Bioequivalence Study of 25 mg Quetiapine Film Coated Tablets in Healthy Indonesian Volunteers

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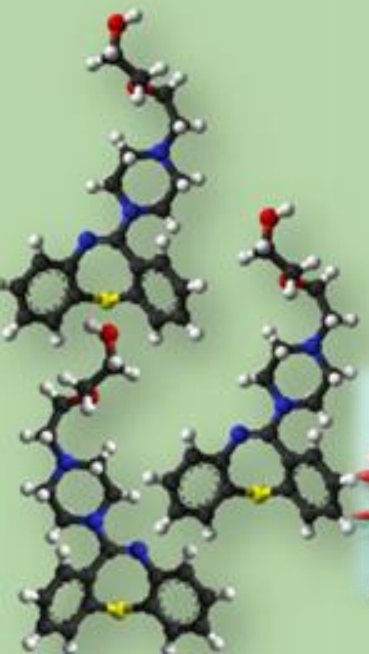
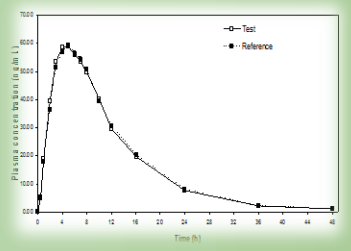
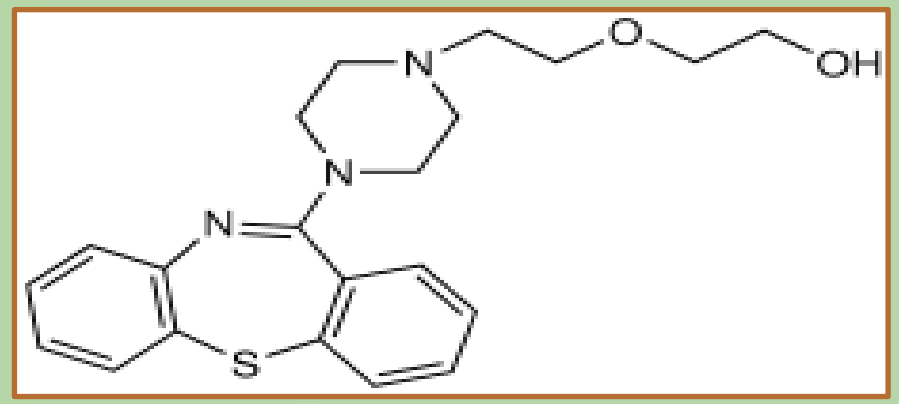




Introduction

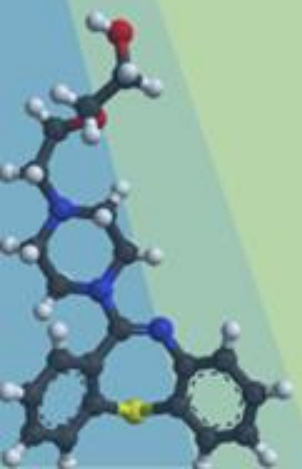
- Quetiapine → antipsychotic agent belonging to the dibenzothiazepine class of drugs.
- Treatment of schizophrenia and of mania associated with bipolar disorder.
- It binds to multiple receptors, most of them with low affinity. It interacts with dopamine D_1 and D_2, serotonin 5-HT_{1A} and 5-HT_2, adrenergic α_1, and histamine H_1 receptors.



2-[2-(4-Dibenzo[*b,f*] [1,4]thiazepin-11-yl-1- piperazinyl) ethoxy] ethanol fumarate

Pharmacokinetic

- Following oral administration, quetiapine absorbed in gastrointestinal tract, time to reach peak blood levels for immediate release is 2 hours and 6 hours for extended release.
- The drug is approximately 83% bound to serum proteins.
- t½ of quetiapine is 7 hours and poor bioavailability (9%) due to extensive first pass metabolism.



Bioequivalence Study

- A film coated tablet containing 25 mg of quetiapine has been developed
- It is compulsory to go through BE study.

The Objective of Research

To compare the bioavailability of two 25 mg quetiapine film coated tablets in healthy Indonesian subjects.

Study Protocol

passed

Subject screening

24 healthy subjects

Signed informed consent

single-dose, open-label, randomized, two-way crossover fasting

Committee of The Medical Research Ethics of the Faculty of Medicine, University of Indonesia and was approved by the NADFC .

Blood pressure, heart rate, body temperature and adverse events were monitored during blood sampling.

