Mass Spectrometry

On-demand Ambient Ionization of Picoliter Samples using Charge Pulses**

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Abstract: *Relay electrospray ionization (rESI) from a capillary containing a sample solution (or from an array of such capillaries) is triggered by charge deposition onto the capillary. Suitable sources of primary ions, besides electrosprays, are plasma ion and piezoelectric discharge plasma sources. With no requirement for physical contact, high-throughput sample screening is enabled by rapidly addressing individual secondary (sample) capillaries. Sub-pL sample volumes can be loaded and sprayed. Polar analytes, including neurotransmitters, phosphopeptides, oligonucleotides, illicit drugs, and pharmaceutical compounds are successfully ionized by rESI with concentration sensitivities (0.1 ppb for acetylcholine) which are similar to nanoESI but absolute sensitivities are orders of magnitude better. Nonpolar analytes (steroids, alkynes) are ionized by rESI using an open-tube secondary capillary and injecting electrolytically generated metal cations from the primary electrospray.*

Rahul Narayanan

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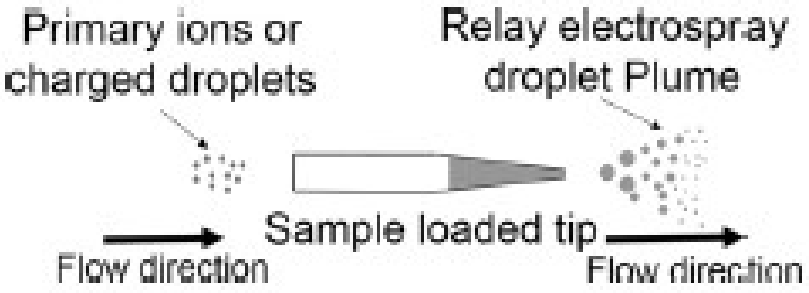
Introduction

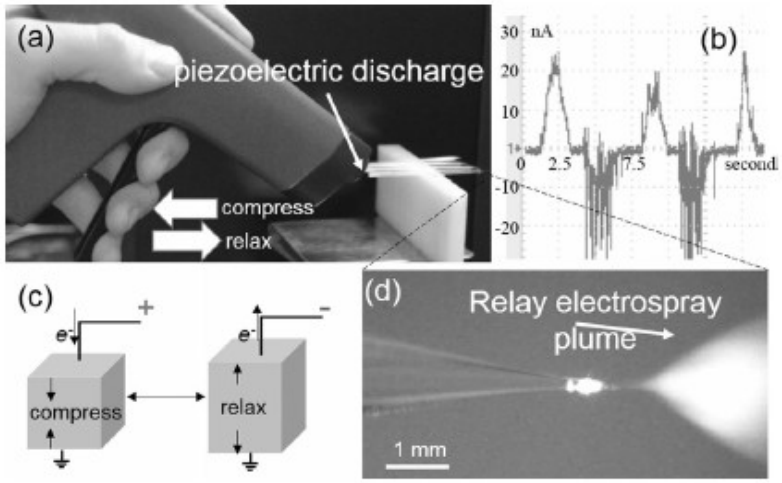
- Electrospray is an electrohydrodynamic phenomenon discovered in the twentieth century. Today it has important applications in mass spectrometry, propulsion, and materials fabrication.
- In ESI, electrical contact with a voltage supply is necessary to generate a continuous spray of charged droplets from a solution. The electrical contact adds dead volume and adsorption surfaces. It also complicates the apparatus configuration, especially for arrays of ESI emitters.
- Desorption electrospray ionization, extractive electrospray, acoustic wave nebulization, and laser ablation electrospray avoid electrode contact with samples but require a sheath gas, laser, or acoustic wave to break up the sample solutions.

This paper

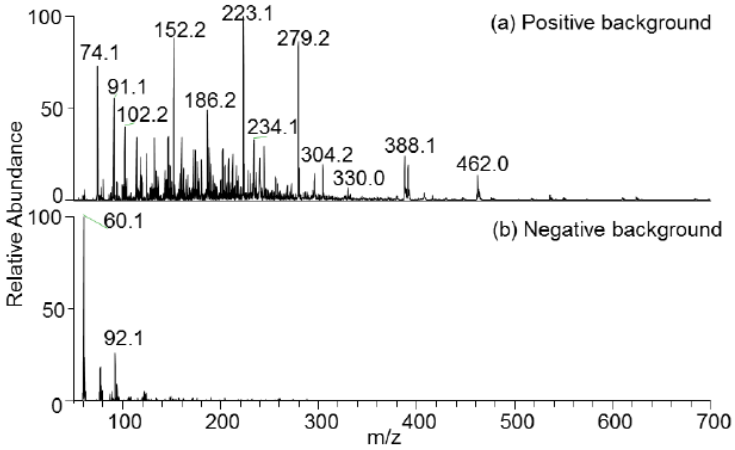
charge is supplied into (open configuration) or onto the outside (closed configuration) of the sample capillary as ions or charged droplets from a primary source (needle discharge plasma, piezoelectric discharge plasma, or electrospray ion source). The relay generates ions from the analyte solution for mass spectrometric analysis.

