Electronic Supplementary Material (ESI) for Analytical Methods.

Electronic Supplementary Information

Portable Paper-In-Tip Spray Ionization for the Direct Mass Spectrometric Analysis of Target Analytes in Biofluid Samples

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Table of Contents

(1) Texture Properties of Paper Substrates Impregnated with Different Polymers

Table S1. Texture properties of paper substrates impregnated with different polymers

Paper substrate	Specific surface area ($m^2\ g^{-1}$)[a]	Average pore diameter [nm][b]	Pore volume [$cm^3\ g^{-1}$]
PMMA	1.68	9.49	0.002
PVA	2.24	14.70	0.003
PET	3.71	4.45	0.336
PE	1.65	6.62	0.001
PAN	5.03	14.90	0.002
PS	3.70	6.77	0.005

Note: [a] Using the standard Brunauer-Emmett-Teller (BET) method; [b] Using the Barret-Joyner-Halenda (BJH) method.

(2) Selected Reaction Monitoring Conditions

Table S2. Selected reaction monitoring (SRM) conditions

Analyte	Parent Ion (*m/z*)	Fragment Ion (*m/z*)	Collision Energy (V)	Tube Lens (V)
amitriptyline	278, $[M + H]^+$	84	25	83
D_3-amitriptyline	281, $[M + H]^+$	87	23	83
clozapine	327, $[M + H]^+$	270	21	89
D_8-clozapine	335, $[M + H]^+$	275	21	91
amisulpride	370, $[M + H]^+$	112	24	95
D_5-amisulpride	375, $[M + H]^+$	117	25	96
quetiapine	384, $[M + H]^+$	253	21	97
D_8-quetiapine	392, $[M + H]^+$	258	23	98
risperidone	411, $[M + H]^+$	191	26	90
D_4-risperidone	415, $[M + H]^+$	195	26	91
aripiprazole	448, $[M + H]^+$	285	25	109
D_8-aripiprazole	456, $[M + H]^+$	293	25	106

(3) Recoveries and Relative Standard Deviations of Different Therapeutic Drugs Using Paper-In-Tube Spray Ionization

Table S3. Recoveries and relative standard deviations (RSDs) of different therapeutic drugs (n = 4)

Drug	Spiked concentration (ng mL^{-1})	Measured concentration (ng mL^{-1})	Recovery (%)	RSD (%)
amitriptyline	10.0	9.9 ± 0.6	99.0	5.86
	100.0	101.1 ± 6.0	101.1	5.92
	1000.0	996.1 ± 39.9	99.6	4.01
clozapine	10.0	10.0 ± 0.4	100.0	3.64
	100.0	99.8 ± 5.3	99.8	5.29
	1000.0	1000.8 ± 43.2	100.1	4.32
amisulpride	10.0	9.9 ± 0.3	99.0	3.28
	100.0	100.9 ± 6.7	100.9	6.62
	1000.0	996.9 ± 63.9	99.7	6.41
quetiapine	10.0	10.3 ± 0.5	103.0	4.48
	100.0	96.7 ± 6.5	96.7	6.74
	1000.0	1011.1 ± 37.1	101.1	3.67
risperidone	10.0	9.9 ± 0.5	99.0	5.49
	100.0	100.6 ± 4.5	100.6	4.48
	1000.0	998.1 ± 50.5	99.8	5.03
aripiprazole	10.0	10.1 ± 0.6	101.0	5.66
	100.0	98.9 ± 6.2	98.9	6.27
	1000.0	1003.8 ± 35.3	100.4	3.52

Note: Spray solvent: acetonitrile; Applied voltage: 3.5 kV; Sample volume: 20 µL of urine spiked with different concentrations of pharmaceutic drugs.

(4) Examination on the Swelling Performance of PS-Impregnated Paper Substrate

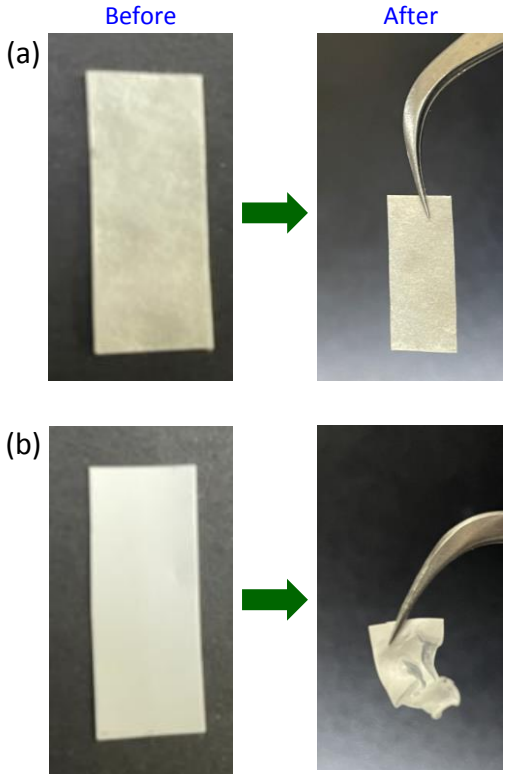

Figure S1. Comparison of the surface structures of **(a)** as-synthesized PS-impregnated paper substrate and **(b)** acetic acid/nitric acid mixed fiber membrane before and after immersing in acetonitrile for 1 min.