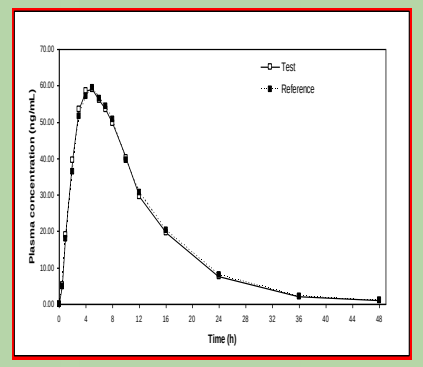
Blood sampling pre dose, 0.25, 0.5, 0.75 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours (one week wash-out period)

9 mL of Blood

blood separation

Plasma was frozen at -20°C until analysis

Validated method
LLOQ 0.25 ng/mL



Subjects

Demographic data for quetiapine bioequivalence study in 24 subjects

	Mean (± SD)	Range
Age (years)	30.7 (8.0)	18-47
Weight (kg)	56.5(8.2)	44-74
Height (m)	163.6 (6.6)	153.5-179
Body Mass Index (kg m^{-2})	21.1 ± 2.8	18-25

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Subjects Screening

Passing Physical examination,
ECG and clinical laboratory tests
(hemoglobin, hematocrite, WBC, platelets,
WBC differential, blood urea nitrogen,
sGPT, sGOT, alkaline phosphatase, total
bilirubin, total protein, fasting glucose,
albumin, creatinine, urine analysis),
pregnancy test , negative results of HBsAg,
anti HBC and anti HIV

Excluded :
Have a history of hepatic, renal and cardiovascular system, take alcohol or other medications for a long period of time, have hypersensitivity to quetiapine, receive any investigation drug within four weeks, & lose more than 450 ml of blood within 3 months prior screening.

24 Subjects were selected
(19 males, 5 females)

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Before Sampling

- All subjects avoided using other drugs for at least two weeks prior to the study and until after its completion.
- They are also refrained from ingesting alcohol, caffeine, chocolate, tea or coke containing beverages at least 48 hours before each dosing and until the collection of the last blood sample.
- Subjects were confined at clinical unit of Clinisindo Laboratories one night before study to assure the fasting condition (10 hours before drug administration).
- On the study day, subjects were given one tablet of either product with 240 ml of water.
- No food was allowed until 4 hours after dose administration. Water intake was allowed 2 hours after the dose. Standard meals were served at 4 hours (± 939 calories) and 11 hours (± 858 calories), snacks were served at 9 hours (± 165 calories) after drug administration. Total calories were calculated by nutritionist.

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Safety Evaluation

Analysis of safety-related data was considered using the more common adverse events which occurred after initiation of study treatment

Causal relation to study drug	Events	Total
Related	Somnolonce	40
	Dizziness	14
	Dry mouth	21
	Nausea	3
	Weakness	2
	Hypotension	1
	Polyuria	5
Total		86

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MS condition

- Scan type : MRM
- Polarity : Positive
- Scan mode : N/A
- Ion source : Turbo Ion Spray (TIS)
- *Compound Dependent Parameters*

Parameter	Quetiapine	Clozapine
Detection Mass	384.1>253.1	327.1>270
De-clustering Potential (DP) (V)	31	70
Entrance Potential (EP) (V)	3.5	12
Collision Cell Entrance Potential (CEP)	32	14
Collision Energy (CE)	17	23
Collision Cell Exit Potential (CXP)	4	4
Dwell Time (msec)	150	150

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Chromatographic Condition

Column : **Synergy 4µ POLAR-RP-80A, 50x2.00 mm, 4µm (Phenomenex®, USA)**
Guard column : **AQ C18, 4 x 2.0 mm (Phenomenex®, USA)**
Column temperature : **40°C**
Mobile Phase : **Gradient**
0.1% formic acid in acetonitrile
0.1% formic acid in water

Time	B (%)
0.01	88
1.00	88
2.00	50
3.00	50
3.20	88
4.50	Stop (Controller)

Flow rate : 0.6 mL/min
Injection volume : 5 µL
Run time : 4.50 minutes

Sample Preparation

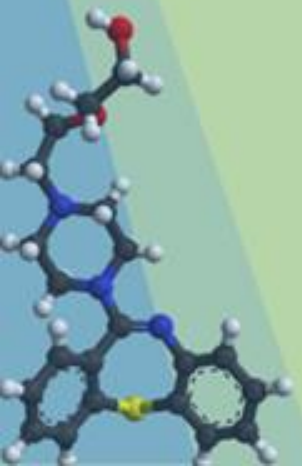
500µL of human plasma sample was added with 20µL of Clozapine (10µg/mL)

-Mixing
-200 µL of 1 N NaOH and
3 mL of ethyl acetate was added
-Vortex mixed for 1 minute
- Centrifuged at 3000rpm for 10 mins

The organic phase was removed and evaporated to dryness under vacuum at 60 ºC for 15 mins

The residue was reconstituted with acetonitrile:water (1:1).