rESI

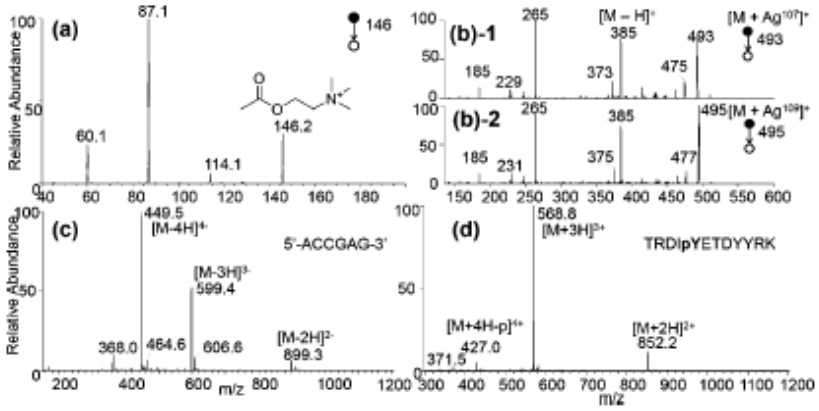




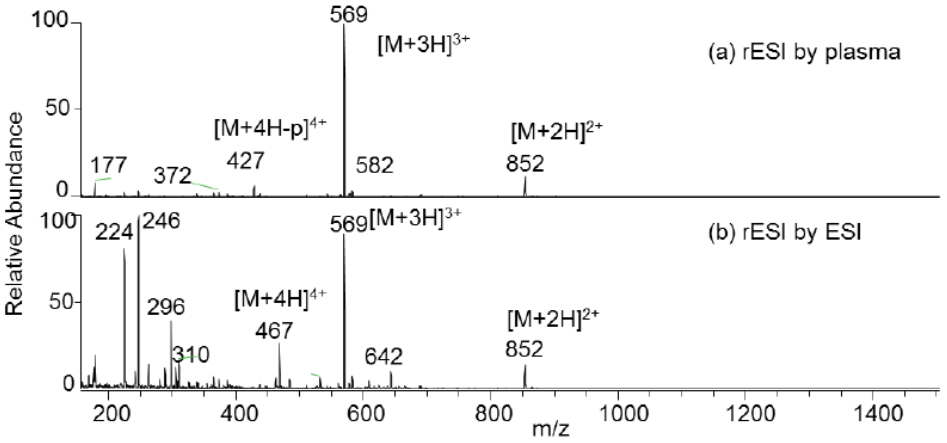
Hand-held piezoelectric direct discharge plasma generator as primary ion source in relay ESI. a) Photograph of set-up; b) rESI current through three positive and two negative cycles; c) electrical operating schematic and d) photograph of relay spray plume.



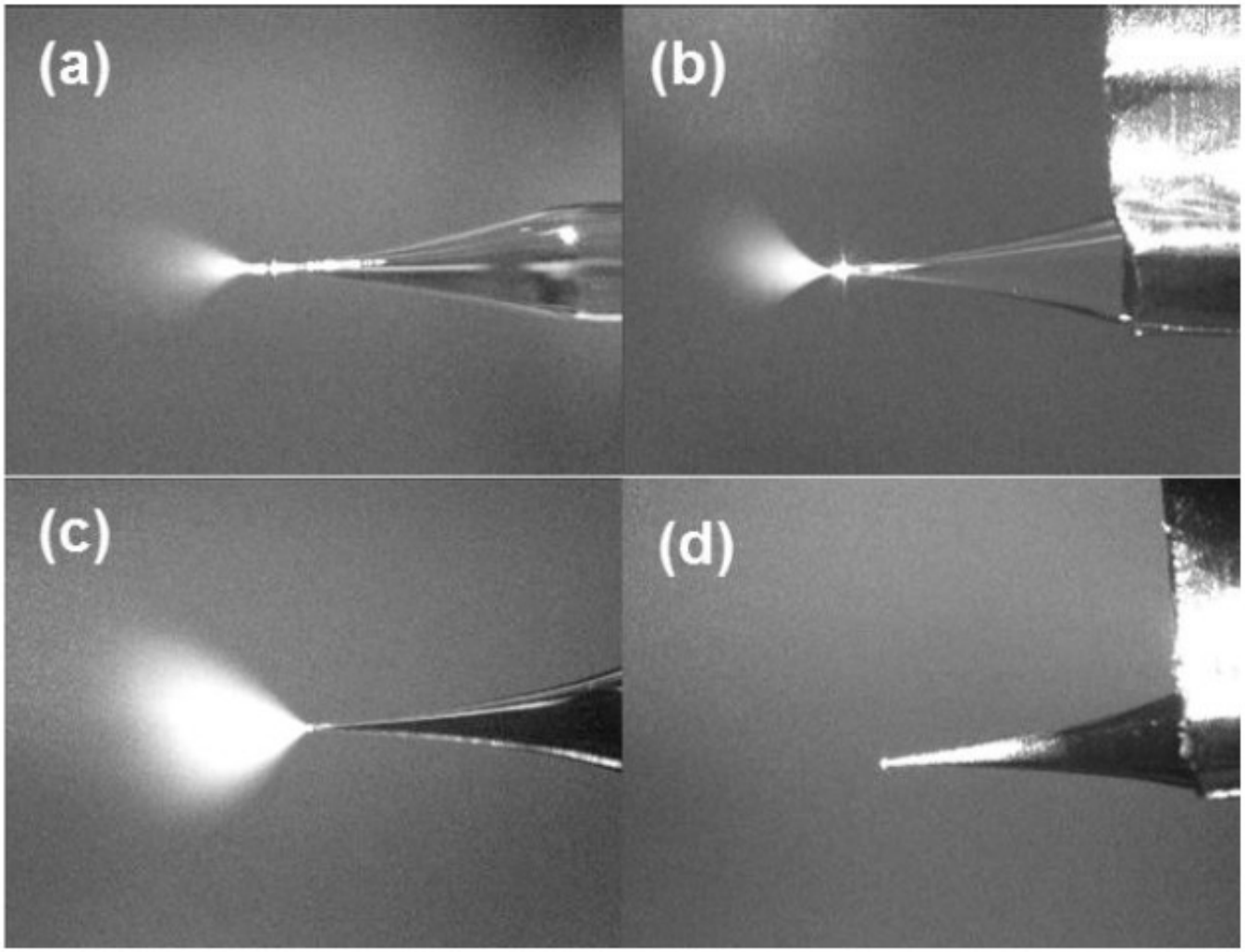
Background ions generated by the piezoelectric discharge plasma in positive (a) and negative (b) modes in a lab environment. The discharge plasma was placed 30 cm away from the mass spectrometer inlet. The absolute intensity (normalized level) for (a) and (b) were 1.1×104 and 5.2×104 respectively.



