Scanning probe electrospray ionization for ambient mass spectrometry imaging

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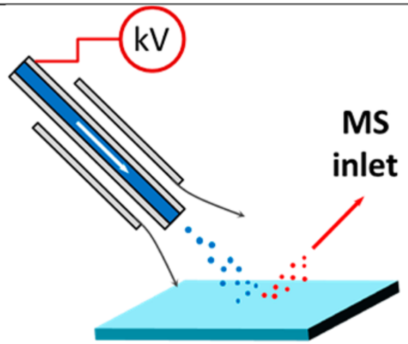
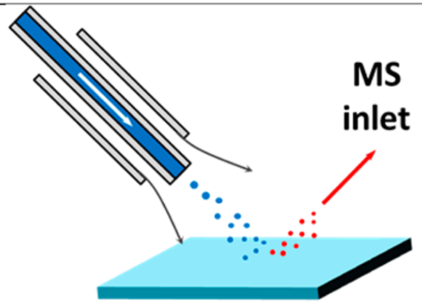
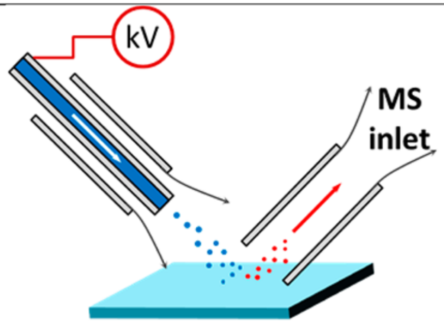
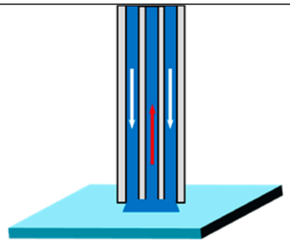
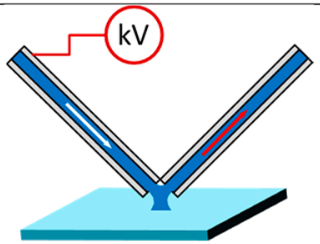
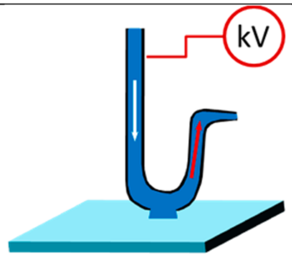
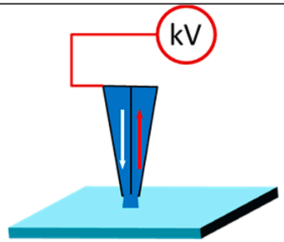
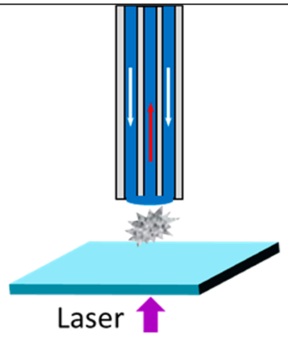
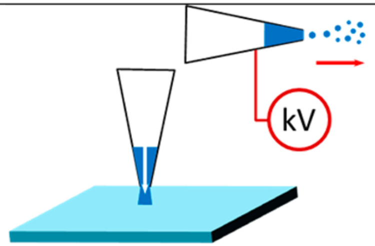
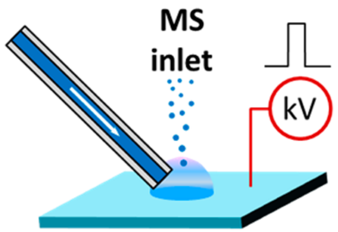
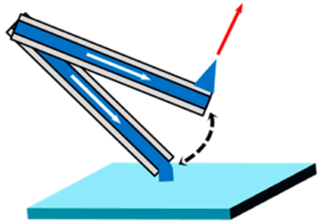
Mass spectrometry imaging (MSI)