(5) Procedures for Paper-In-Tube Spray Ionization (PITSI)

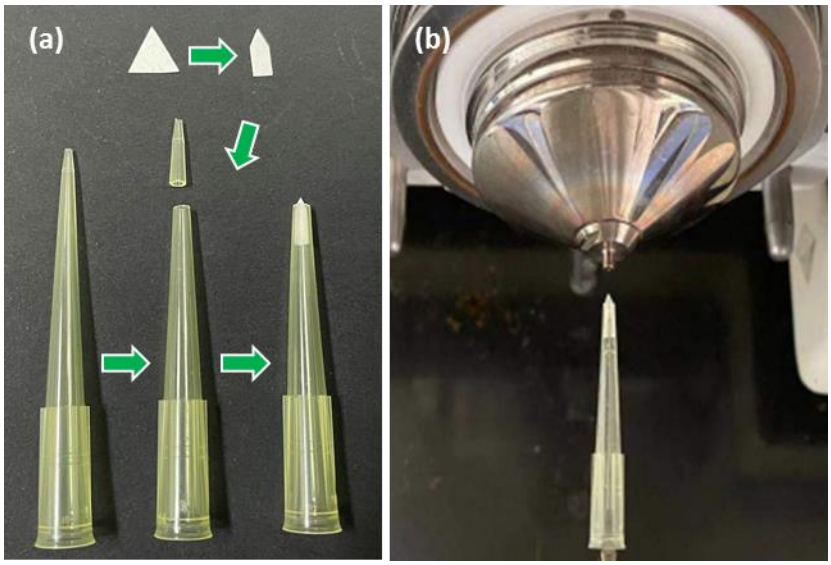

Figure S2. Photographic images **(a)** for preparing paper-in-tube unit and **(b)** for PITSI-MS.

(6) Surface Properties of Polymer-Impregnated Paper Substrates

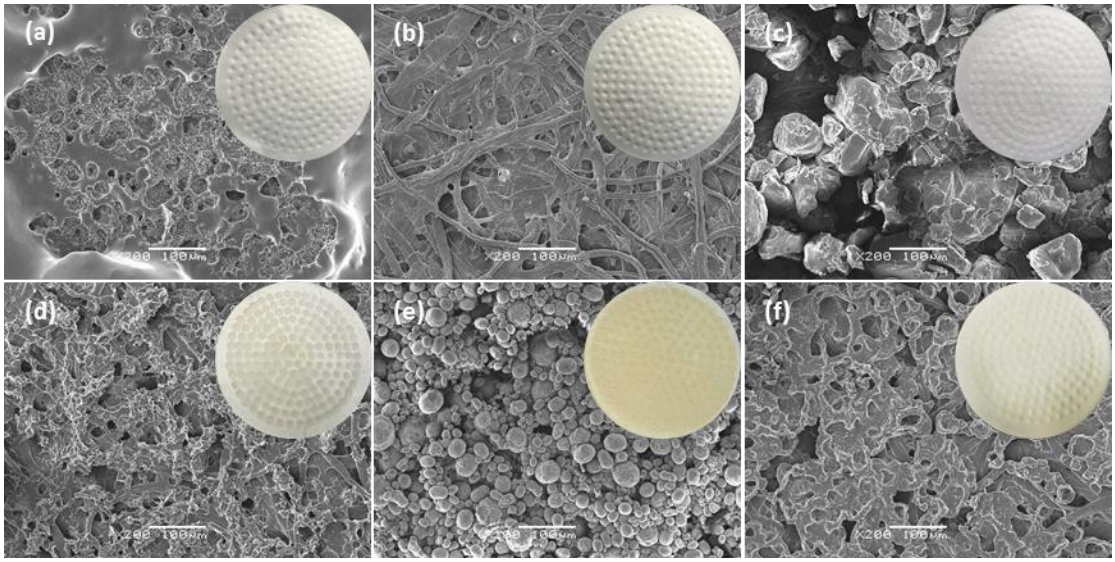

Figure S3. SEM images of paper substrates impregnated with different polymers: **(a)** PMMA, **(b)** PVA, **(c)** PET, **(d)** PE, **(e)** PAN and **(f)** PS (Note: The insets are the corresponding photographic images of coated papers).

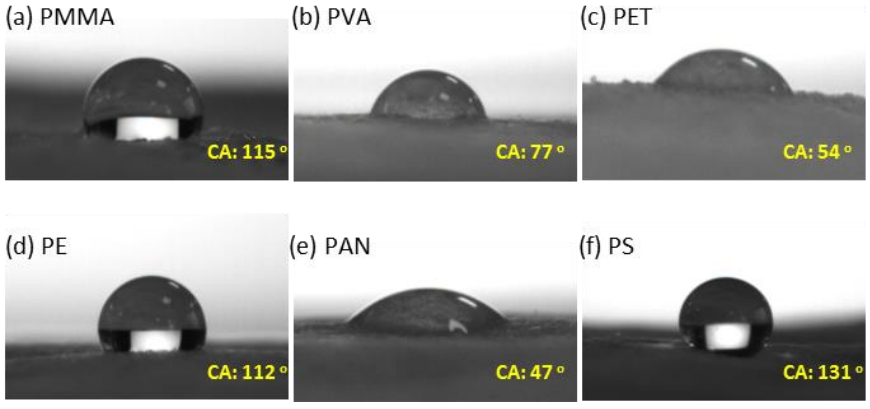

Figure S4. Photographic images of the hydrophobic properties of paper substrates impregnated with different polymers at room temperature: **(a)** PMMA, **(b)** PVA, **(c)** PET, **(d)** PE, **(e)** PAN and **(f)** PS (Note: CA means the water contact angel).

