Quetiapine (active)

CYP3A4   CYP3A4   CYP3A4, CYP2D6

Quetiapine sulfoxide (inactive)   Norquetiapine (active)   7-Hydroxyquetiapine (active)

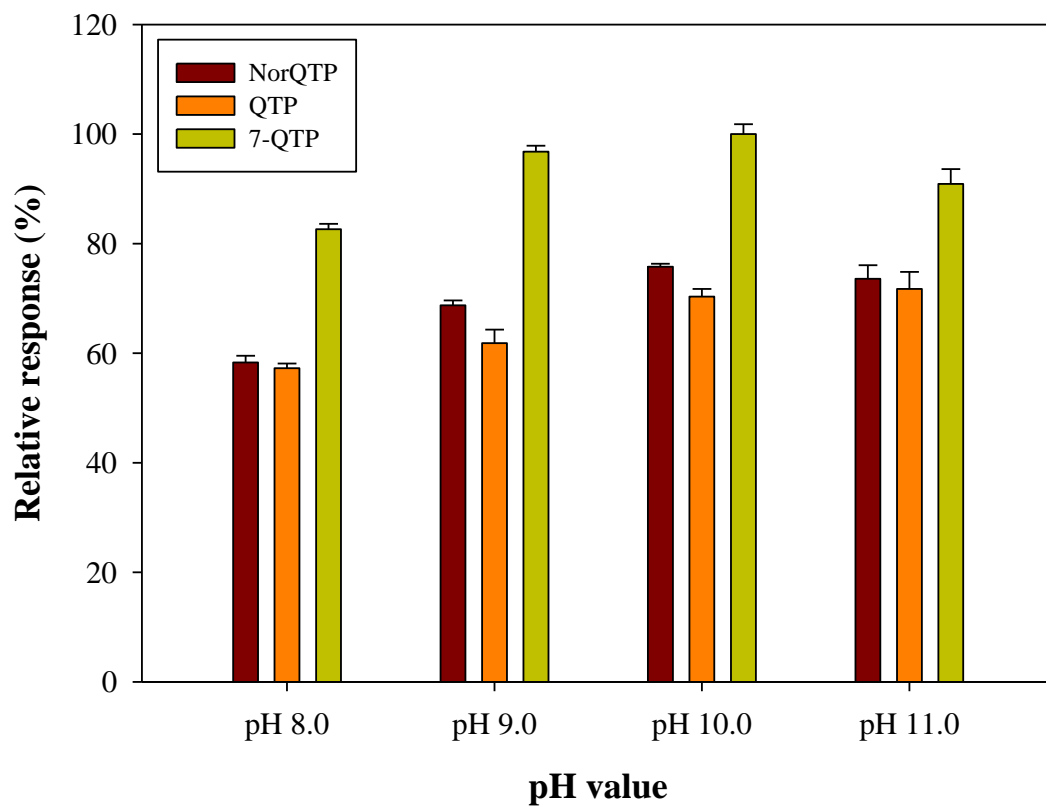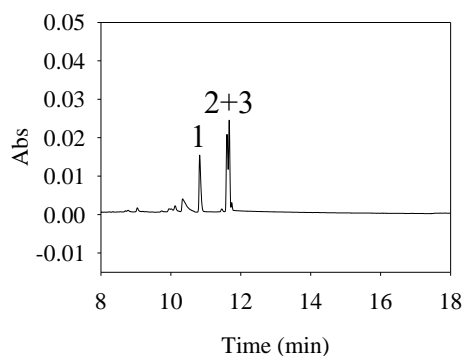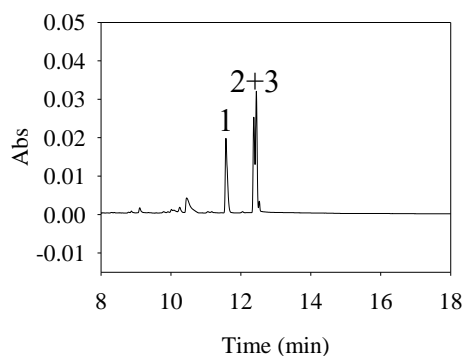Fig. S1. Metabolic pathways of Quetiapine.