5µL aliquot
was injected into LC-MS/MS system



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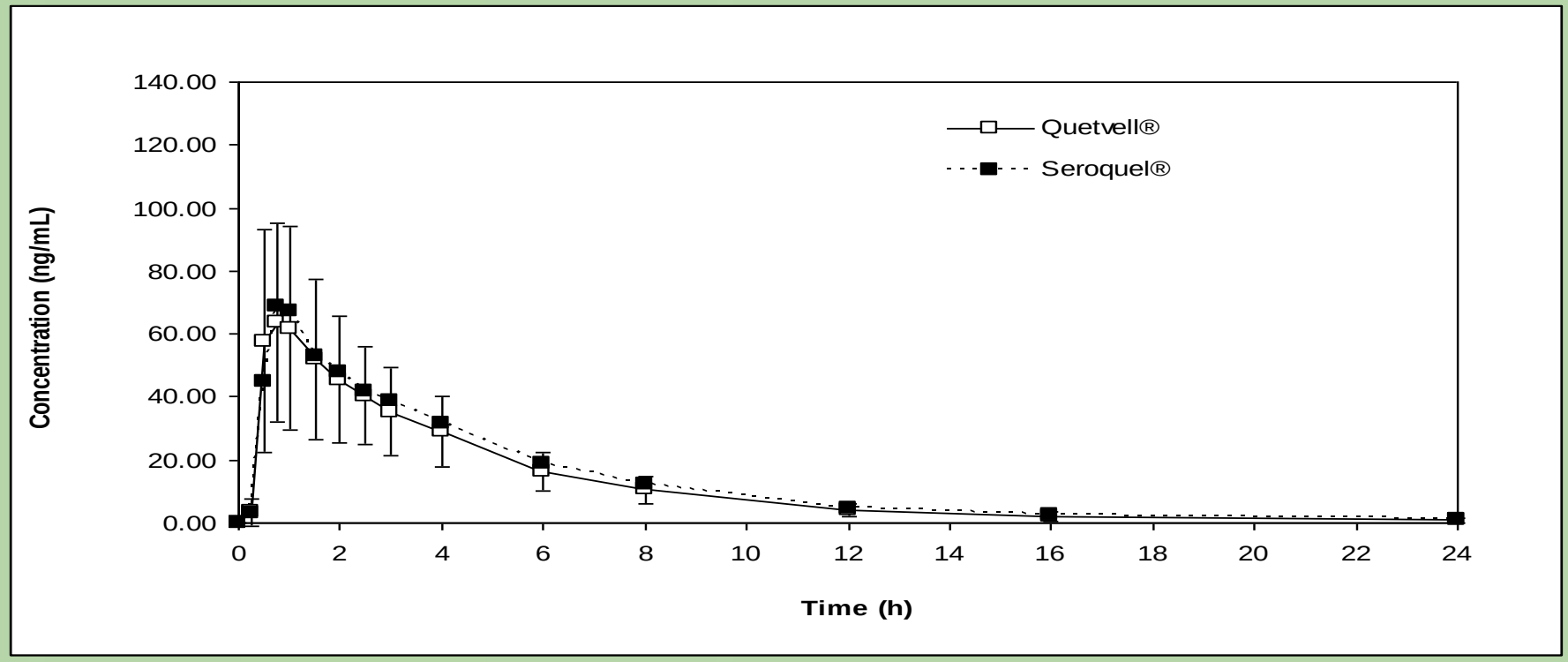
Pharmacokinetic & Statistical Analysis

- The bioequivalence parameters, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}.
- Cmax and tmax ⟹ individual drug plasma concentration time data, and were used as measures of rate of absorption.
- (AUC_{0-t}) was calculated using the trapezoidal rule.
- Kel ⟹ least-squares regression from the data of the last 3-8 points of each plasma concentration data curve
- t½ = (ln 2) / Kel
- For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} a multiplicative model was assumed, and analysis of variance (ANOVA) was applied using the respective ln-transformed data.
- Bioequivalence the 90% CI of the geometric mean (T/R) for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were calculated assuming a multiplicative model
- The accepted bioequivalence range for these parameters was 80.00-125.00%.
- All statistical analyses were performed using EquivTest version 2.0 software (Statistical Solution, Cork, Ireland).

RESULT AND DISCUSSION

Arithmetic mean plasma concentration-time profiles of quetiapine after a single dose of two 25 mg quetiapine film coated tablets of two different formulations



Pharmacokinetic evaluation

Table 1. Mean pharmacokinetic characteristic of Quetiapine after administration the two formulations

Parameter	Test Formulation	Reference Formulation
C_{max} (ng/mL) Geometric Mean Range	71.53 21.26 – 168.60	75.03 28.43 – 161.50
AUC_{0-t} ngxh/ml) Geometric Mean Range	266.94 103.03 – 559.60	298.27 183.32 – 516.70
$AUC_{0-\infty}$ (ngxh/ml) Geometric Mean Range	272.09 105.29 – 599.48	304.46 186.26 – 553.42
t½ (h) Geometric Mean Range	3.69 2.45 – 6.53	3.93 2.57 – 7.89
t_{max} (h) Median	0.75	0.75

Pharmacokinetic evaluation

Table 2. Statistical evaluation of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for quetiapine of two formulations

Parameter	T/R Point Estimate	Confidence Limits Range	Intra-Subject CV
C_{max} (%)	100.09	93.31-107.36	27.39
AUC_{0-t} (%)	99.89	94.89 -105.15	21.66
$AUC_{0-\infty}$(%)	99.90	94.85 - 105.23	21.68

Discussion

- 90% confidence intervals (CI) of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} ratios of quetiapine were included into the range of bioequivalence, i.e. 80-125%.