(7) Effect of the Type of Polymer-Impregnated Paper on Analysis Sensivity

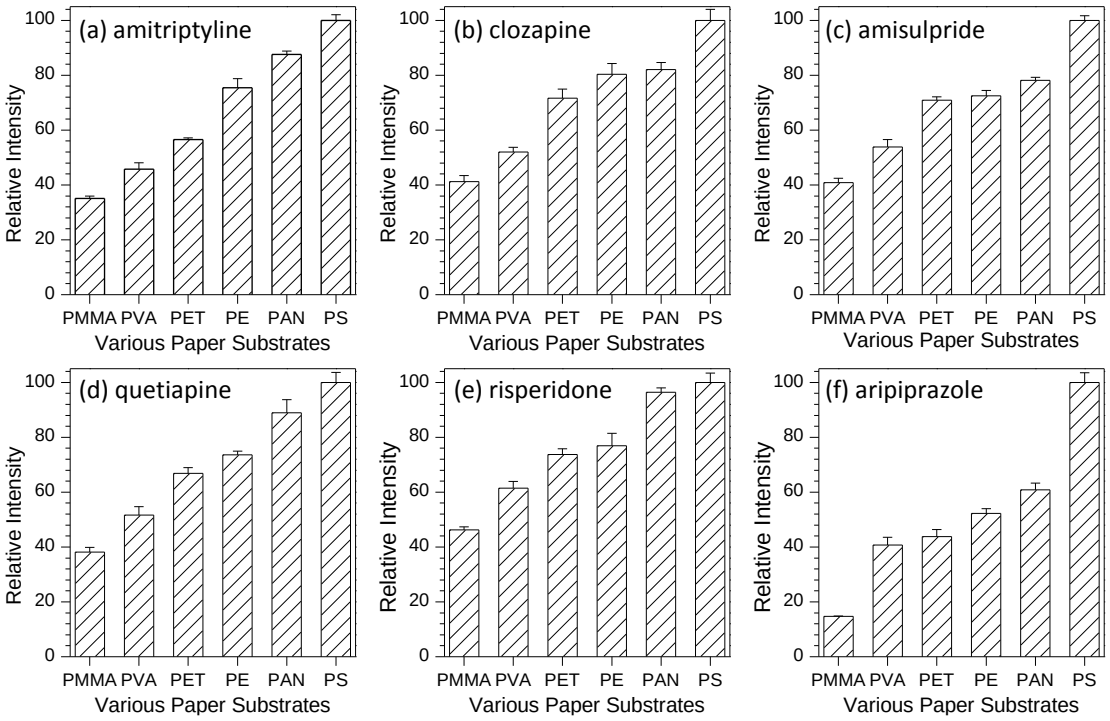

Figure S5. Effect of the type of polymer impregnated paper substrate on the analysis performance of different pharmaceutical drugs in urine: **(a)** amitriptyline, **(b)** clozapine, **(c)** amisulpride, **(d)** quetiapine, **(e)** risperidone and **(f)** aripiprazole (spray solvent: 20 µL of acetonitrile; applied voltage: 3.5 kV; concentration of drugs: 100 ng mL^{-1}).

(8) Effect of the Distance betweem Paper Tip and the Orifice of Pipette Tip on the Spray Duration of Chronogram

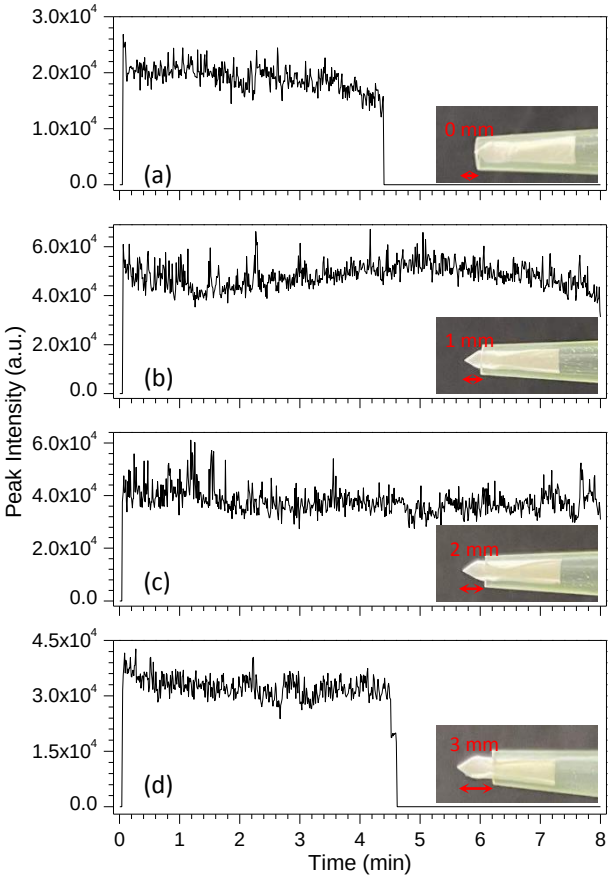

Figure S6. Effect of the distance of paper tip far away from the orifice of pipette tip on the duration of chronogram recorded using clozapine: **(a)** 0 mm, **(b)** 1 mm, **(c)** 2 mm, and **(d)** 3 mm (spray solvent: 20 µL of acetonitrile; applied voltage: 3.5 kV; concentration of clozapine: 100 ng mL^{-1}).

(9) Effect of the Concentration of Clozapine in Urine on the Spray Duration of Chronogram