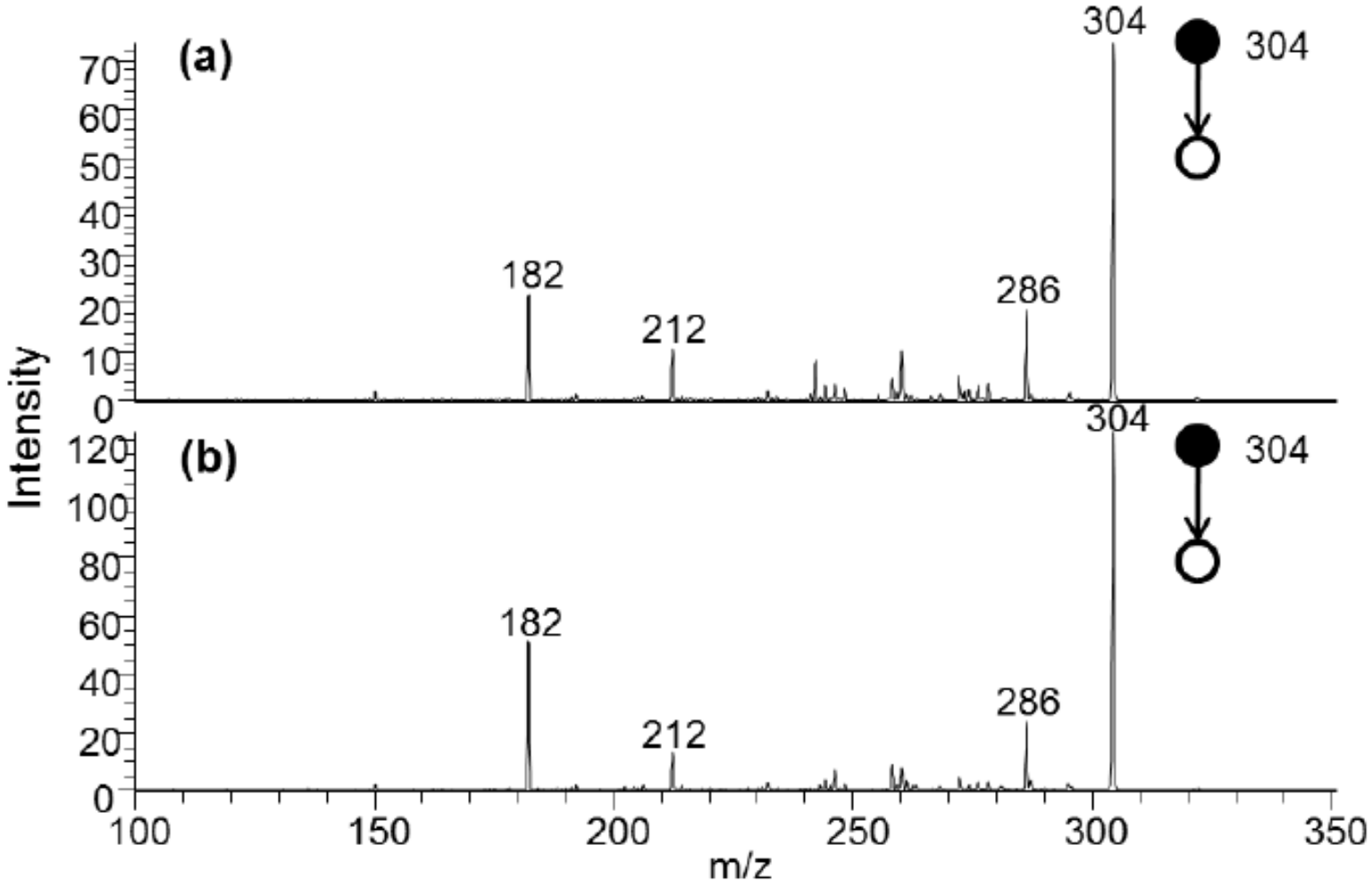
Relay electrospray MS analysis of a) ca. 1 pL of 0.5 ppb acetylcholine, MS/MS of m/z 146. b) 100 ppb cholesterol, MS/MS of isotopic [M+Ag]+ ions, c) 1 µM DNA oligomer in negative ion mode, and d) 1 µM phosphopeptide.



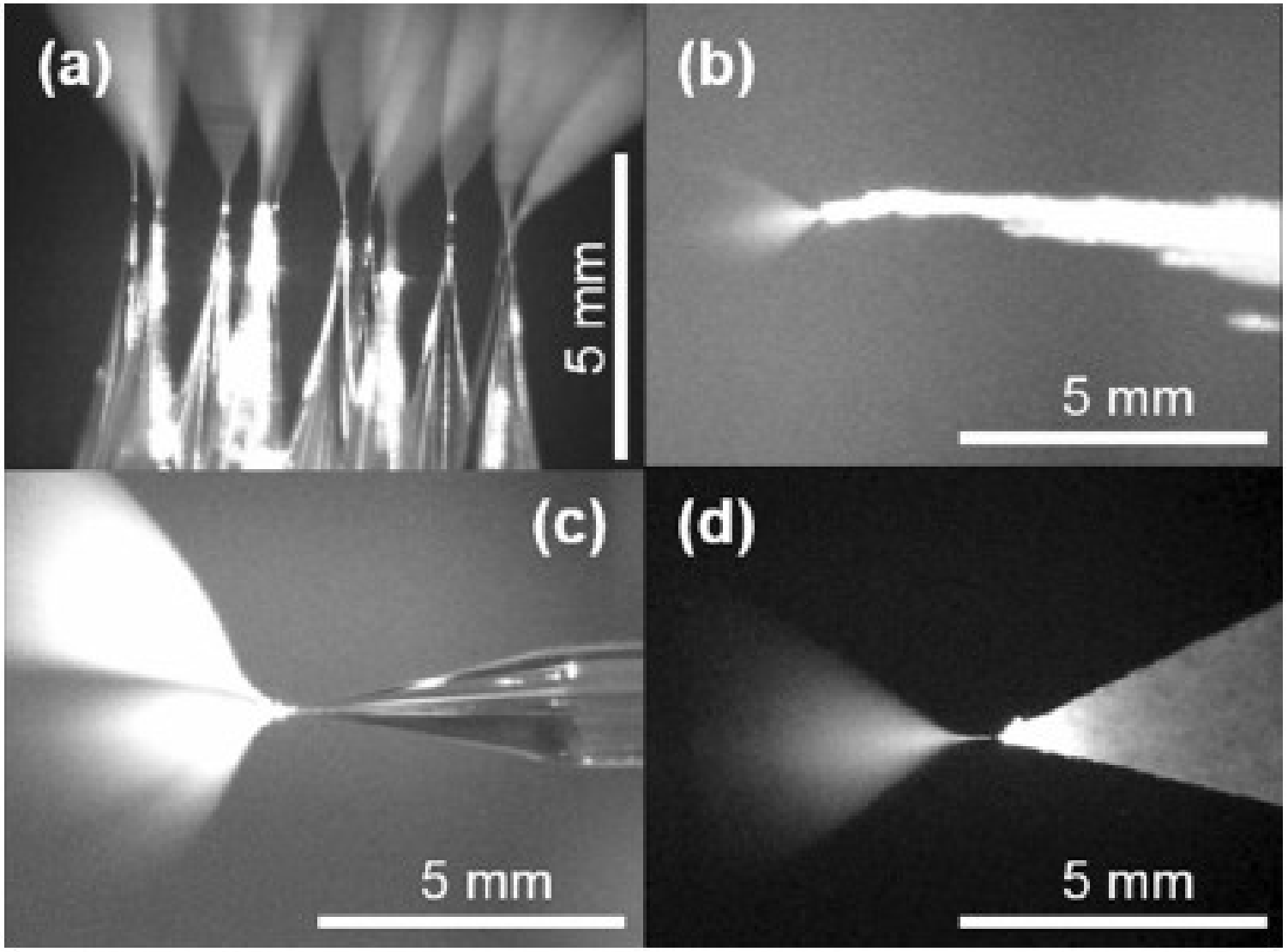
When using a piezoelectric plasma discharge as a primary ion source in a relay experiment run in with an open secondary capillary (a), a small degree of dephosphorylation was observed for the highly charged phosphopeptide ion [M+4H-p]4+ as compared to the native forms observed by ESI or conventional nanoESI. The absolute intensity (normalized level) for (a) and (b) were 1.1×103 and 1.5×103 respectively.