Fig. S2. Effect of different pH values of plasma in LLE procedure. Analytes concentrations: NorQTP: 50 ng/mL, QTP: 50 ng/mL, 7-QTP: 50 ng/mL. Other conditions were shown in Fig. 2.
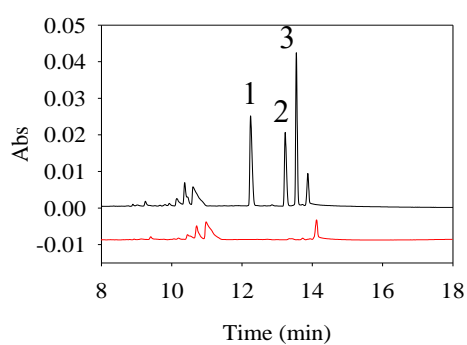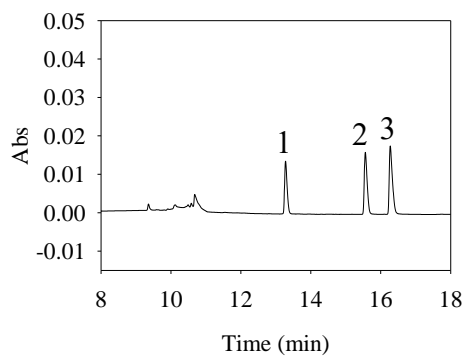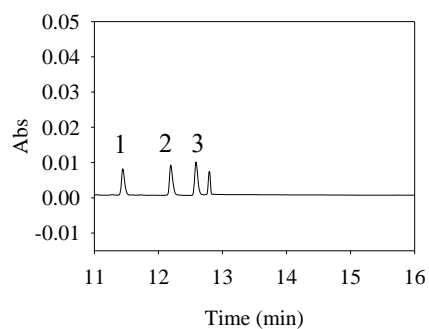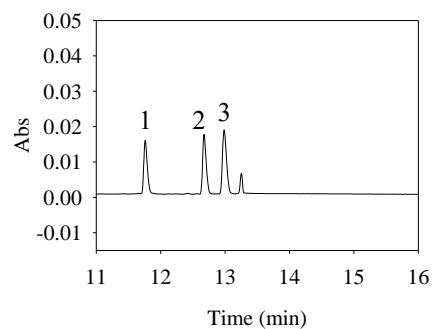
(a) pH 3.0

(b) pH 3.5

(c) pH 4.0

(d) pH 5.0

Fig. S3. Electropherograms of different pH values of phosphate buffer in BGS. (a) pH 3.0, (b) pH 3.5, (c) pH 4.0, (d) pH 5.0. Analytes concentrations: peak 1: NorQTP (50 ng/mL), peak 2: QTP (50 ng/mL), peak 3: 7-QTP (50 ng/mL). Other conditions were shown in Fig. 2.
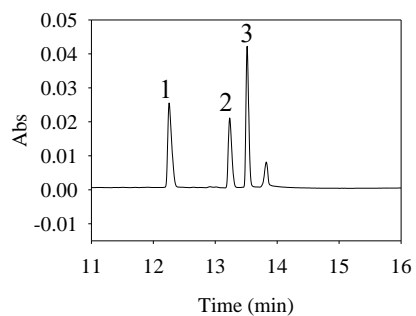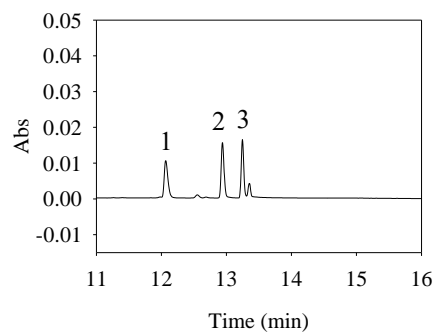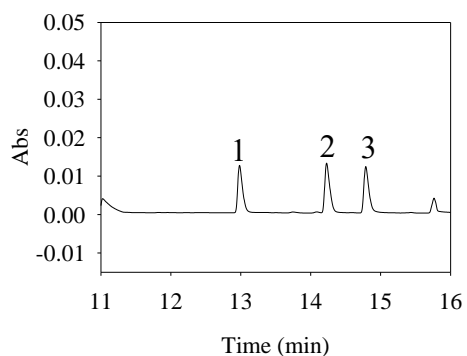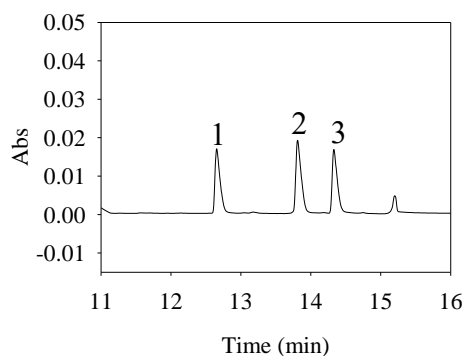
(a) 0%