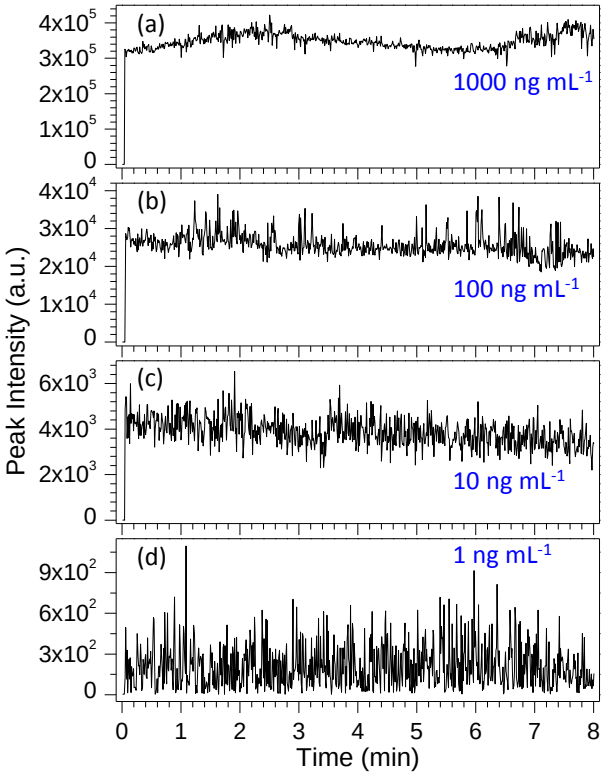

Figure S7. Effect of the concentration of clozapine in urine on the duration of chronogram: **(a)** 1000 ng mL^{-1}, **(b)** 100 ng mL^{-1}, **(c)** 10 ng mL^{-1}, and **(d)** 1 ng mL^{-1} (spray solvent: 20 µL of acetonitrile; applied voltage: 3.5 kV; distance of paper tip far away from the orifice of pipette tip: 2 mm).

(10) Effect of Experimental Conditions on the Analysis Sensivity of PITSI-MS

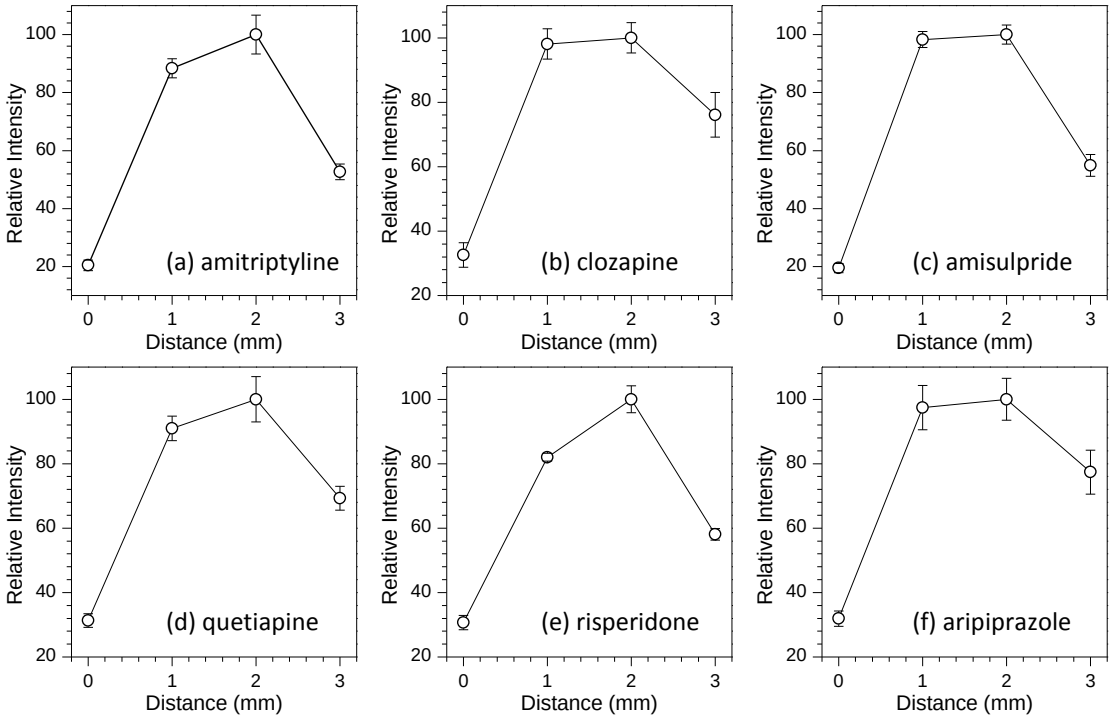

Figure S8. Effect of the distance of paper tip far away from the orifice of pipette tip on the analysis sensitivity of different therapeutic drugs: **(a)** amitriptyline, **(b)** clozapine, **(c)** amisulpride, **(d)** quetiapine, **(e)** risperidone, and **(f)** aripiprazole (spray solvent: 20 μL of acetonitrile; applied voltage: 3.5 kV; concentration of drugs: 100 ng mL^{-1}).