- The mean ratio of $AUC_{0-t}/AUC_{0-\infty}$ for all individuals and for both products was around 1%, indicate an adequate sampling time since the extrapolated portion of the total AUC is less than 20%.

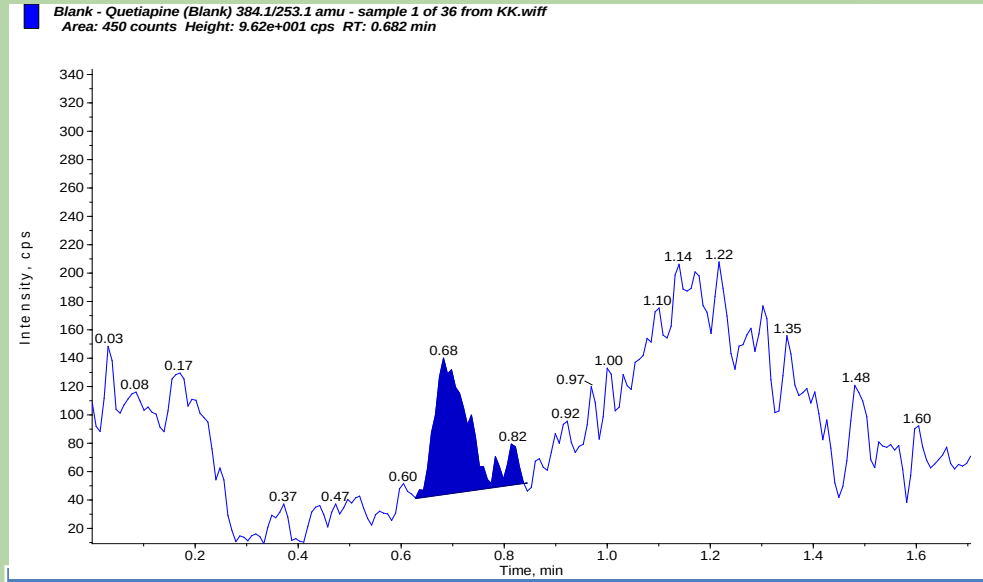
- The intra-subject variability of quetiapine in the AUC_{0-t} was 21.66 % ⟹ sample size of 24 subjects was sufficient in order to conclude bioequivalence with the power of 80% at the 5% nominal level (Diletti et al., 1991).

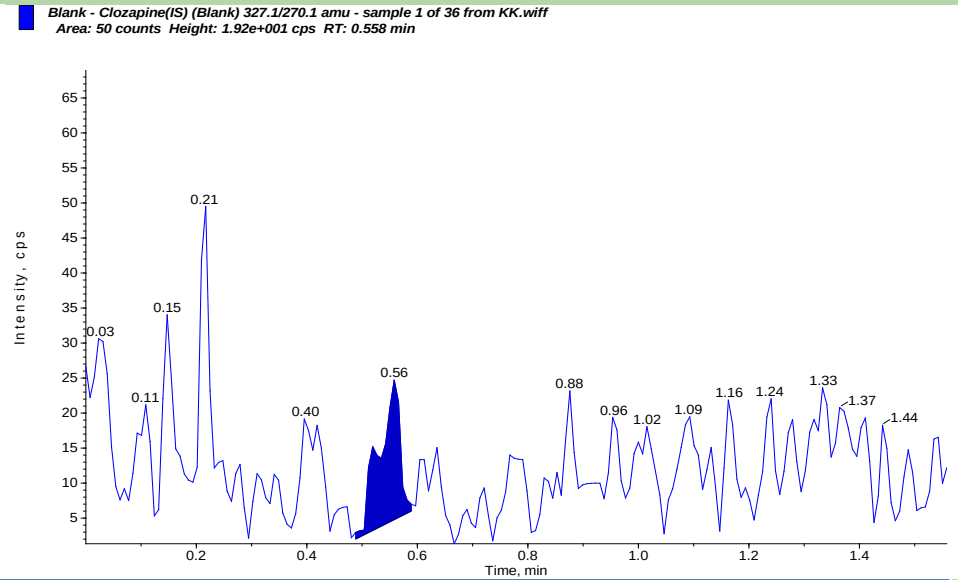
Con'd

- The t_{max} was not statistically different between the two formulations and the median t_{max} for both formulations (0.75h)