(b) 0.001%

(c) 0.005%

(d) 0.01%

Fig. S4. Electropherograms of different PVP proportions in BGS. (a) 0%, (b) 0.001%, (c) 0.005%, (d) 0.01% (w/v). Analytes concentrations: peak 1: NorQTP (50 ng/mL), peak 2: QTP (50 ng/mL), peak 3: 7-QTP (50 ng/mL). Other conditions were shown in Fig. 2.

Fig. S5. Electropherograms of different kinds of plug. (a) without plug, (b) water, (c) acetontrile, (d) methanol. Analytes concentrations: peak 1: NorQTP (50 ng/mL), peak 2: QTP (50 ng/mL), peak 3: 7-QTP (50 ng/mL). Other conditions were shown in Fig. 2.
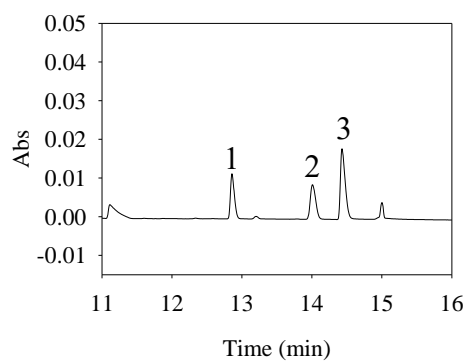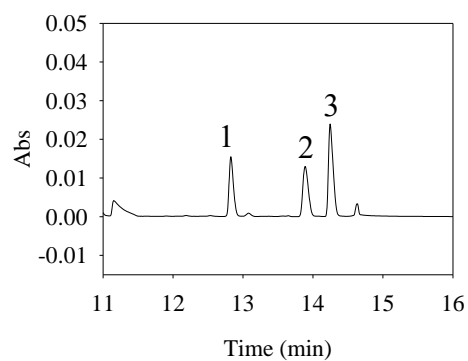
Fig. S6. Electropherograms of different durations of sample injection. (a) 50 s, (b) 60 s, (c) 70 s, (d) 80 s by +10 kV. Analytes concentrations: peak 1: NorQTP (50 ng/mL), peak 2: QTP (50 ng/mL), peak 3: 7-QTP (50 ng/mL). Other conditions were shown in Fig. 2.
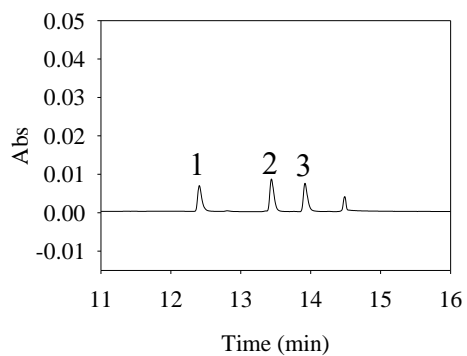
(a) CZE