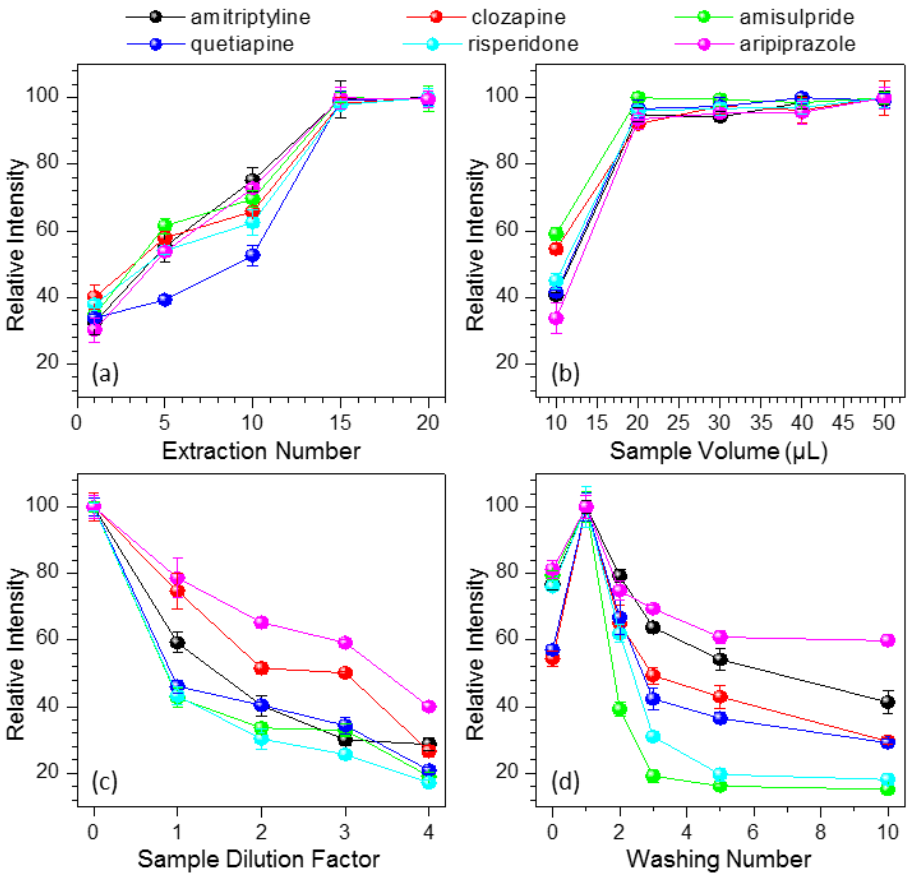

Figure S9. Effect of the experimental conditions on the analysis sensitivity of different drugs: **(a)** extraction number, **(b)** sample volume, **(c)** sample dilution factor, and **(d)** washing number (spray solvent: 20 μL of acetonitrile; applied voltage: 3.5 kV; distance of paper tip far away from the orifice of pipette tip: 2 mm; size of pipette tip: 100 μL; concentration of drugs in urine: 100 ng mL^{-1}).

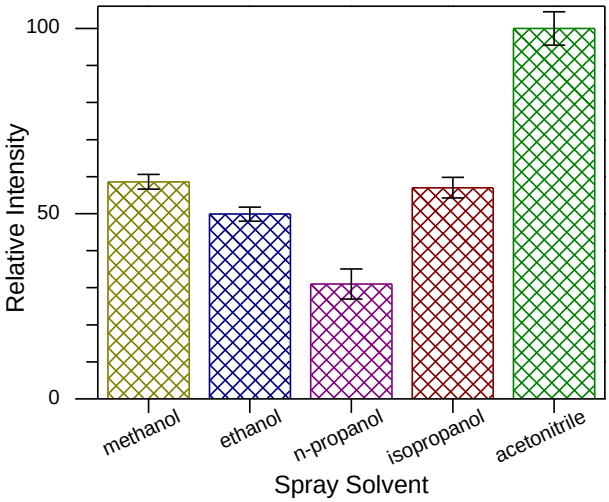

Figure S10. Effect of the spray solvent on the analysis sensitivity of verapamil (volume of spray solvent: 20 µL; applied voltage: 3.5 kV; distance of paper tip far away from the orifice of pipette tip: 2 mm; concentration of verapamil in urine: 100 ng mL^{-1}).

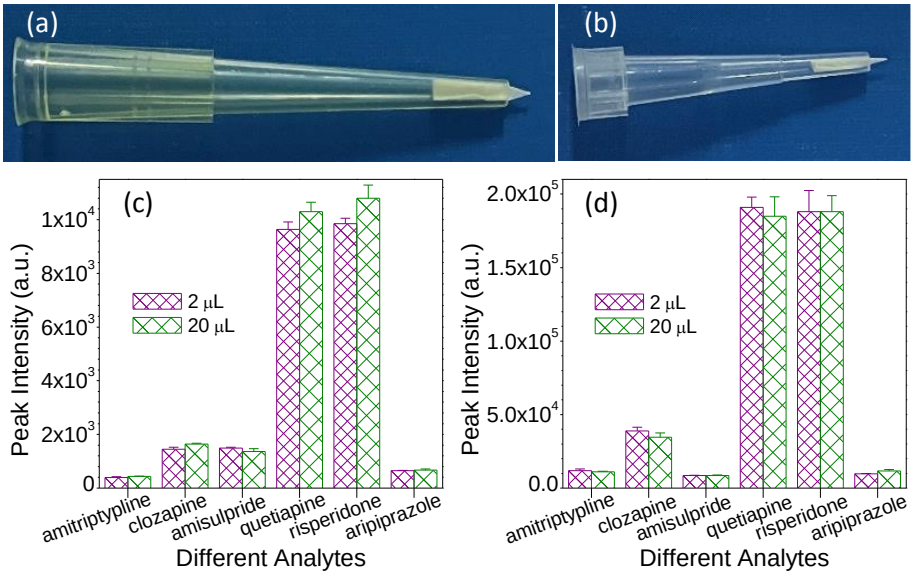

Figure S11. Photographic images of **(a)** 100 µL and **(b)** 10 µL of pipette tips incorporated with PS-impregnated paper substrate; comparison of the analysis sensitivity of different analytes with concentrations of **(c)** 1 ng mL^{-1} and **(d)** 100 ng mL^{-1} in urine and sample volumes of 2 µL and 20 µL (note: for the experiment with 2 µL of urine, both the washing volume of water and the spray volume of acetonitrile were 2 µL; for the experiment with 20 µL of urine, both the washing volume of water and the spray volume of acetonitrile were 20 µL).

