 81.90</td>
<td>-159.68</td>
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<tr>
<td>9.00</td>
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<td>-112.37</td>
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<tr>
<td>10.00</td>
<td>44.964 22.56</td>
<td>212.287 101.36</td>
<td>-199.79</td>
<td>-134.85</td>
</tr>
<tr>
<td>11.00</td>
<td>40.308 15.52</td>
<td>158.531 74.52</td>
<td>-141.90</td>
<td>-94.55</td>
</tr>
<tr>
<td>12.00</td>
<td>40.376 13.67</td>
<td>182.520 79.29</td>
<td>-167.16</td>
<td>-117.13</td>
</tr>
<tr>
<td>13.00</td>
<td>36.794 13.11</td>
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<td>-150.25</td>
<td>-104.81</td>
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<td>14.00</td>
<td>34.805 12.76</td>
<td>146.774 72.56</td>
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<td>-89.06</td>
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<tr>
<td>15.00</td>
<td>24.288 12.34</td>
<td>104.547 58.18</td>
<td>-90.26</td>
<td>-61.62</td>
</tr>
<tr>
<td>16.00</td>
<td>13.216 8.31</td>
<td>51.136 35.49</td>
<td>-35.92</td>
<td>-26.58</td>
</tr>
<tr>
<td>17.00</td>
<td>3.102 3.10</td>
<td>16.282 14.21</td>
<td>-13.18</td>
<td>-6.73</td>
</tr>
<tr>
<td>18.00</td>
<td>2.235 1.27</td>
<td>4.969 3.35</td>
<td>-2.73</td>
<td>-1.00</td>
</tr>
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</table>

Table 10: Pharmacokinetic parameters of Quetiapine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cmax (mg/ml)</th>
<th>Tmax (h)</th>
<th>AUC (mg*h/ml)</th>
<th>P value</th>
<th>Rate of elimination Kel (1/h)</th>
<th>Half-life t0.5 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine 50 mg</td>
<td>49.058</td>
<td>4.5</td>
<td>837.401</td>
<td>0.000</td>
<td>0.07993</td>
<td>8.6</td>
</tr>
<tr>
<td>Quetiapine 200 mg</td>
<td>262.355</td>
<td>4.5</td>
<td>3551.602</td>
<td>0.000</td>
<td>0.09207</td>
<td>7.5</td>
</tr>
</tbody>
</table>

CONCLUSION

Accurate, selective and sensitive LC tandem MS method for estimation of quetiapine concentrations in human plasma was developed and validated upon relatively wide dynamic range, in order to cover all study unknown samples from both deferent dosing (50 and 200) mg. all validation sections were satisfied for all European and US guidelines for bioavailability studies. This study found that the maximum time of absorption of quetiapine in human plasma for both doses is similar, while significant and linear increase in the maximum concentration of high dose...
was detected. In spite of the elimination time constant of 200 mg dose was a little bit higher than 50 mg dose, it’s clear that the tolerance of quetiapine was smoothly achieved.

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