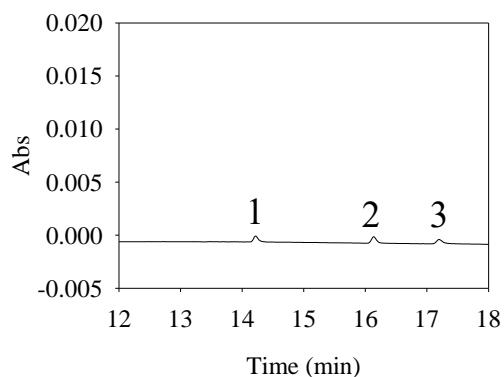
(b) FESS
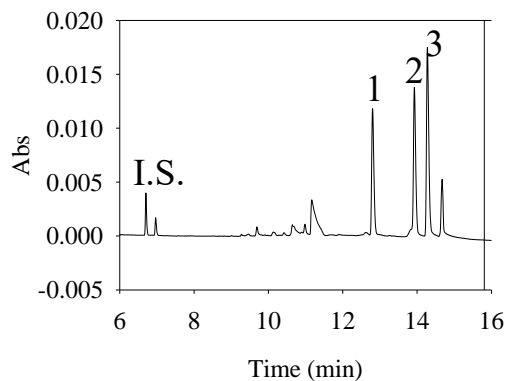
Fig. S7. Electropherograms of QTP, NorQTP, 7-QTP by (a) CZE, (b) FESS. Analytes concentrations: CZE: peak 1: NorQTP (1 µg/mL), peak 2: QTP (1 µg/mL), peak 3: 7-QTP (1 µg/mL); FESS: IS: 4-aminopyridine (20 ng/ mL), peak 1: NorQT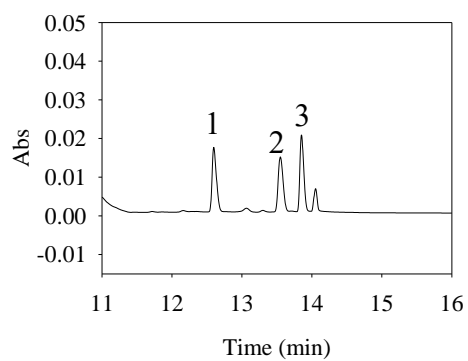P (50 ng/mL), peak 2: QTP (50 ng/mL), peak 3: 7-QTP (50 ng/mL). CZE condition: sample injection: 0.5 psi, 10 s; CE condition: separation buffer, 120 mM phosphate (pH 4.0) containing 0.005% (w/v) PVP and 40% (v/v) methanol; methanol plug: 0.3 psi, 6 s; separation voltage, +26 kV; detection wavelength, 214 nm; temperature: 20°C.
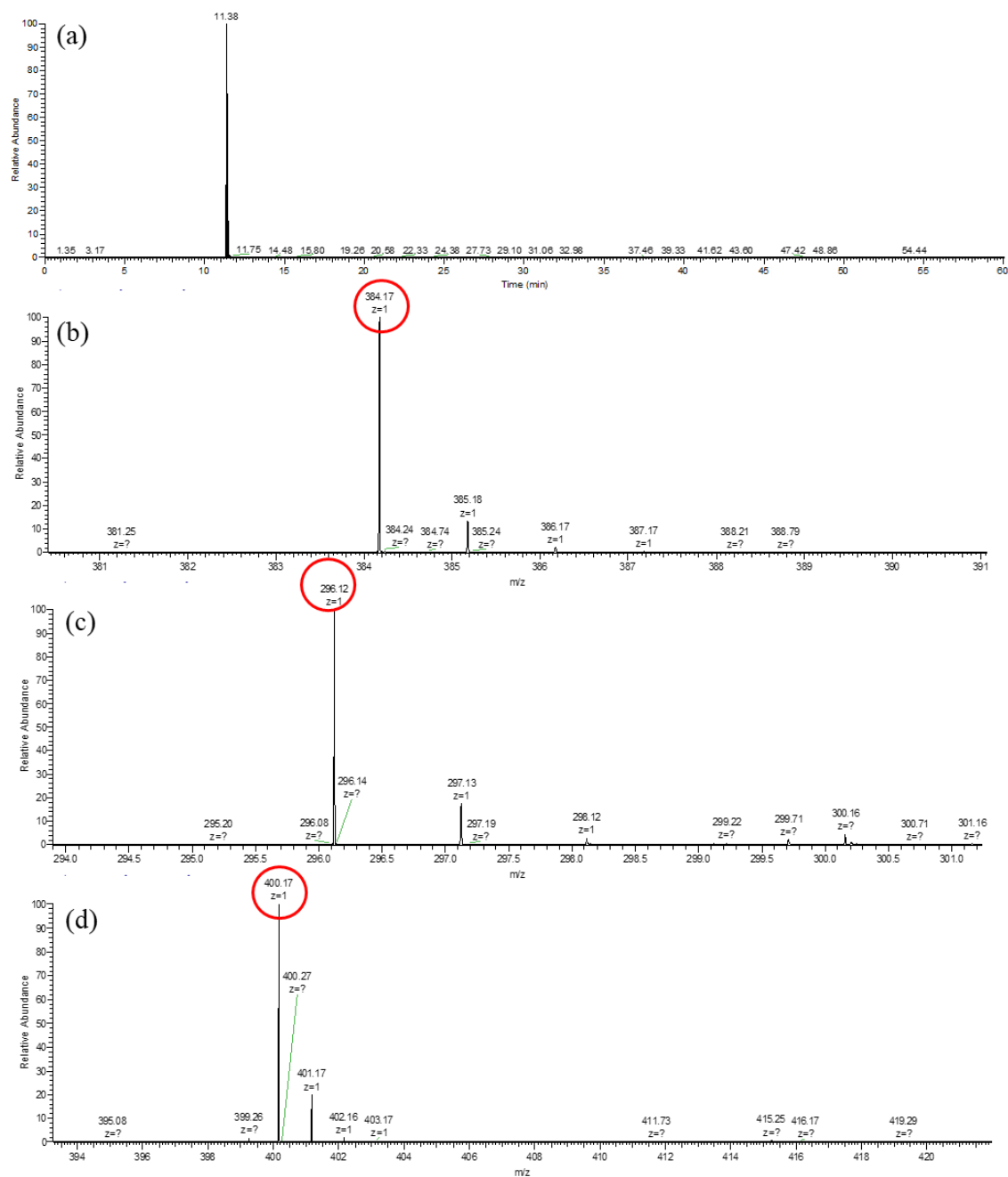
Fig. S8. The spectra of QTP in plasma sample 1 from 1 hour after dosing. (a) LC, (b) MS. Peak: [M+H$^+$]: QTP (*m/z* 384.17), (c) MS. Peak: [M+H$^+$]: NorQTP (*m/z* 296.12), (d) MS. Peak: [M+H$^+$]: 7-QTP (*m/z* 400.16)