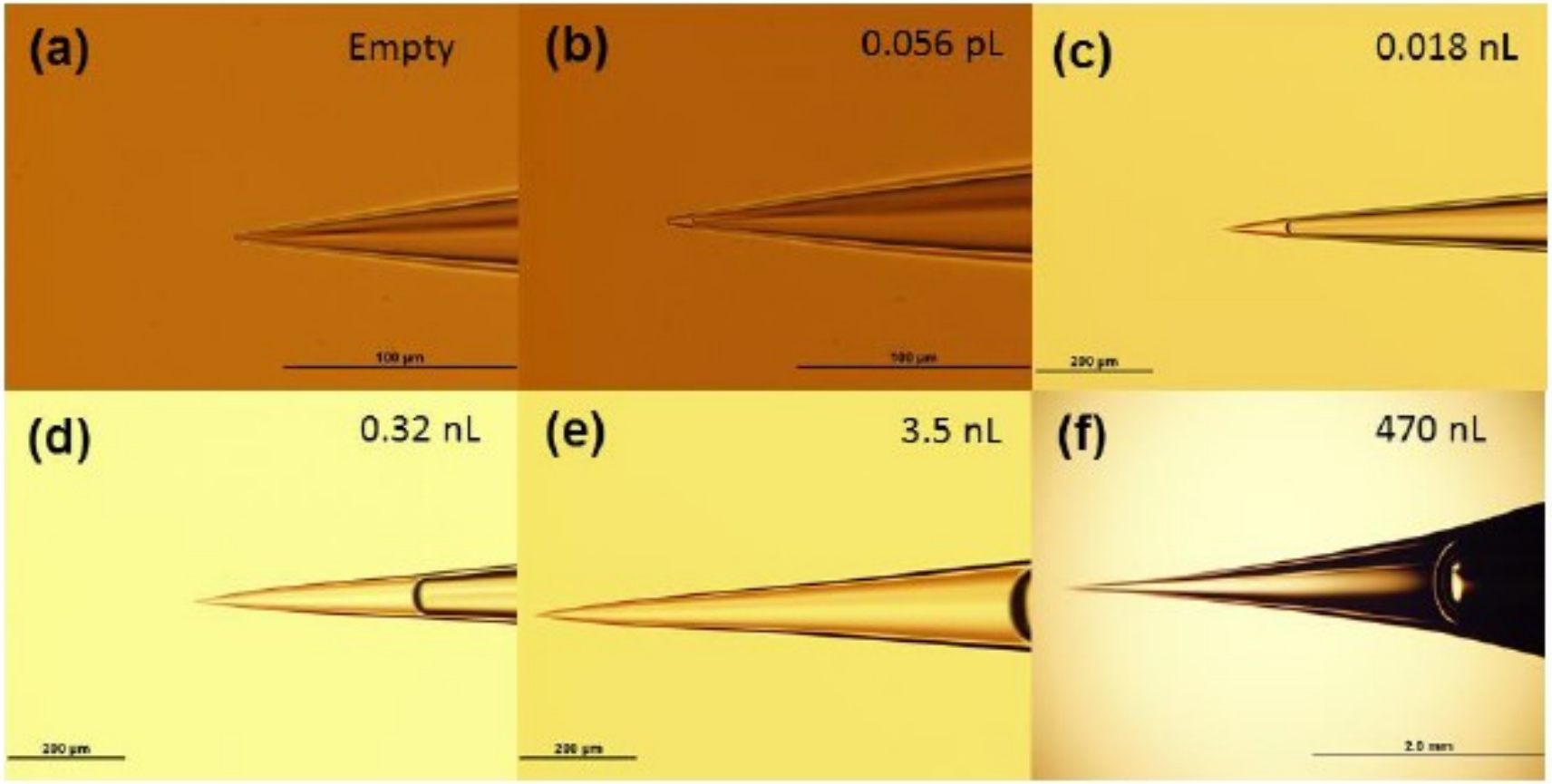
Relay electrosprays could be generated from the distal end (a) of capillaries sealed at the proximal end; even when (b) the sealed capillary's outer wall was partially grounded using a copper tape, and (c) the capillary's outer wall was sputter coated with ~5 nm Au/Pd. Only (d) when this coated outer wall was grounded could the relay spray be avoided.



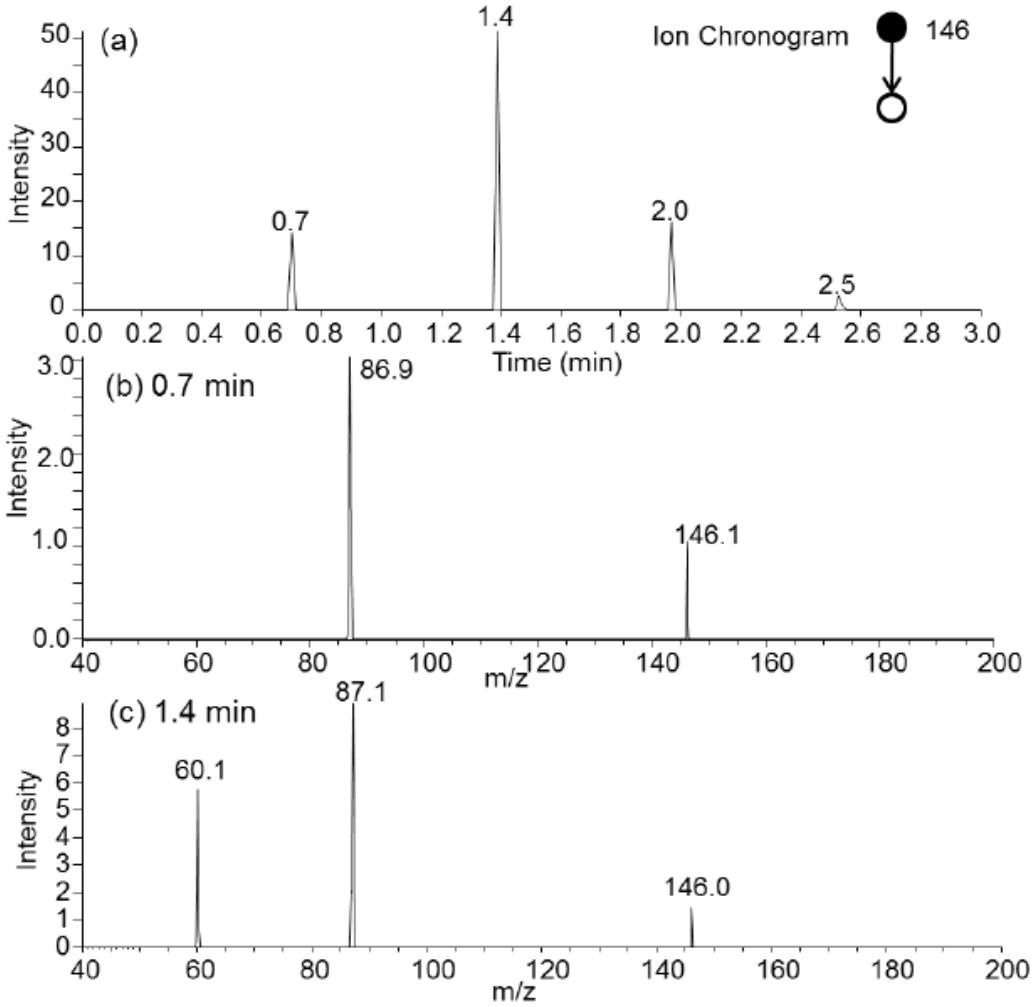
MRM intensity (absolute intensity on y axis) from the same (1 ppb) cocaine solution from the same secondary emitter (a) after and (b) before sealing the proximal end. Comparison of the data indicates a 40% decrease in signal after sealing the end.



