Supporting Information (SI)

3D-PRINTED PAPER SPRAY IONIZATION CARTRIDGE WITH INTEGRATED DESOLVATION FEATURE AND ION OPTICS

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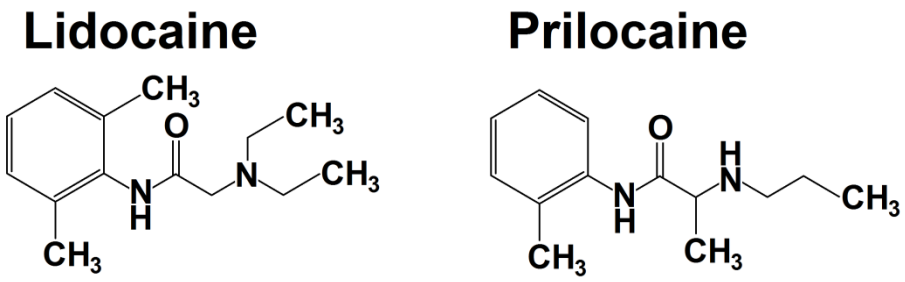

Figure S1: Structural formulas of lidocaine (M.W. 234) and prilocaine (M.W. 220).

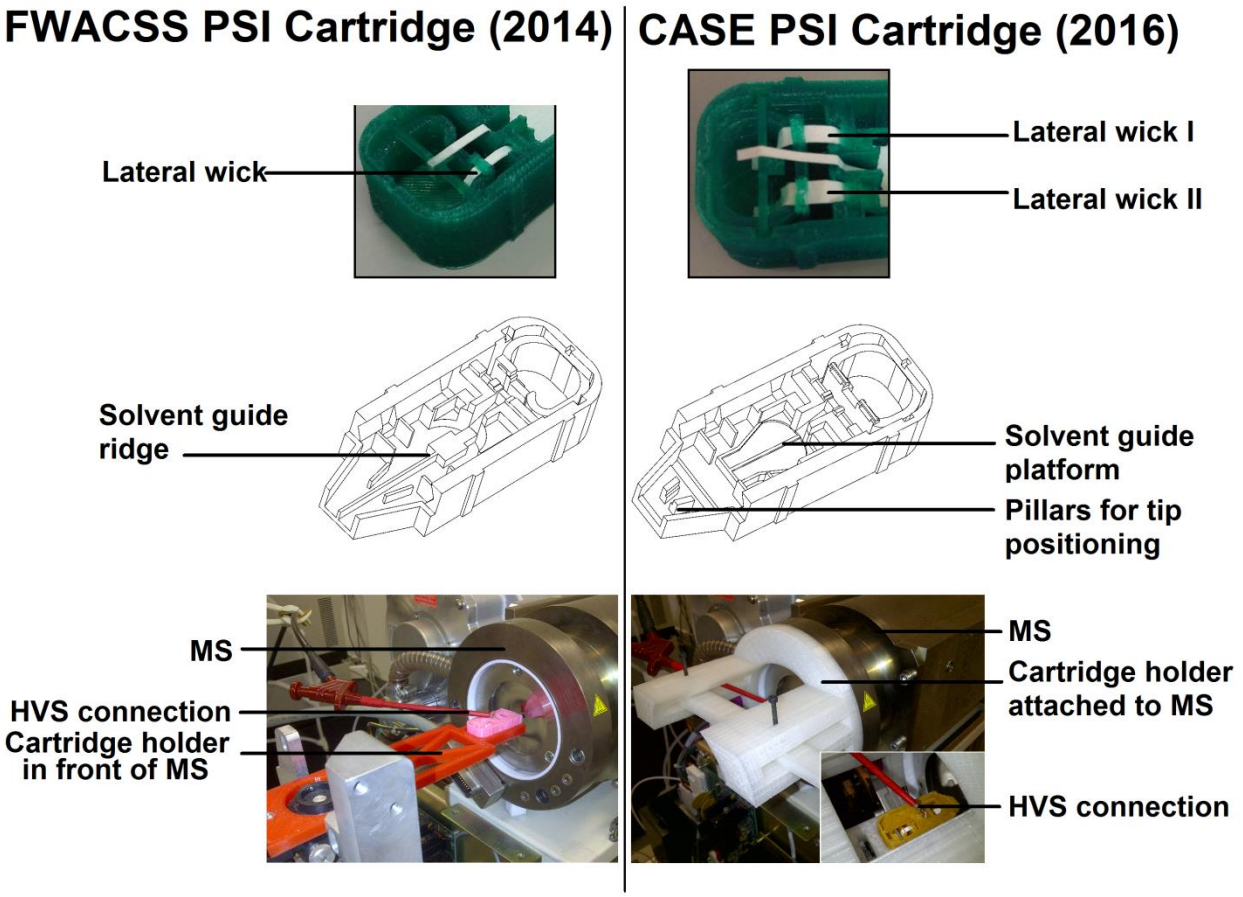

Figure S2: Upgrade from the *fast wetting and continuous solvent supply (FWACSS) paper spray ionization (PSI) cartridge* (2014) to the *controlled and symmetric elution (CASE) PSI cartridge* (2016). Two broad lateral wicks are used instead of one small wick for continuous wetting, which allow a symmetrical and increased supply of solvent. Furthermore, the central solvent guide ridge in the FWACSS PSI cartridge, which is essential for fast spreading of solvent over the tip, was changed to a solvent guide platform in the CASE model, which allows fast spreading of solvent up to the end of the platform. After that, a slower, more controlled wetting of the tip is obtained, which is more favorable for elution of compounds. Since it is a platform, rather than a ridge, it can also hold a relatively large amount of solvent, serving as an overflow chamber and secondary reservoir at the same time. Moreover, the interaction between the spray tip and the cartridge is reduced. Where the tip used to lie on top of a PLA ridge in the FWACSS design, it is positioned by suspension between two pillars in the CASE model, which have limited contact with the borders of the paper tip. These changes were made to minimize (unpredictable) cartridge-paper interactions at this critical site in the device. Finally, the holder for interfacing the cartridge with the MS was upgraded from a model which was not attached to the MS (left) to one which is fixed to the MS (right). This change led to more reproducible positioning of the paper tip.

Video S1: Experiment to determine air distribution through the lens and nozzles (LAN) cartridge. The LAN cartridge is connected to 1 inlet tube. This tube is connected to an air supply (0.2 bar), which is opened at around 3 seconds in the video. An additional 4 pieces (same length) of tubing are attached to the nozzles of the cartridge. The other end of each piece of tubing is placed beneath the opening of a water-filled bottle that is placed upside-down in a water bath. As the air supply is opened, air displaces water in each of the water-filled bottles. At around 30 seconds in the video, the air supply is closed again. The volume of displaced water can be read from the bottles, and thus the air distribution over the four nozzles can be calculated.