(11) Comparison of the Spray Current of PITSI, PSI, CBSI, and TSI

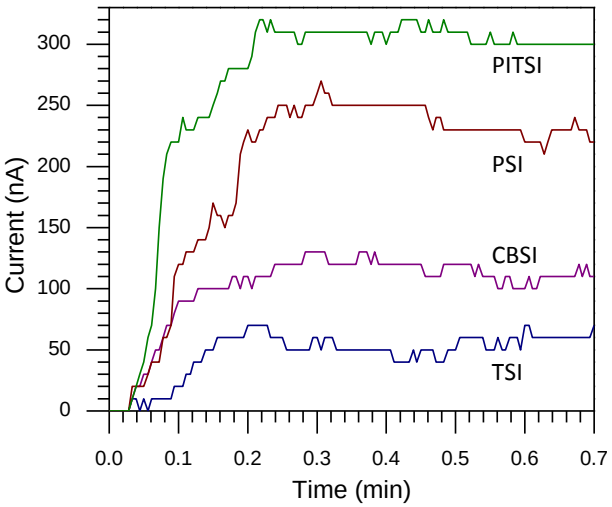

Figure S12. Comparison of the spray current of different ionization techniques (spray solvent: 20 µL of 1:1 methanol/water containing 0.1% acetic acid; paper substrate: PS-impregnated paper; applied voltage: 3.5 kV).

(12) Repeatability of PITSI in Analysis of Different Drugs in Urine

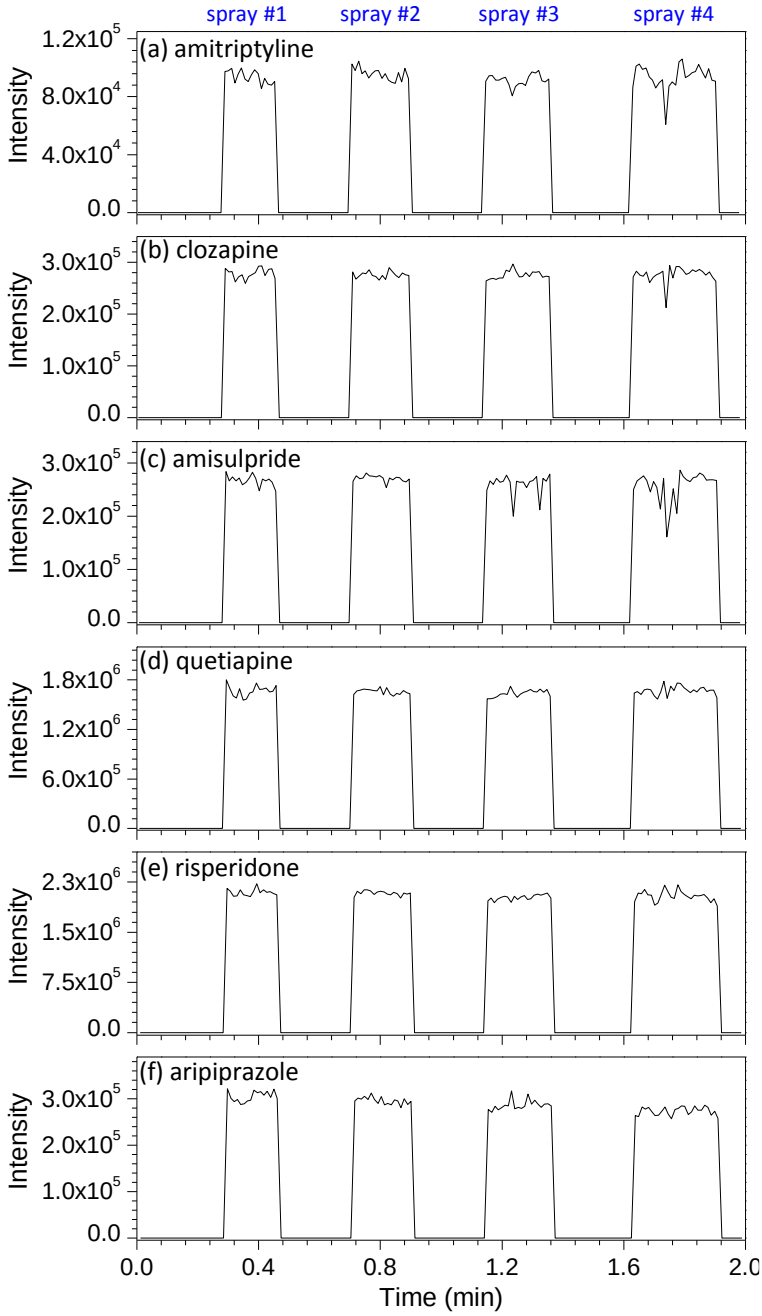

Figure S13. Simultaneous determination of different therapeutic drugs in urine with each concentration of 1 μg mL^{-1}, and ion chronograms for **(a)** amitriptyline, **(b)** clozapine, **(c)** amisulpride, **(d)** quetiapine, **(e)** risperidone, and **(f)** aripiprazole using SRM mode of a Thermo TSQ (spray solvent: 20 μL of acetonitrile; applied voltage: 3.5 kV).