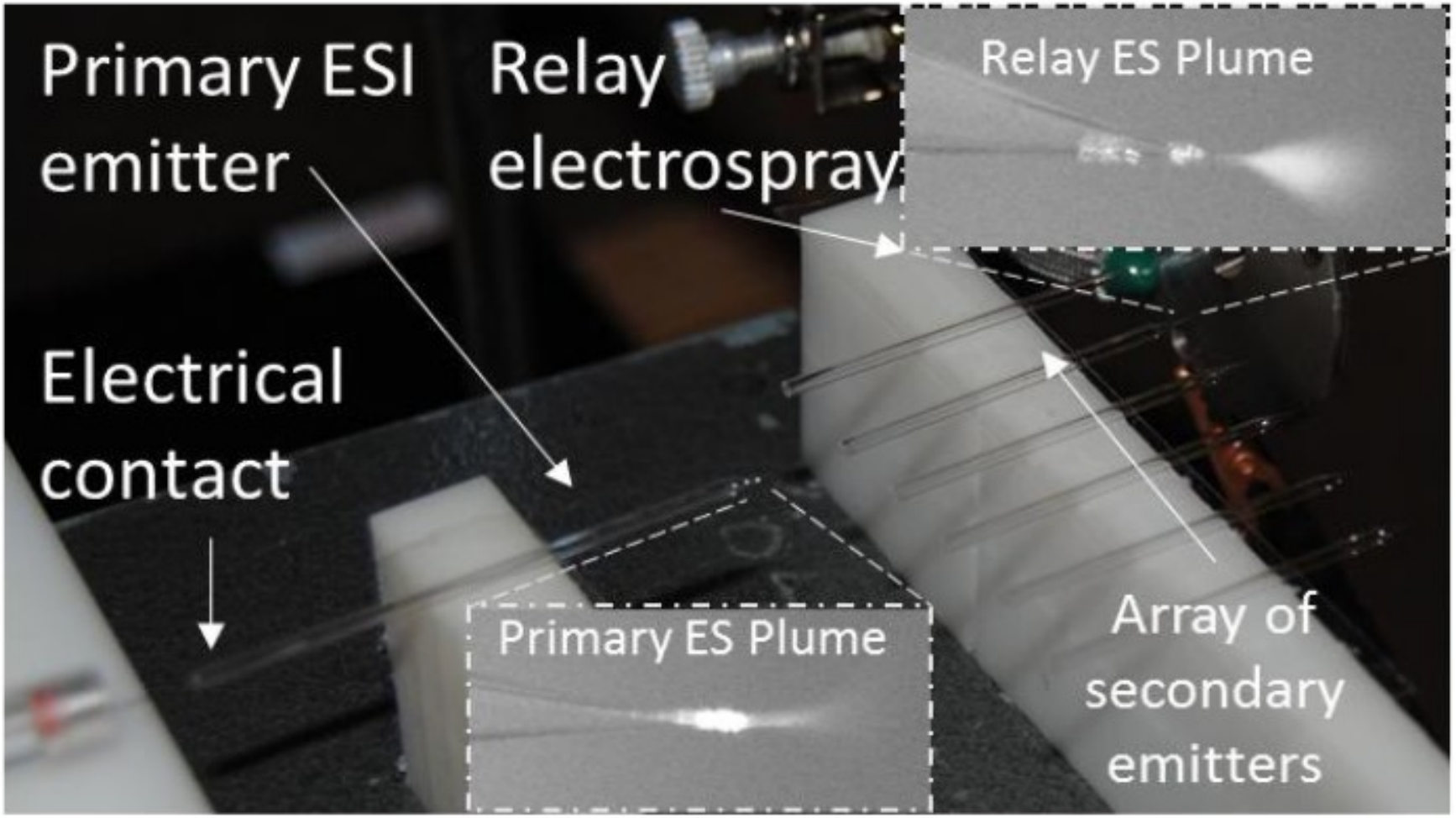
Relay spray from several different emitters: a) bundle array of 11 nanoESI emitters; b) sharp end of a wooden pick; c) pulled thetashaped tip, and d) filter paper triangle.