  ⟹ the literature 2 h

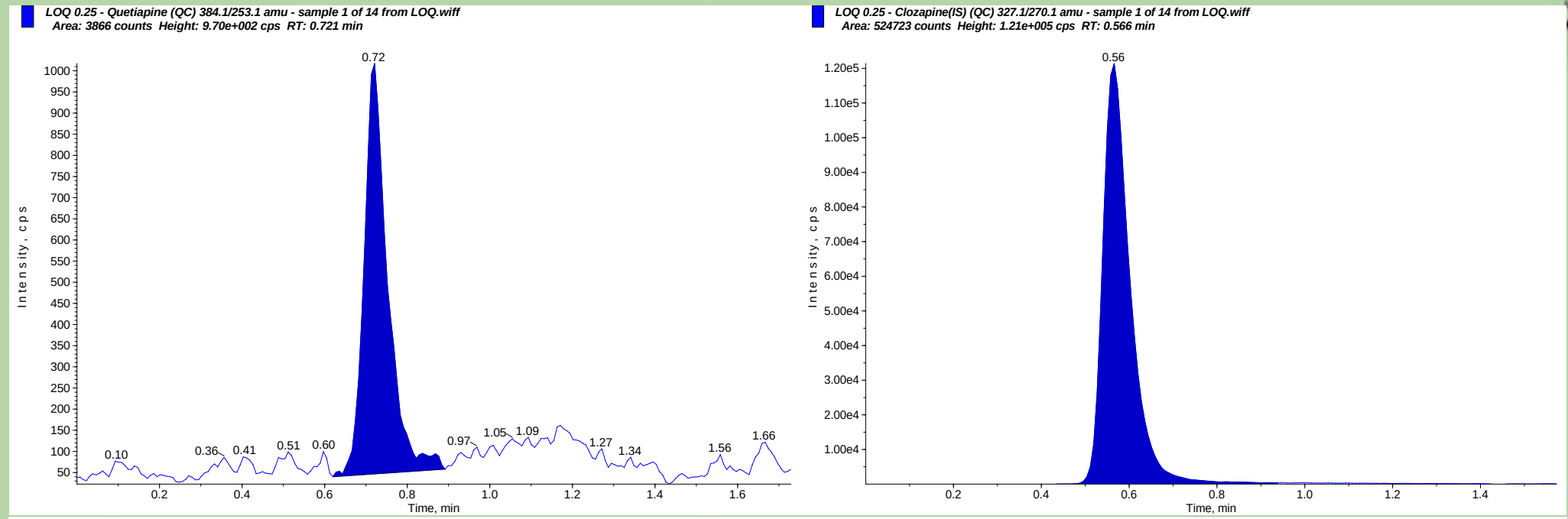
- t½ in the study (2.45 – 6.53 h for test product and 2.57 – 7.89 h for reference product) while the results reported in the literatures about 7 hours.





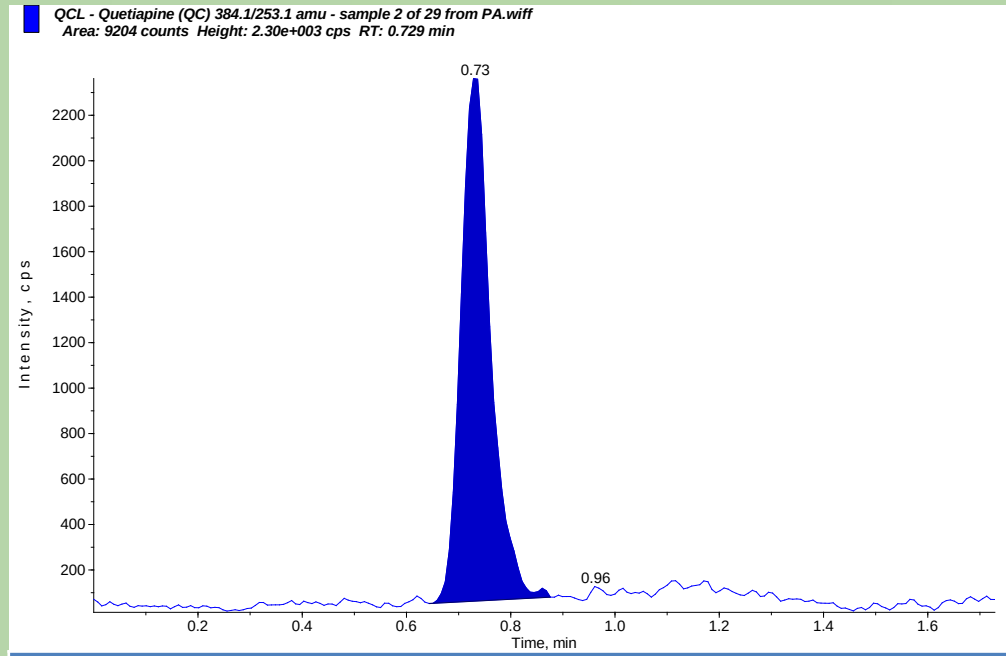
Quetiapine (384.1/253.1 amu)	Clozapine (327.1/270.1 amu)
Sample Name:	Blank (384.1/253.1 amu)
Analyte Area:	450.00
Analyte RT:	0.682
IS Area:	50.00
IS RT:	0.56
Analyte/IS Ratio:	9.04
Cal Conc (ng/mL)	N/A (ng/mL)