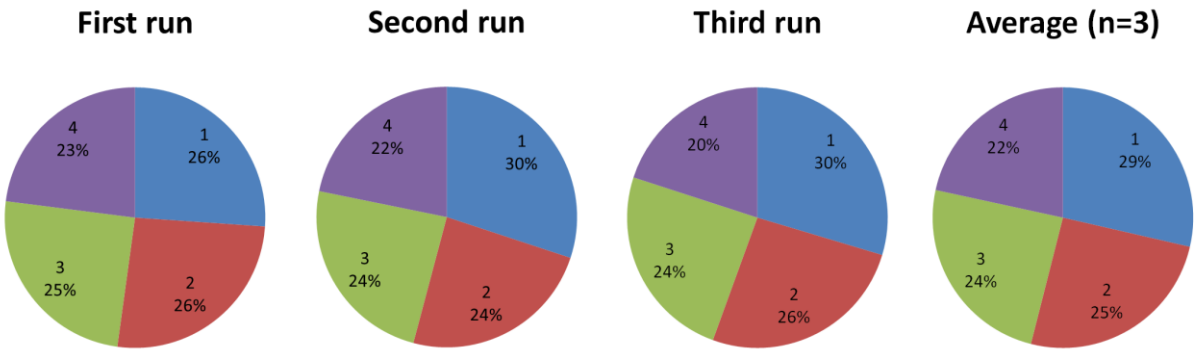

Figure S3: Characterization of air distribution through a PSI cartridge with electrostatic lens and nozzles for sheath gas delivery (LAN). In three different experiments with the same cartridge, the displacement of water from a bottle was simultaneously observed for each of the four individual spray nozzles. All four nozzles were supplied with air via the same inlet at the rear of the cartridge (0.2 bar).

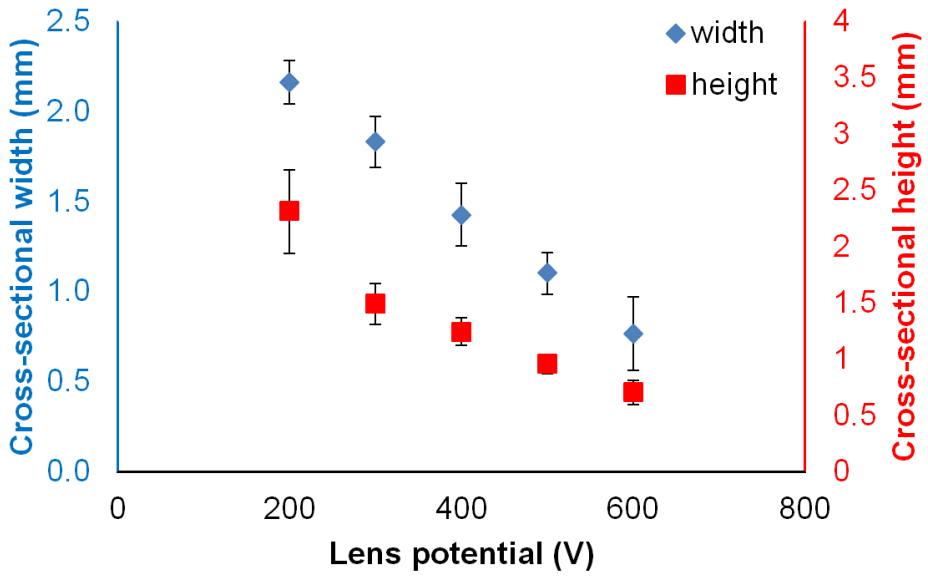

Figure S4: Characterization of the electrostatic lens in a LAN PSI cartridge. A fixed potential of 2.3 kV was applied to a paper tip. The lens potential was varied between 200 and 600 V. Spray solvent with blue dye (methanol with 1% formic acid and blue food dye) was sprayed onto a grounded, vertically positioned metal plate. This experiment was performed three times, with the same setup and cartridge to exclude as many other variables as possible. The height and width of the spots were measured with ImageJ from a photograph (a ruler was used as size reference) and plotted as a function of the lens potential. Error bars show the standard deviation.

