Electronic Supplementary Material (ESI) for Analytical Methods.
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Table S1: Mass Spectrometry information for all analytes in this method

Compounds name	Precursor Ion	Product Ion	Declustering potential (V)	Collison Energy (V)	Collison Cell Exit Potential (V)
Fentanyl	337.2	188 105	80 80	30 46	10 13
Fentanyl D5	342.3	188	80	30	10
Morphine	286.2	152.1 128	130 130	85 79	15 13
Morphine D3	289.3	152.1	130	81	12
Buprenorphine	468.4	396.3 267.2	60 60	49 62	31 31
Buprenorphine D4	472.6	400.3	80	54	39
Norbuprenorphine	414.2	187.1 200.1	176 176	48 43	31 16
Norbuprenorphine D3	417.3	187.2	120	54	24
Oxycodone	316.1	241.1 256.1	70 70	38 35	22 25
Oxycodone D3	319.1	241.1	70	38	25
Tapentadol	222	107.1 121.1	85 85	30 28	12 19
Tapentadol D3	225	107.1	45	22	16
Naloxone	328.2	310.2 212.1	77 77	27 49	15 5
Naloxone D5	333.2	315.1	80	25	19
Alfentanil	417.3	197.1 268.2	40 40	31 27	40 17
Alfentanil D3	420.2	271.3	85	23	15
Norfentanyl	233.4	84 150.1	101 101	24 21	12 18
Norfentanyl D5	238.5	84.3	101	24	12
Tramadol	264.2	58 42	70 70	42 123	8 5
Tramadol D3	268.2	58	70	42	8
Noroxycodone	302.2	227.1 284.2	130 130	43 27	33 36
Noroxycodone D3	305.4	287.2	151	25	24
O desmethyl tramadol	250.2	58	45	55	10

		42.1	45	70	15
O desmethyl tramadol D6	256	64	70	50	17

Table S2. Results of Quality Assurance/Quality Control.

	Tapentadol	Norfentanyl	Tramadol	Morphine	Noroxycodone	Oxycodone	Naloxone	Fentanyl	Norbuprenorphine	Alfentanil	Buprenorphine	O desmethyl tramadol
QC at 0.1 ng/mL	0.09±0.01	0.09±0.01	0.14±0.01	0.09±0.02	#DIV/0!	0.08±0.01	0.09±0.01	0.1±0.01	nd	0.09±0.01	0.09±0.03	0.1±0.01
QC at 5 ng/mL	5.01±0.11	4.98±0.05	5.11±0.11	4.87±0.13	5.03±0.05	4.96±0.10	4.78±0.18	5.32±0.12	5.16±0.26	4.98±0.12	5.4±0.10	4.92±0.14
QC at 20 ng/mL	20.2±0.7	21.4±0.8	20.6±0.8	20.3±1.2	20.2±1.0	20.6±0.6	20.1±1.0	21.3±0.7	20.2±0.2	20.7±0.6	22.6±1.0	20.4±1.4
Duplicate 1	nd	nd	22.3±0.09	nd	nd	nd	nd	0.03±0.001	nd	nd	nd	1.41±0.04
Duplicate 2	nd	nd	0.05±0.001	0.024±0.004	nd	nd	nd	0.11±0.001	nd	nd	nd	0.015±0.001
Duplicate 3	nd	nd	0.08±0.02	0.47±0.01	nd	nd	nd	0.03±0.001	nd	nd	nd	0.02±0.004
Duplicate 4	nd	nd	0.06±0.005	nd	nd	nd	nd	0.02±0.002	nd	nd	nd	0.014±0.001
Duplicate 5	nd	nd	0.05±0.001	nd	nd	nd	nd	0.071±0.001	nd	nd	nd	0.014±0.002
Solvent blank	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
Procedural blank	nd	nd	0.47±0.001	nd	nd	nd	0.09±0.02	nd	nd	nd	nd	0.014±0.0006

Section S1: QuEChERS method

Firstly, 100 µL of plasma samples were spiked with 100 µL of labeled standards (100 µg/L). Secondly, 4800 µL volume of acetonitrile was added to get a final volume at 5 mL. Thirdly, samples were vortexed for 30 seconds and transferred into a QuEChERS kit. Then, samples were vortexed for 30 seconds, shake for 5 minutes and centrifuged at 10625g for 15 minutes. Then the upper level was transferred into a new tube and was put in -20 freezer overnight. On the next day, firstly, we transferred 1ml of ACN containing 0.1% formic acid to a Captiva 3ml non-drip lipid (part number: A5300635) followed by 500µL of the supernatant then filter into a high recovery screw vial. Then the supernatant was centrifuged for 10 min at 4000 rpm at 4°C and then was filtered into a vial via 13mm PTFE 0.2µm (part: 5190-5265). Samples were then evaporated to dryness under a gentle stream of nitrogen at 40 ^{o}C. The residue was reconstituted with 1000 µL of mobile phase (5% methanol, 95% milliQ water, 0.1% Formic acid) and 200ul of samples were transferred to analyze.

Section S2: simplified QuEChERS method

Firstly, 20 µL of plasma samples were spiked with 20 µL of labeled standards (100 µg/L). Secondly, an 1960 µL volume of acetonitrile was added to get a final 2ml total volume. Thirdly, samples were vortexed for 15 seconds and centrifuged at 10625g for 15 minutes. Then, the upper level was extracted and transferred into a 2 mL centrifuge tube containing 50 mg of PSA and 100 mg of MgSO4. Samples were vortexed for 60 seconds and centrifuged at 18,000 rpm for 3 min. And then we transfered the supernatant to analyze.