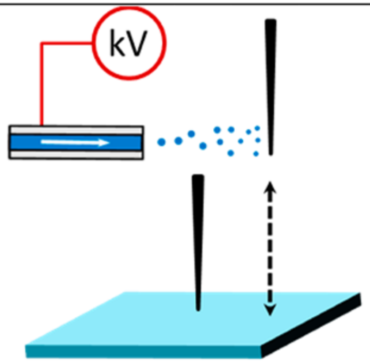
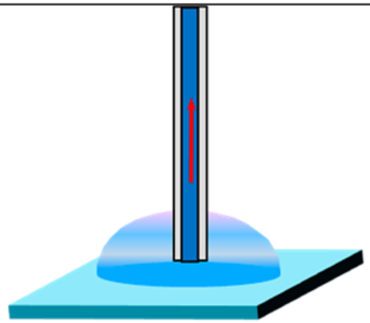
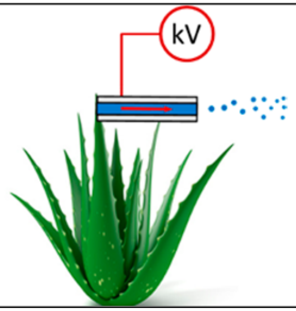
- Mass spectrometry imaging (MSI) is a powerful analytical technique that enables label-free spatial localization and identification of molecules in complex samples.

- Ambient ionization techniques enable direct analysis of complex samples under atmospheric pressure without special sample pretreatment. In fact, in ambient ionization mass spectrometry, sample processing (e.g., extraction, dilution, preconcentration, or desorption) occurs during the analysis. This substantially speeds up analysis and eliminates any possible effects of sample preparation on the localization of molecules in the sample.

Technique	Schematic Drawing	Characteristics
Spray-Based Techniques		
Desorption electrospray ionization (DESI)		• A fast stream of primary droplets generates secondary droplets containing analyte molecules • Commercially available, broadly used • Spatial resolution 150-250 µm (typical), 35 µm (best reported)
Easy ambient sonic spray ionization (EASI)		• Similar to DESI but the sensitivity is typically lower • The absence of high voltage may be advantageous for sensitive samples
Air-flow-assisted DESI (AFADESI)		• Similar to DESI, improved sensitivity

	Direct Liquid Extraction Techniques	
Liquid microjunction surface sampling probe (LMJ/SSP), Flow probe		• Analyte extraction into a continuous liquid flow • Electrospray ionization • Commercially available (Flowprobe) • Spatial resolution ~500-1000 μm • Probe position relative to the sample is important
Nanospray Desorption Electrospray Ionization (nano-DESI)		• Analyte extraction into a continuous liquid flow • Nanospray ionization • Spatial resolution 100-150 μm (typical), 12 μm (best reported) • Independent optimization of the capillary positions is advantageous for improved spatial resolution • Probe position relative to the sample is important
Swan Probe		• Analyte extraction into a continuous liquid flow • Nanospray ionization • Spatial resolution is determined by the aperture size, typically ~200 μm • Primary and secondary capillaries incorporated into a single device • Probe position relative to the sample is important
Single-probe		• Analyte extraction into a continuous liquid flow • Nanospray ionization • Primary and secondary capillaries incorporated into a single device • Spatial resolution 8.5 μm (best reported) • Probe position relative to the sample is important

Technique	Schematic Drawing	Characteristics
	Direct Liquid Extraction Techniques	
Laser ablation liquid capture surface analysis (LA/LCSA)		• Capture of material desorbed by LA into a static droplet or continuous liquid flow • Spatial resolution 50 µm (best reported) • Electrospray ionization
Liquid exctraction surface analysis probe (LESA) and pressurized LESA (PLESA)		• Analyte extraction into a static solvent droplet • Nanospray ionization • Commercially available • Spatial resolution 1 mm (typical), 350 µm (best reported)
Electrostatic spray ionization, polarization-induced ESI		• Analyte extraction into a continuously replenished solvent droplet • Nanospray ionization directly from the droplet • Spatial resolution 110 µm (best reported)
Scanning Probe Electrospray Ionization (SPESI)		• Analyte extraction into a continuously replenished solvent droplet • Nanospray ionization from the droplet formed on the other side of the probe capillary • Spatial resolution 35 µm (best reported)

	Substrate Spray Techniques	
Probe electrospray ionization (PESI), touch spray ionization (TS)		• Direct transfer of analyte molecules to a sharp solid needle or analysis from sharp objects naturally present in the sample • Nanospray ionization directly from the needle or ESI-assisted ionization • Enhanced sensitivity and selectivity achieved by applying different coatings to the probe • Spatial resolution 60 μm (best reported) • Depth profiling with 20 μm resolution
Scanning Probe		• Direct sampling from liquid surfaces and buried liquid interfaces using a short tapered capillary • Nanospray ionization directly from the capillary
Substrate spray		• Extraction of analytes directly from plants into a capillary • Nanospray ionization directly from the capillary