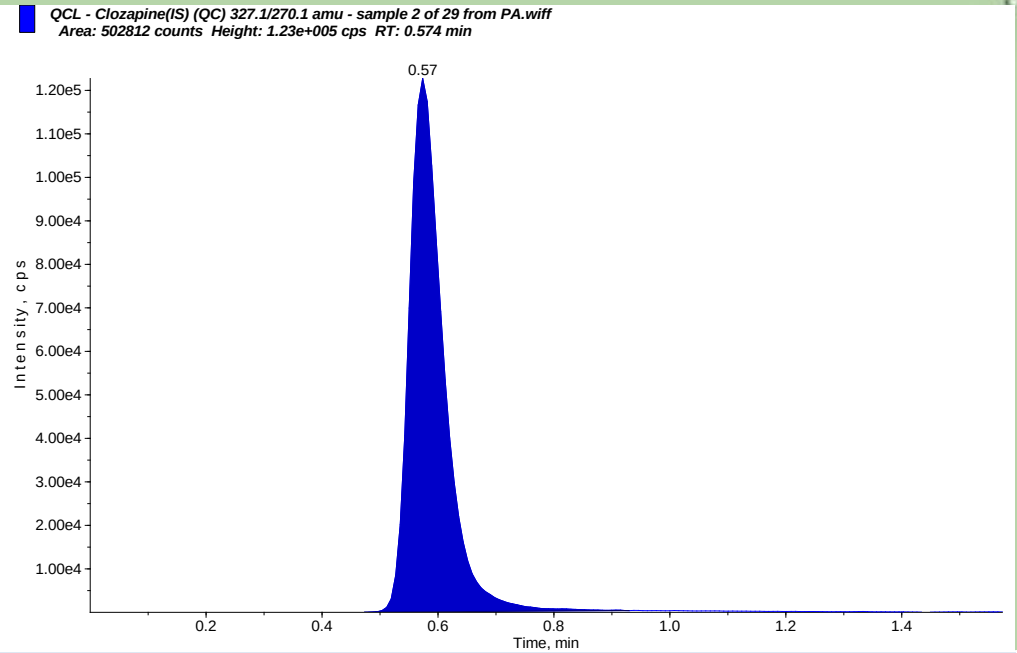
Figure 1. Chromatogram of blank plasma of Quetiapine



Quetiapine (384.1/253.1 amu)	Clozapine (327.1/270.1 amu)
Sample Name:	LOQ 0.25 (384.1/253.1 amu)
Analyte Area:	3866.00
Analyte RT:	0.721
IS Area:	524723.00
IS RT:	0.57
Analyte/IS Ratio:	0.01
Cal Conc (ng/mL)	0.2484 (ng/mL)

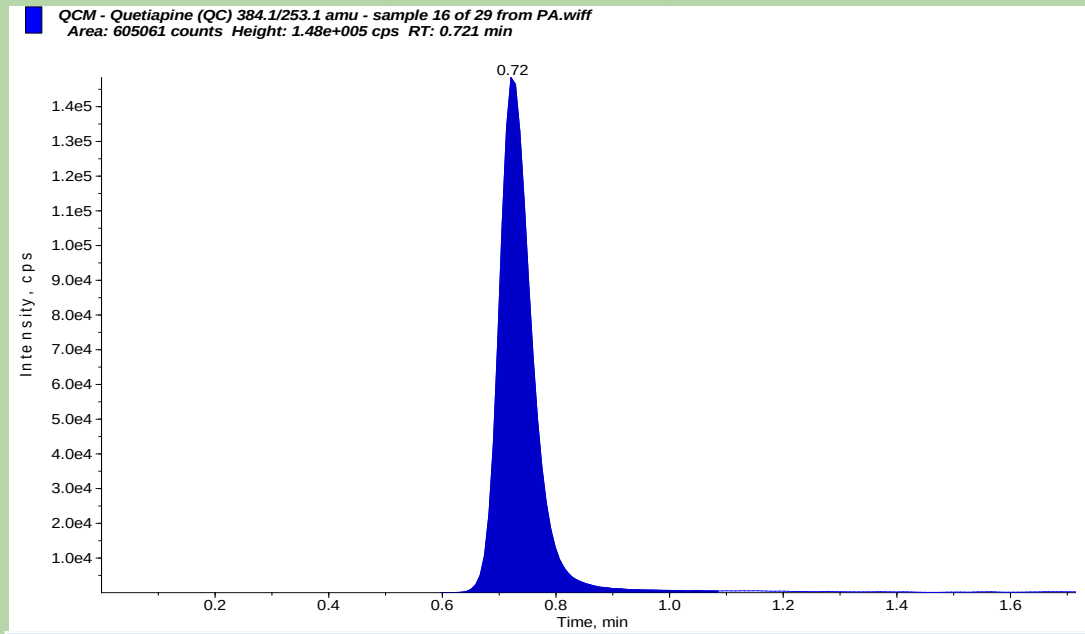
Figure 2. Chromatogram of LOQ of Quetiapine