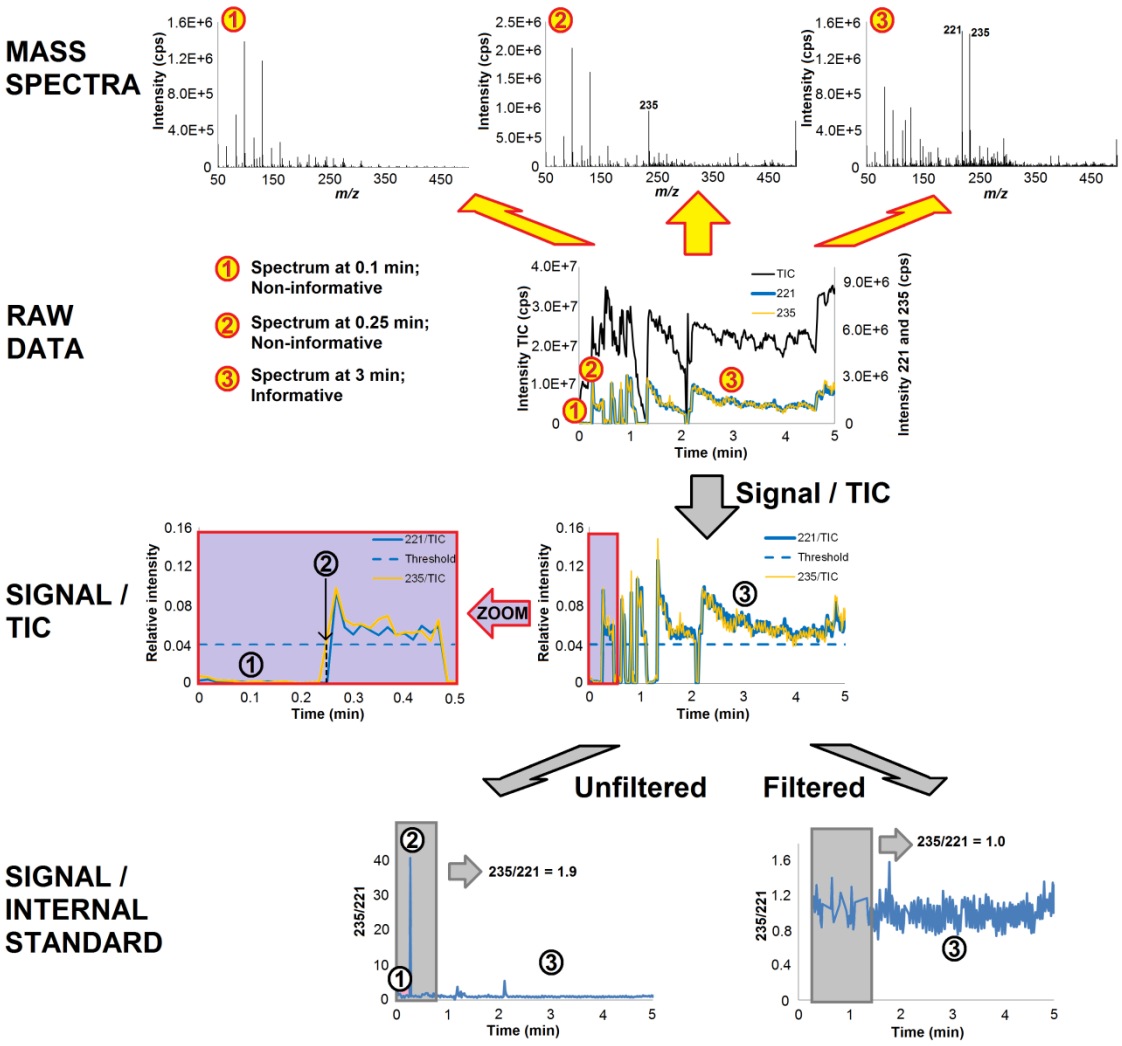

Figure S5: Data processing of PSI spectra. The experiment was performed with a CASE PSI cartridge, a sample containting 10 µM lidocaine, and 20 µM prilocaine in water, and a 5 µL sample spot. The raw data that is shown contains a total ion current (TIC), and traces for *m/z* 221 (protonated prilocaine) and 235 (protonated lidocaine). The traces for lidocaine and prilocaine almost completely overlap, which means that a calculated ratio between them should approximate 1. Mass spectra are shown from 3 specific time points: 0.1, 0.25 and 3 min. These spectra are examples of non-informative (1, 2) and informative (3) data. The goal of the data processing is to eliminate non-informative spectra, to obtain only high-quality data. In order to achieve this, the signal/TIC ratios for lidocaine and prilocaine (used as a measure for spectral complexity) were calculated and plotted. A signal threshold was then manually selected in the 221/TIC trace just below the maximum signal range to remove spectra with a lower 221/TIC value (dashed blue line). An expanded view of the first 30 seconds of the 221/TIC plot shows the traces at time points 1 and 2, which were chosen as representative of non-informative data. These data points are effectively filtered out by the application of a threshold. Finally, the lidocaine : prilocaine ratio (analyte : internal standard) is plotted over time for unfiltered and filtered data. The first 50 spectra from both data sets (gray boxes) were used to calculate the average ratio. It is clear that the inclusion of the non-informative time-point 2 leads to an erroneous peak, which in turn leads to misinterpretation of the data. Filtration based on an 221/TIC threshold of 0.04 in this example successfully prevents incorrect quantification of the sample concentration, as it yields a lidocaine : prilocaine ratio of 1, as expected by inspection of the raw data. Ideally, an algorithm would be used for threshold selection, making this step easier while ensuring uniformity of data treatment.