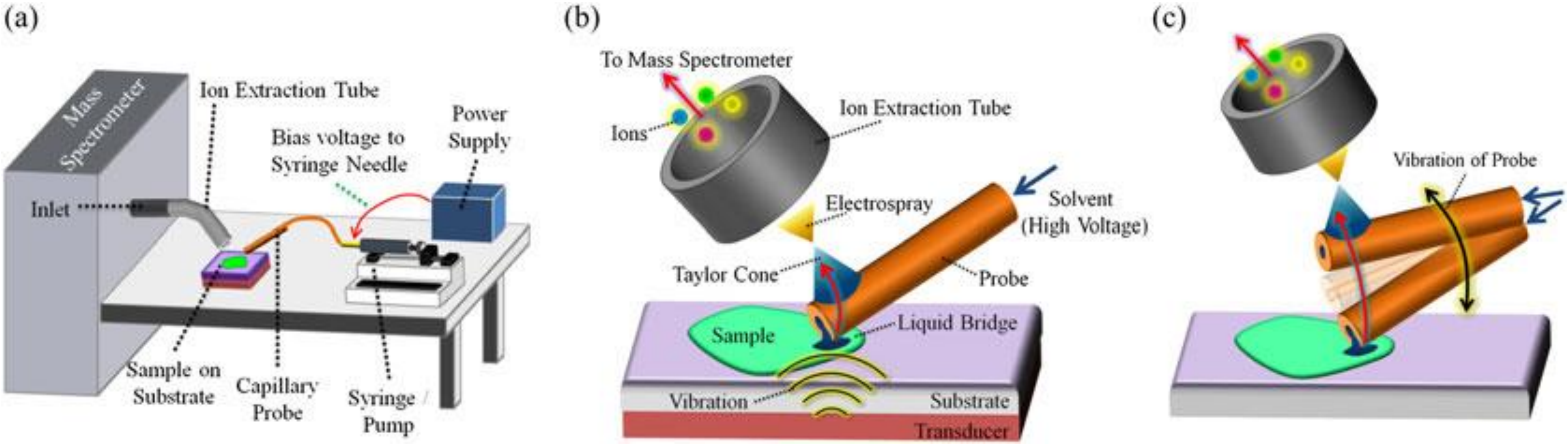
Scanning probe electrospray ionization (SPESI)

- SPESI uses a capillary and a charged solvent in the same way as other ionization methods do, but it has the advantage that the configuration of the ionization source is simple; it does not require high-pressure gas or the alignment of capillaries.
- A single capillary is used as the probe for both sampling and ionization.
- The sampling occurs in the liquid bridge that is formed between the probe tip and the sample
surface, and the ionization occurs where the electrospray coexists with the Taylor cone. As the sampling and ionization processes occur in a short time, this method offers rapid sampling and ionization under atmospheric conditions.