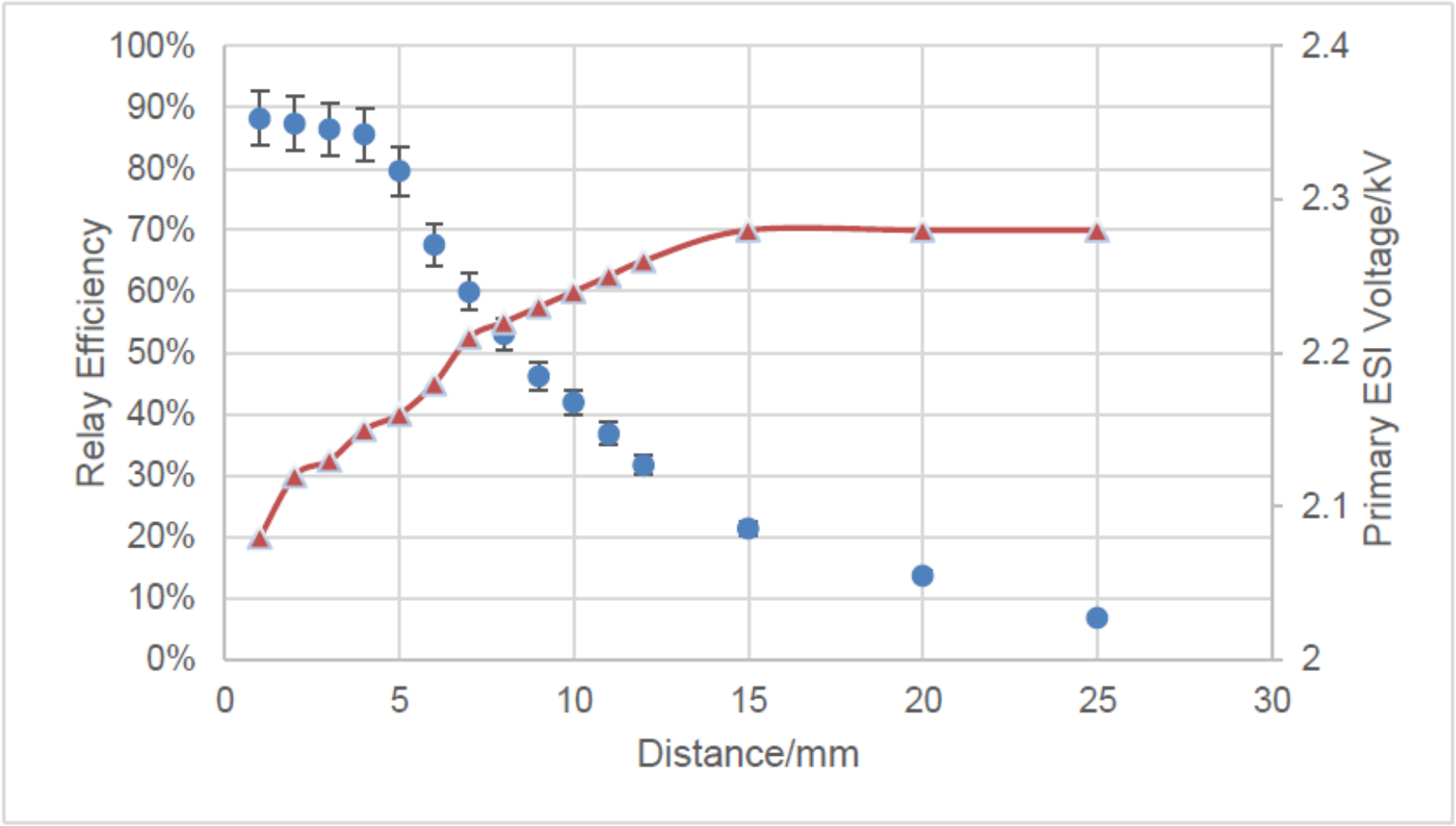
Ultra-low volume (from sub picoliters to microliters) sample solution (to the left of the meniscus) was loaded into the sharp tip of the relay capillary. Relay electrospray phenomenon was observed for all of these loaded tips.



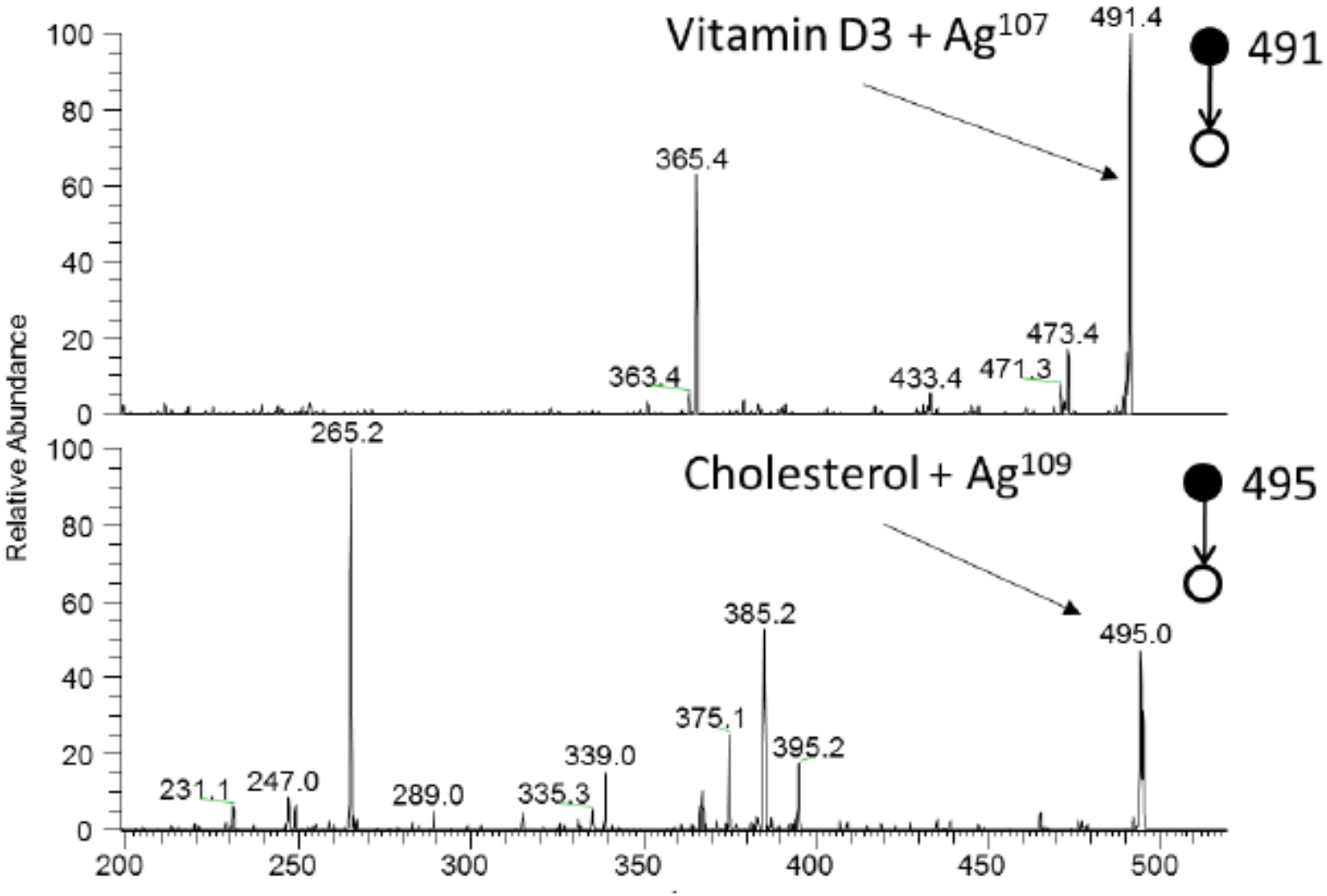
Total instrument count (a) and MS/MS spectra (b) and (c) obtained from rESI of ~1 pL of a 0.5 ppb acetylcholine solution (estimated as 0.5 attogram, 3 zmol, 2,000 molecules) loaded into a apillary and analyzed by rESI. Four separate experiments were done as shown in the total ion count showing the repeatability and deviations in the data.