(13) Quantitative Analysis of Different Drugs in Various Matrixes

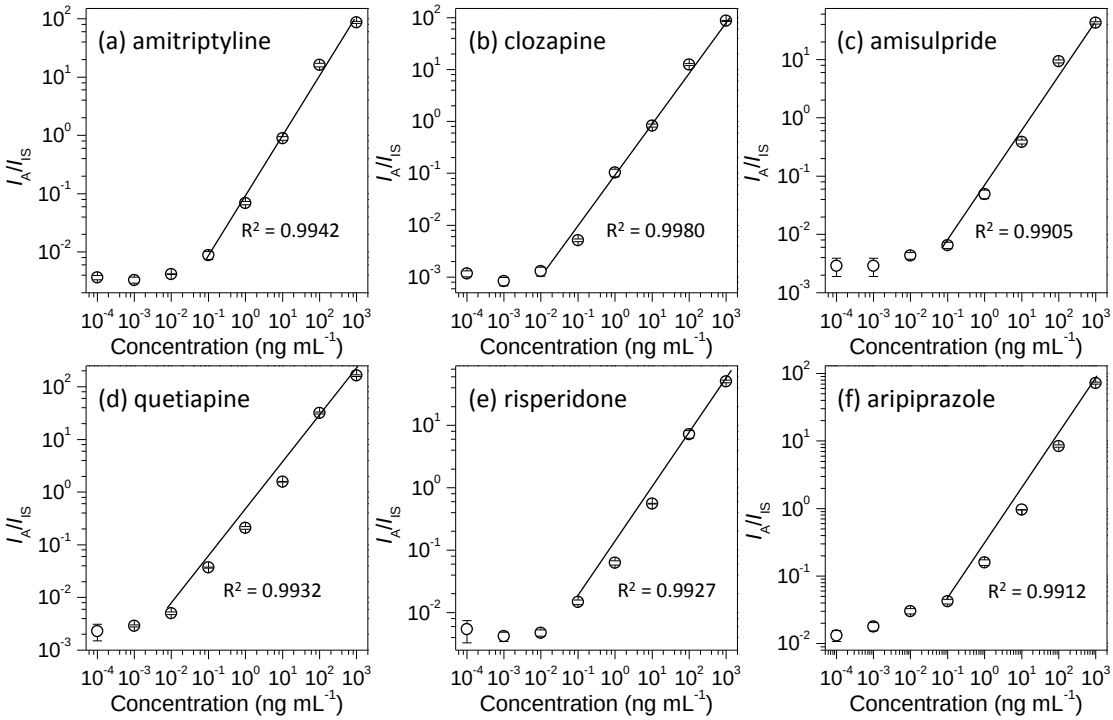

Figure S14. Quantitative analysis of urine samples spiked with **(a)** amitriptyline, **(b)** clozapine, **(c)** amisulpride, **(d)** quetiapine, **(e)** risperidone, and **(f)** aripiprazole (0.001 – 1000 ng mL^{-1}) and its isotopomers (10 ng mL^{-1}). Note: spray solvent: 20 µL of acetonitrile; applied voltage: 3.5 kV; Bars represent the standard deviation of analysis for four replicates.

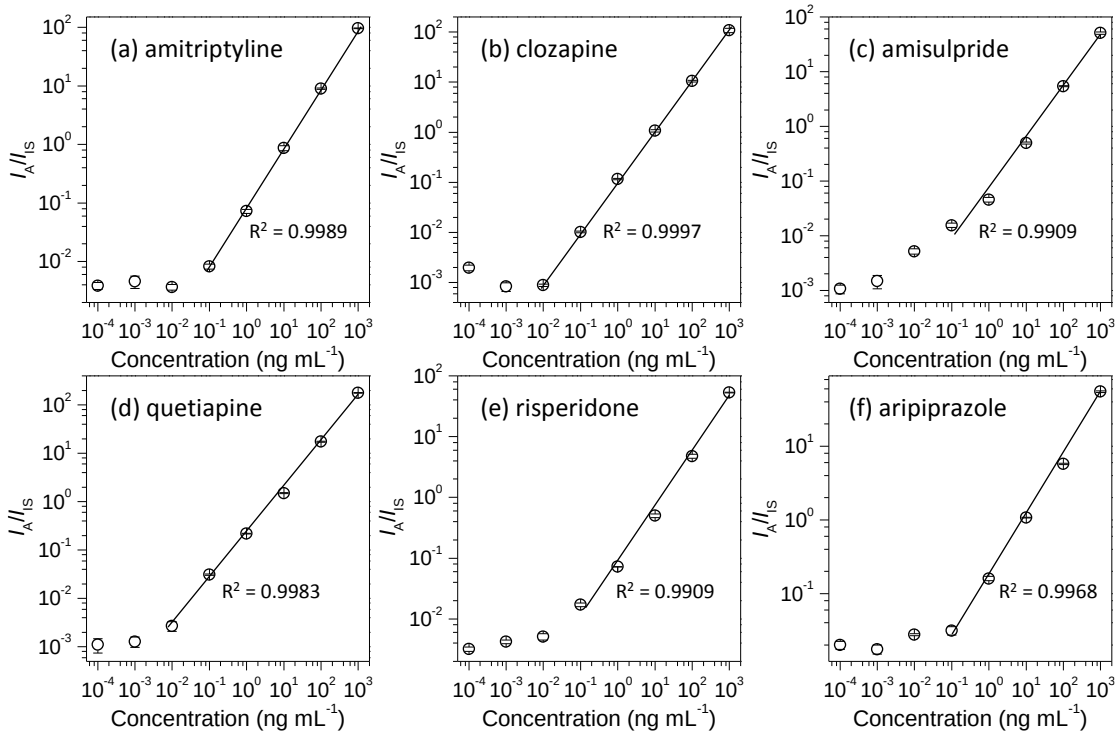

Figure S15. Quantitative analysis of 0.9% saline samples spiked with **(a)** amitriptyline, **(b)** clozapine, **(c)** amisulpride, **(d)** quetiapine, **(e)** risperidone, and **(f)** aripiprazole (0.001 – 1000 ng mL^{-1}) and its isotopomers (10 ng mL^{-1}). Note: spray solvent: 20 µL of acetonitrile; applied voltage: 3.5 kV; Bars represent the standard deviation of analysis for four replicates.