Operation modes

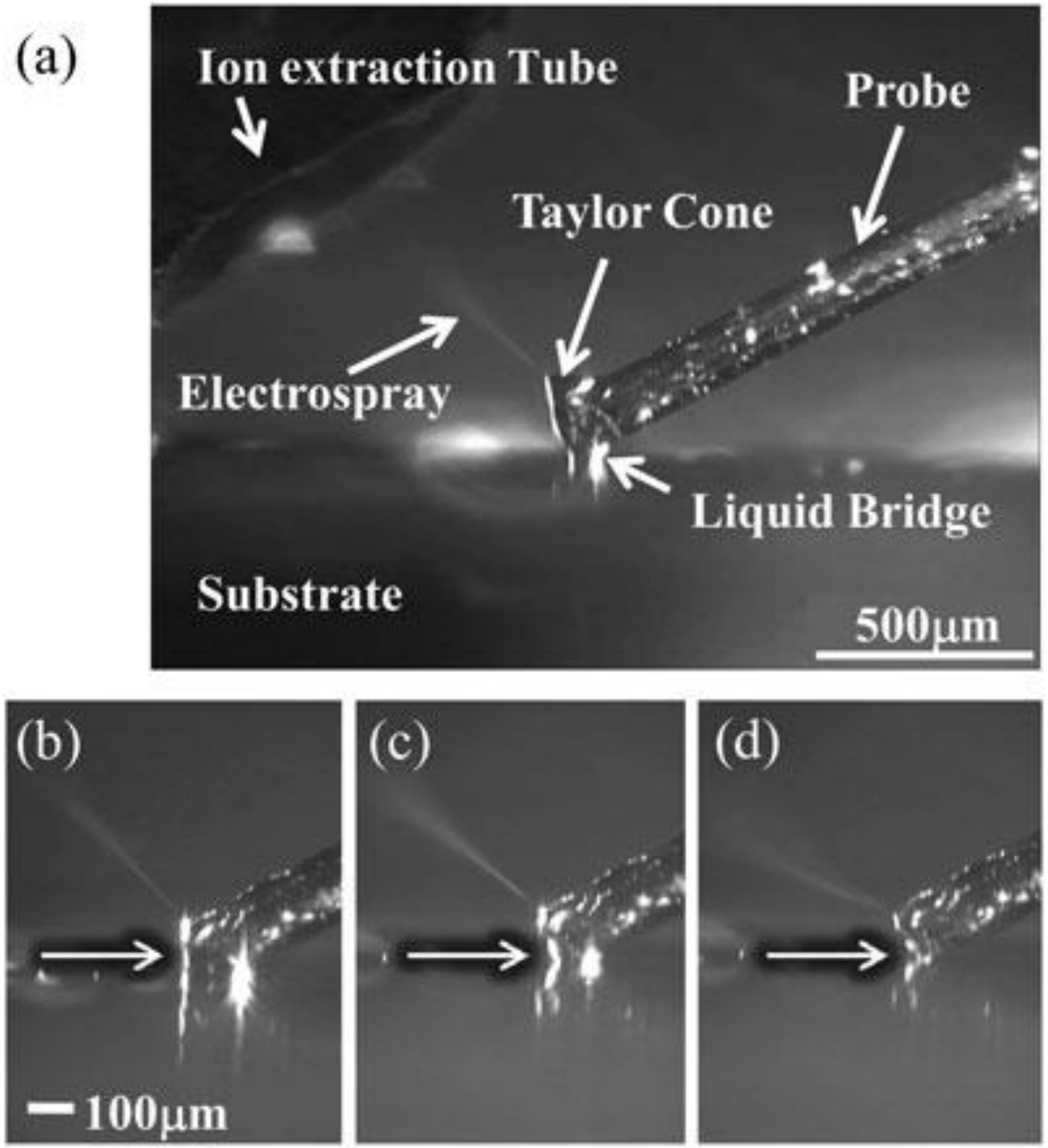
- Two operation modes: contact-mode SPESI (c-SPESI) and tapping mode SPESI (t-SPESI).

- In the c-SPESI mode, the substrate vibrates while the probe is static, whereas, in the t-SPESI mode, the probe vibrates while the substrate is static.