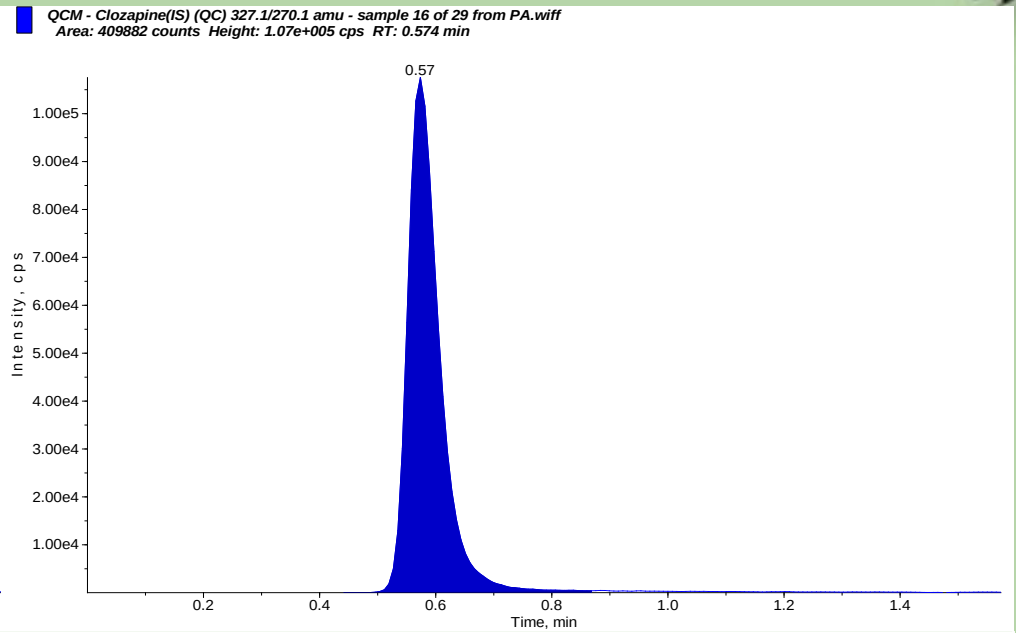




Quetiapine (384.1/253.1 amu)	Clozapine (327.1/270.1 amu)
Sample Name:	QCL (384.1/253.1 amu)
Analyte Area:	9204.00
Analyte RT:	0.729
IS Area:	502812.00
IS RT:	0.57
Analyte/IS Ratio:	0.02
Cal Conc (ng/mL)	0.8364 (ng/mL)

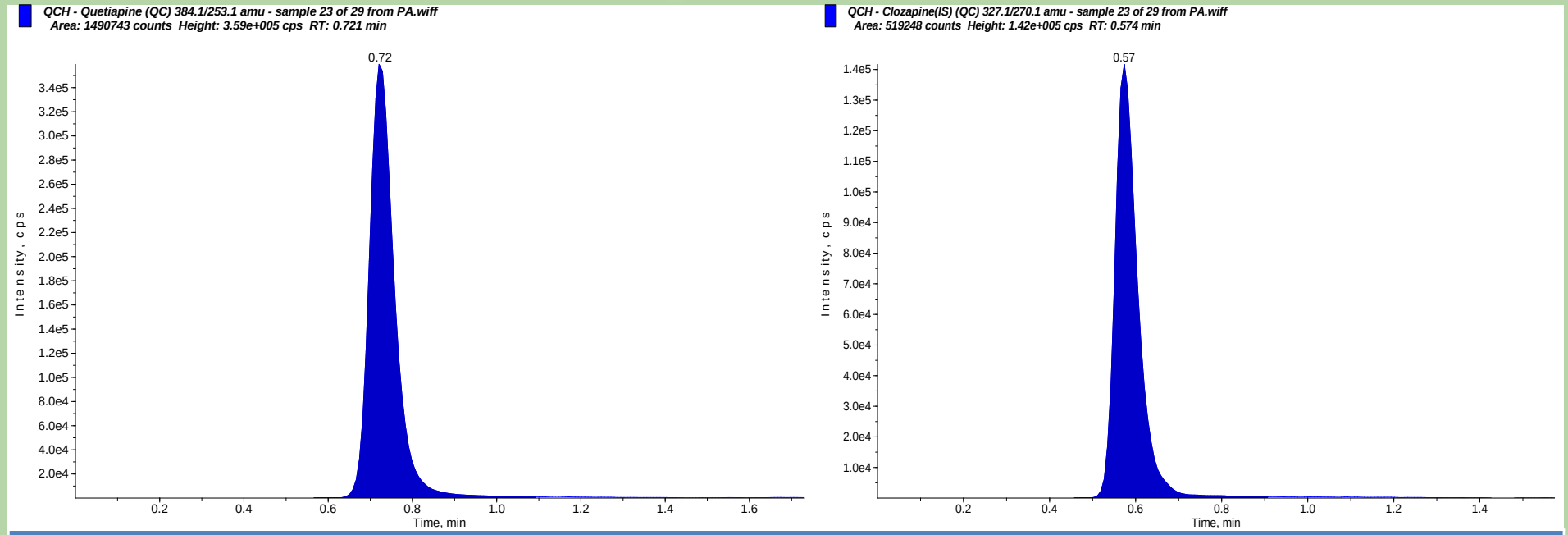
Figure 3. Chromatogram of Low QC of Quetiapine