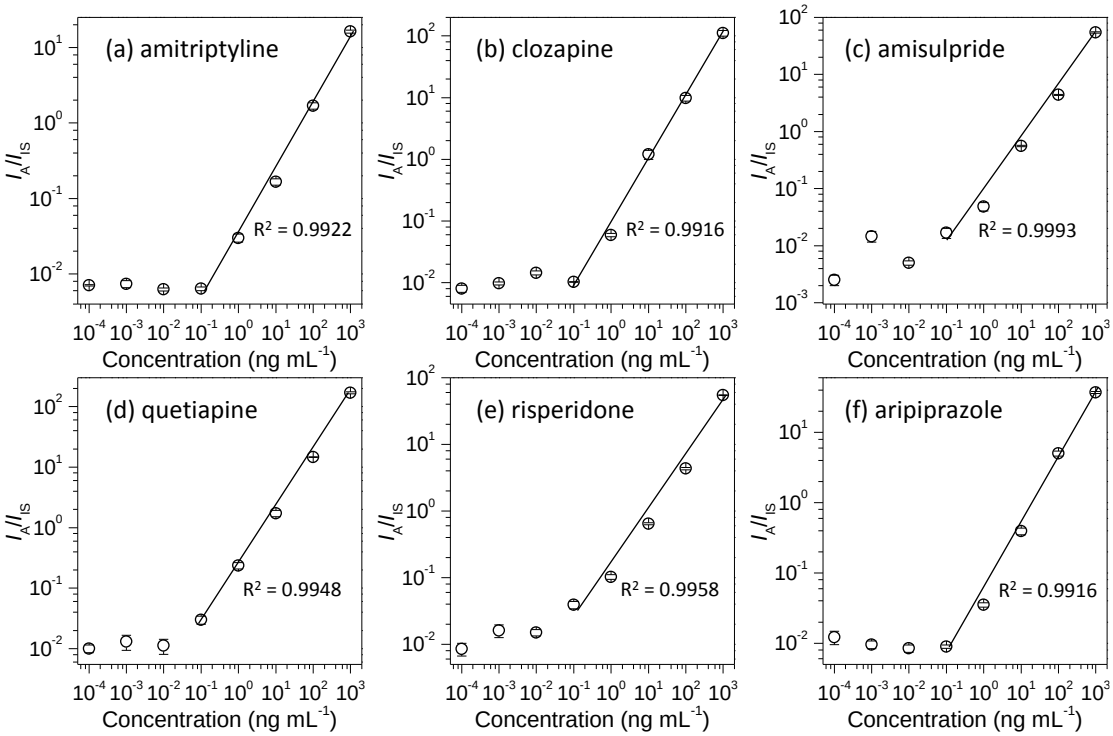

Figure S16. Quantitative analysis of serum samples spiked with **(a)** amitriptyline, **(b)** clozapine, **(c)** amisulpride, **(d)** quetiapine, **(e)** risperidone, and **(f)** aripiprazole (0.001 – 1000 ng mL^{-1}) and its isotopomers (10 ng mL^{-1}). Note: spray solvent: 20 µL of acetonitrile; applied voltage: 3.5 kV; Bars represent the standard deviation of analysis for four replicates.

(14) Comparison of the Performance of PSI and PITSI in the Analysis of Proteins

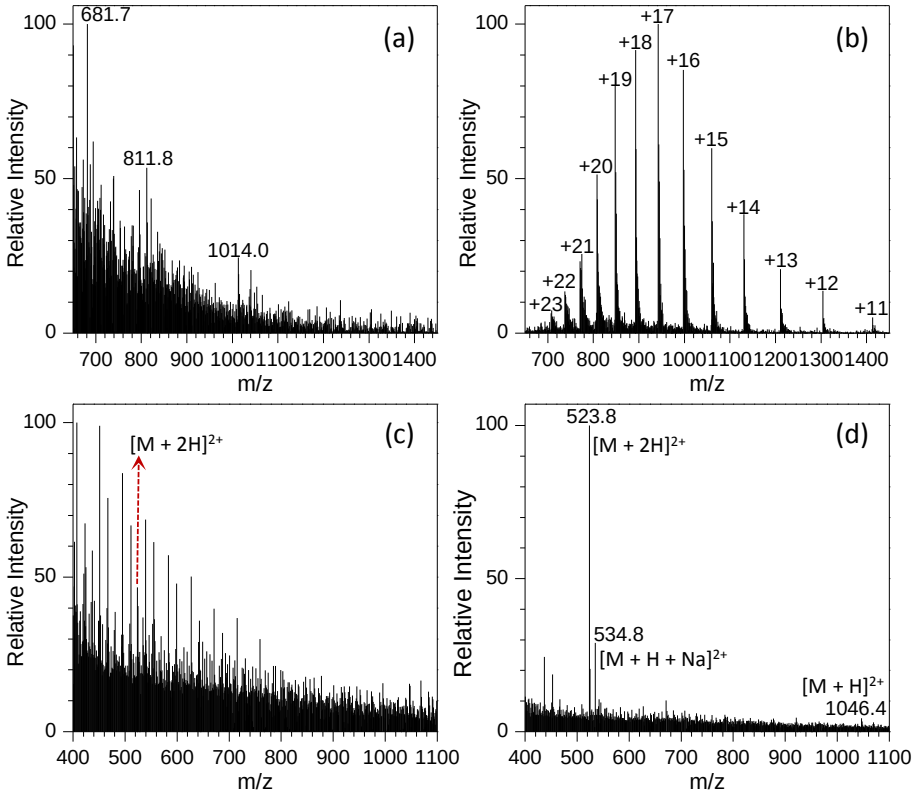

Figure S17. Comparison of the performances of (**a**, **c**) PSI and (**b**, **d**) PITSI in the analysis of different proteins in various matrices: (**a**, **b**) 200 μg mL^{-1} of myoglobin in serum; (**c**, **d**) 100 μg mL^{-1} of angiotension II (spray solvent: 20 μL of 1:1 methanol/water containing 0.5% acetic acid for PITSI and 20 μL of 1:1 methanol/protein solution containing 0.5% acetic acid for PSI ; applied voltage: 3.5 kV; distance of paper tip far away from the orifice of pipette tip: 2 mm).