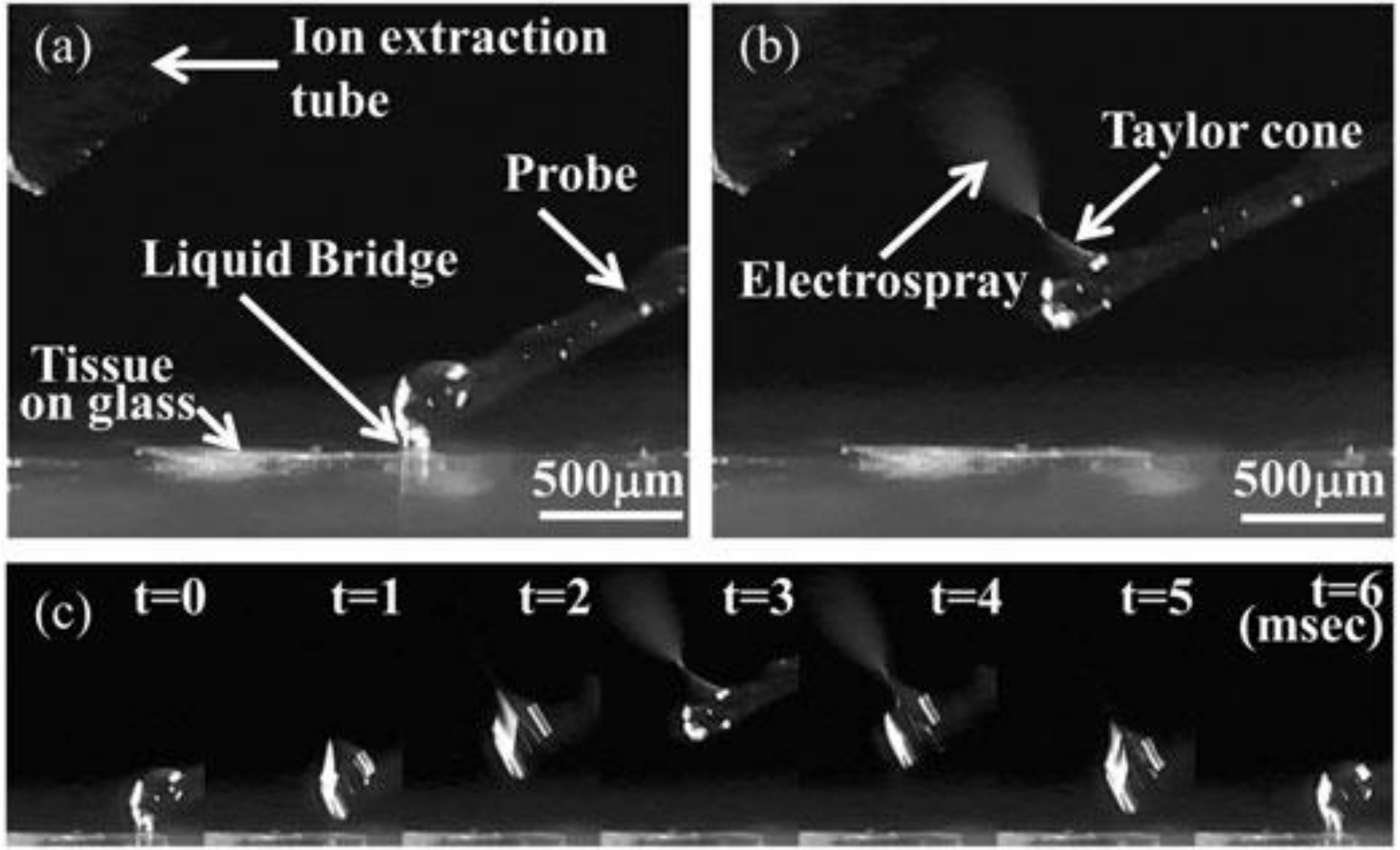
Schematic illustrations of SPESI. (a) Connection diagram of the main components in SPESI. (b) Ionization area in c-SPESI (c) Ionization area in t-SPESI

Contact mode SPESI



(a) Photograph of the capillary probe of c-SPESI. (b–d) Effect of substrate vibration on the size of the liquid bridge. The input voltage to transducer was (b) 10, (c) 20, and (d) 40 Vrms. The liquid bridge was formed under all conditions, as indicated by the arrows. The size of the liquid bridge decreased as the vibration amplitude increased.

Tapping mode SPESI



Photograph of the vibrating capillary probe used for t-SPESI. (a) The liquid bridge was formed as the probe approached the substrate. (b) The Taylor cone was formed and electrospray occurred when the probe came close to the ion extraction tube. (c) A sequence of photographs of the vibrating probe.

t-SPESI Vs c-SPESI

- In t-SPESI sample deformation is minimized; during imaging mass spectrometry, the probe is connected to the sample surface via the liquid bridge for only milliseconds, which minimizes the scratching or dragging of the sample by the scanning probe. In c-SPESI, however, the probe is kept close to the sample, and soft samples such as tissues may be accidentally scratched by the probe.
- The formation of the liquid bridge and the electrospray are separated in time in t-SPESI, the quantity of the spray at each sample position could be defined by controlling the vibration frequency and the sample position. This is difficult in c-SPESI because the electrospray occurs randomly during the operation.
- t-SPESI method minimizes the spread of the solvent. The liquid bridge is formed for only a few milliseconds, the spread of solvent is small compared with that in c-SPESI.

Thank you