Table S1: Data for the individual experiments with the CASE PSI cartridge. Prilocaine (20 µM) was used as internal standard.

Experiment nr.	Conc. (µM)	n	221/TIC	221/TIC Filter (>)	235/221	Time between 1st and 50th data point (min)	RSD of 50 data points in m/z 221 XIC (%)
1	blank	1	0.038	0.03	0.052	1.76	32.2
2	blank	2	0.072	0.045	0.015	1.26	8.94
3	blank	3	0.072	0.04	0.019	1.14	27.4
4	blank	4	0.055	0.03	0.023	1.26	29.6
5	blank	5	0.051	0.04	0.02	0.92	33.0
6	0.1	1	0.064	0.04	0.042	1.16	30.2
7	0.1	2	0.09	0.04	0.037	1.43	34.7
8	0.1	3	0.039	0.04	0.039	2.60	46.5
9	0.5	1	0.068	0.05	0.092	1.19	33.5
10	0.5	2	0.074	0.06	0.089	1.26	16.1
11	0.5	3	0.049	0.035	0.092	1.27	68.8
12	1	1	0.075	0.05	0.14	1.44	30.7
13	1	2	0.063	0.03	0.14	0.96	41.5
14	1	3	0.088	0.05	0.12	0.87	15.9
15	5	1	0.065	0.045	0.51	1.34	50.7
16	5	2	0.053	0.04	0.58	0.94	19.9
17	5	3	0.056	0.025	0.60	3.62	23.9
18	10	1	0.073	0.06	0.94	0.84	12.8
19	10	2	0.041	0.025	0.94	2.16	33.6
20	10	3	0.069	0.04	1.00	1.39	39.3

Table S2: Data for the individual experiments with the LAN PSI cartridge. Prilocaine (20 µM) was used as internal standard.

Experiment nr.	Conc. (µM)	n	221/TIC	221/TIC Filter (>)	235/221	Time between 1st and 50th data point (min)	RSD of 50 data points in m/z 221 XIC (%)
1	blank	1	0.16	0.12	0.012	1.31	9.00
2	blank	2	0.13	0.1	0.017	1.59	9.84
3	blank	3	0.15	0.08	0.012	0.87	11.3
4	blank	4	0.12	0.06	0.016	1.06	26.4
5	blank	5	0.12	0.1	0.013	1.17	9.13
6	0.05	1	0.13	0.1	0.023	0.82	6.71
7	0.05	2	0.18	0.15	0.015	0.82	2.84
8	0.05	3	0.14	0.12	0.019	1.01	4.91
9	0.1	1	0.15	0.08	0.026	0.89	13.6
10	0.1	2	0.10	0.04	0.029	1.84	11.1
11	0.1	3	0.14	0.1	0.028	2.70	8.45
12	0.5	1	0.11	0.08	0.086	0.89	7.19
13	0.5	2	0.096	0.07	0.10	0.82	6.36
14	0.5	3	0.12	0.07	0.077	0.82	19.2
15	1	1	0.14	0.1	0.14	0.82	5.53
16	1	2	0.13	0.1	0.15	0.82	5.72
17	1	3	0.11	0.08	0.18	1.01	11.3
18	5	1	0.095	0.08	0.62	1.06	4.98
19	5	2	0.099	0.08	0.63	1.53	4.89
20	5	3	0.14	0.1	0.66	1.83	9.72