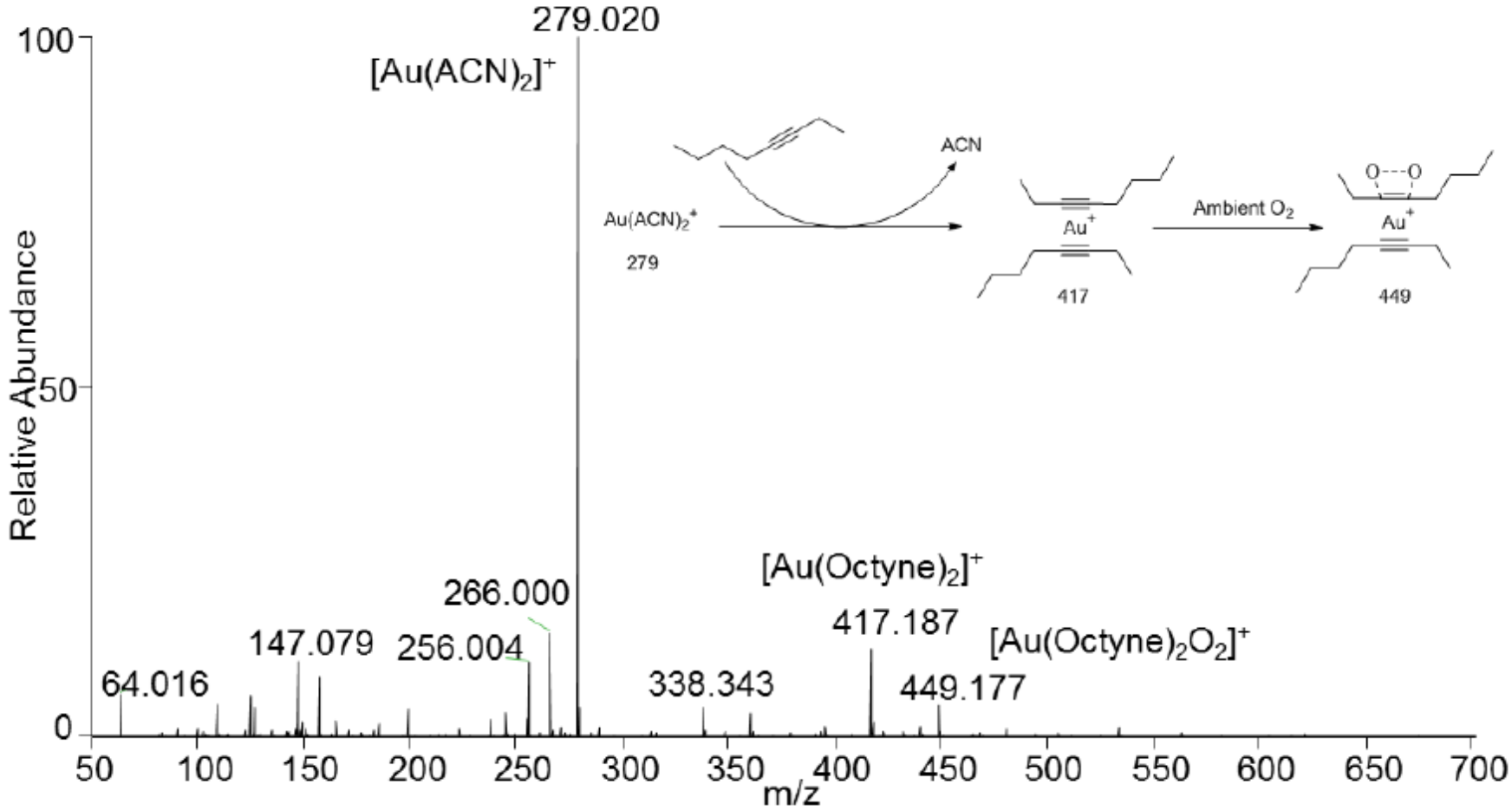
Using a regular wire-in nanoelectrospray emitter as the primary ion source, a spray plume from the sample loading relay (secondary) tip was captured by camera under illumination. In a typical experiment, stable ion currents of 8-10 nA were generated by the relay (secondary) tip when the primary ESI emitter was operated at 12 nA.



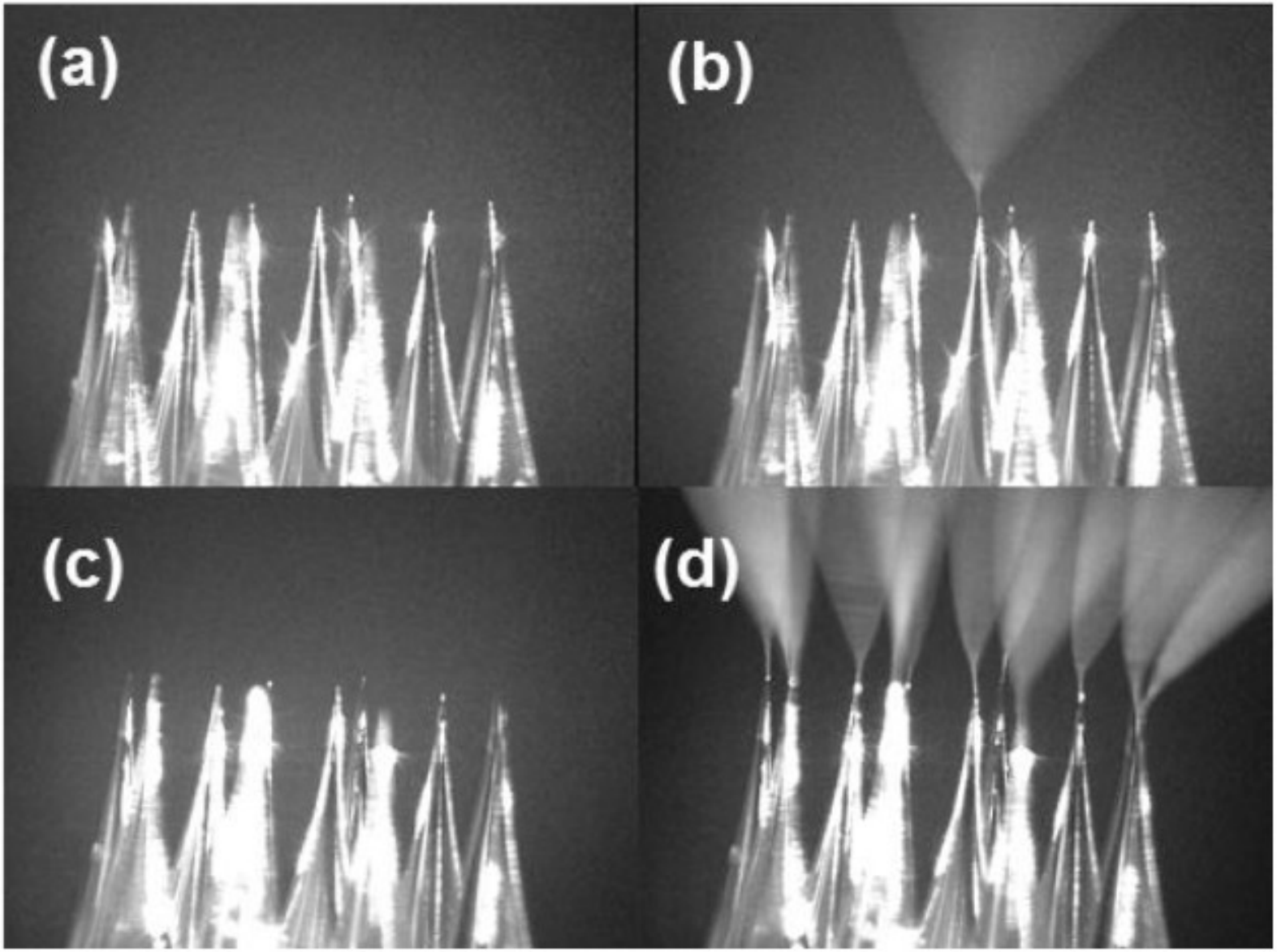
ESI-ESI relay efficiency and primary voltage vs. emitter to emitter distance, the primary ESI current was held at 12 nA by adjusting the applied voltage (triangles), the current from the secondary (relay) ESI is presented as a percentage of the primary current (dots) for different distances (primary tip end to secondary proximal end) between the two emitters.