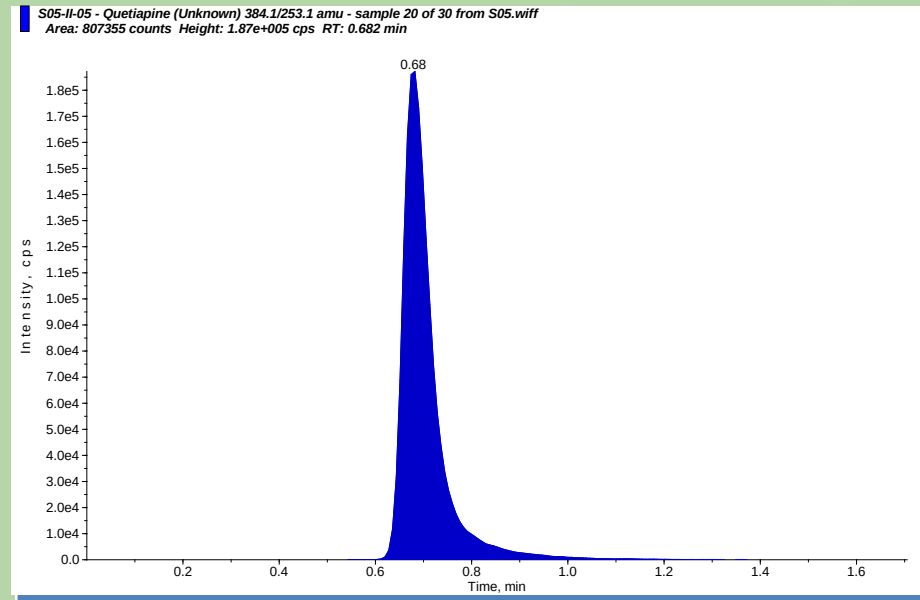
Quetiapine (384.1/253.1 amu)	Clozapine (327.1/270.1 amu)
Sample Name:	QCM (384.1/253.1 amu)
Analyte Area:	605061.00
Analyte RT:	0.721
IS Area:	409882.00
IS RT:	0.57
Analyte/IS Ratio:	1.48
Cal Conc (pg/mL)	78.412 (ng/mL)

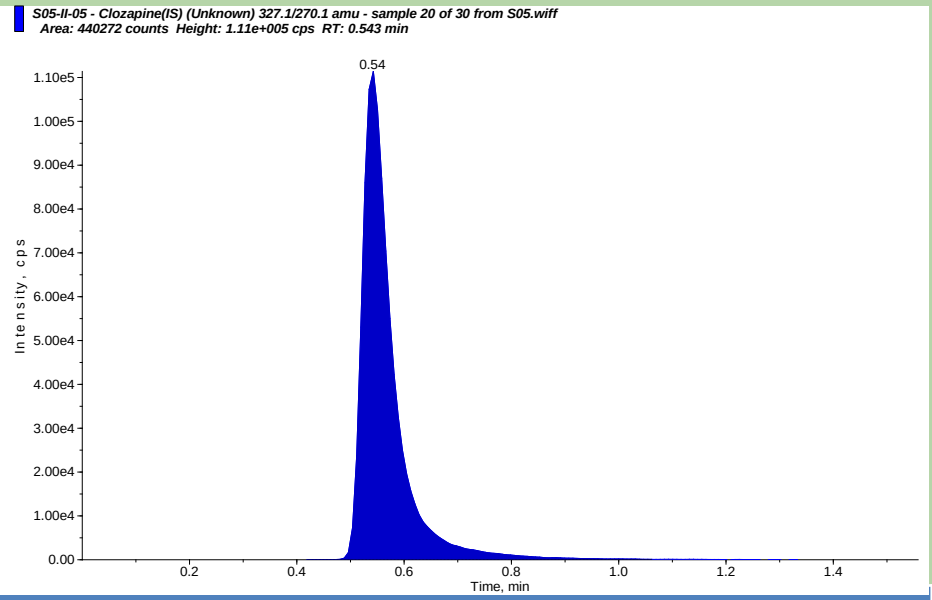
Figure 4. Chromatogram of Medium QC of Quetiapine



Quetiapine (384.1/253.1 amu)	Clozapine (327.1/270.1 amu)
Sample Name:	QCH (384.1/253.1 amu)
Analyte Area:	1490743.00
Analyte RT:	0.721
IS Area:	519248.00
IS RT:	0.57
Analyte/IS Ratio:	2.87
Cal Conc (ng/mL)	154.55 (ng/mL)

Figure 5. Chromatogram of High QC of Quetiapine





	Quetiapine (384.1/253.1 amu)	Clozapine(327.1/270.1 amu)
Sample Name:	S05-II-05 (384.1/253.1 amu)	
Analyte Area:	807355.00	
Analyte RT:	0.682	
IS Area:	440272.00	
IS RT:	0.54	
Analyte/IS Ratio:	1.83	
Cal Conc (ng/mL)	75.27 (ng/mL)	

Figure 6. Chromatogram of Quetiapine in Sample

Conclusion

The two quetiapine formulations were equivalent with respect to the rate and extent of absorption and it can be assumed to be therapeutically equivalent and exchangeable in clinical practice.

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Thank You