Table S1. The extraction recoveries (%) of different extraction solvents.

Extraction solvents	QTP	Nor-QTP	7-QTP
tert-butyl methyl ether	55.3	20.6	52.9
dichloromethane	59.7	26.7	47.9
chloroform	51.1	15.2	32.1
ethyl acetate	30.3	7.32	34.4

Table S2. The extraction recoveries (%) of different t*ert*-butyl methyl ether volumes.

tert-butyl methyl ether volumes	QTP	Nor-QTP	7-QTP
500 μL	37.5	11.7	31.5
750 μL	43.0	18.6	41.1
1000 μL	55.3	20.6	52.9
1250 μL	28.8	8.9	38.0

Table S3. Linear range and LODs for CE system with FESS method.

	Linear range (ng/mL)	[a]LODs (ng/mL)
QTP	3-120	0.25
NorQTP	3-120	0.50
7-QTP	3-120	1.00

[a]LODs: limit of detection (S/N=3)

Table S4. Regression analysis for determination of QTP and its metabolites in intra-day (n=3) and inter-day (n=5).

Analytes	Regression equation	Correlation coefficient (r)
Intraday (n=3)		
QTP	y=(0.0337±0.0045)x+(0.0460±0.0478)	0.999
NorQTP	y=(0.0531±0.0041)x+(0.0390±0.0295)	0.999
7-QTP	y=(0.0346±0.0014)x+(0.0619±0.0299)	0.999
Inter-day (n=5)		
QTP	y=(0.0352±0.0040)x+(0.0355±0.0367)	0.999
NorQTP	y=(0.0514±0.0039)x+(0.0349±0.0268)	0.999
7-QTP	y=(0.0357±0.0022)x+(0.0443±0.0340)	0.999