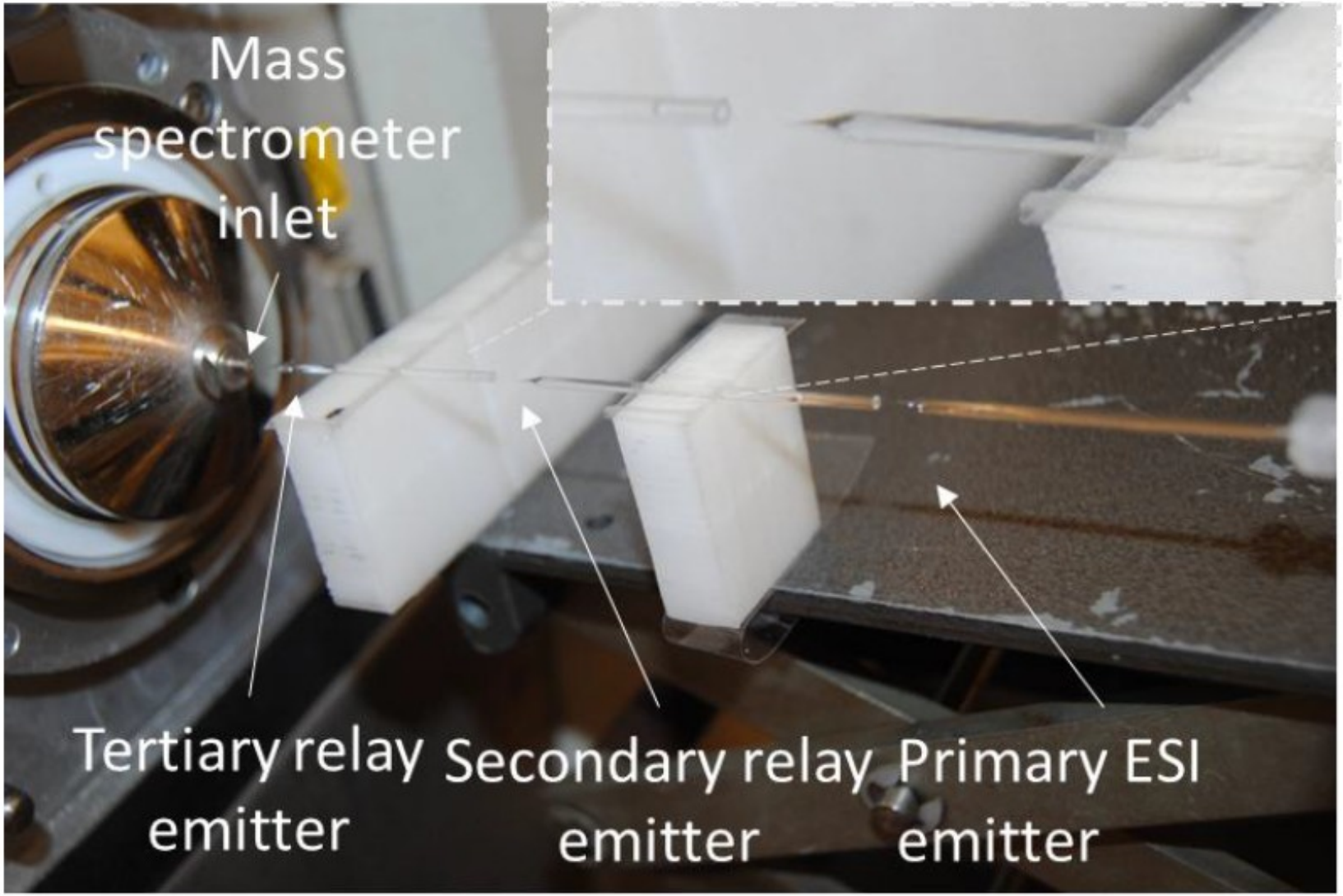
Product ion MS/MS using CID of silver cationized cholesterol (MW=386) and vitamin D3 (MW=384). The silver cations were generated in the primary ion source using electrolytic spray under aprotic conditions.



Au+ generated from electrolytic ionization of gold wire in the primary ESI source and deposited onto an alkyne (3-octyne, 100 ppbv in acetonitrile) in the secondary emitter allowed ionization by Au+ clustering, (m/z 417). High resolution MS confirmed the peak assignments. For the labeled peaks mass errors are all positive and smaller than 5 ppm.



Array of emitters (a) before and (b) upon selective triggering of one channel; (c) before and (d) upon simultaneous triggering of all 11 emitters in the array.



Triple serial electrospray relay of as a demonstration of multiple stage capability. This configuration has an overall current transmission efficiency of 36%. Similarly, quadruple serial relays were constructed using a needle plasma discharge as primary ion source, with overall current transmission efficiency of only 4%.

Conclusion

- All these capabilities associated with rESI bring opportunities to develop portable, high-throughput biochemical analysis systems and to perform small-volume reactions and reaction intermediate studies.
- The ability to measure mass spectra from samples consisting of several thousand molecules will advance these objectives and other low-level measurements including single-cell mass spectrometry.

Thank you