Stevanato Group

IS HIGH VOLTAGE LEAK DETECTION (HVLD) READY FOR ANNEX I AND USP1207?

Authors: V. Turato, M. Corradin, A. Sardella

Abstract

- The last revision of Annex I and USP1207 has raised the bar of the expectations for CCIT performances. Pharmaceutical companies are debating whether to implement 100% CCIT online or to reinforce the sampling testing strategy and container closure system studies.
- High voltage leak detection is one of the technologies available to fulfill the regulatory requirements but lacked scientific evidence of fitting the regulations until now.
- In this poster, we will provide leak detection data covering defects size from 1 µm to 20 µm in the conductive range covering from 1µS/cm to 120mS/cm and density from 1 to 10 Centipoise to simulate most of the pharmaceutical products on the market.

CCIT 100% ON-LINE DETERMINISTIC METHODS COMPARISON

Technique	Principle	Advantages	Disadvantages	LOD
HVLD	Based on conductivity measurement. In the presence of leakage container resistance will decrease.	• Non-destructive • Fast • Perform under atmospheric pressure • No special sample preparation • Highly Sensitive • Low risk of impact and no risk of contamination	• Not applicable to oily or solid products • Wet leak path required • Ozone production • Risk of product degradation • No leak's dimensional information • Localized measurement, complex to implement in whole area of container	1 µm
Vacuum Decay	Container placed in a specially designed vacuum camber, increase in pressure is a sign of leakage.	• Nearly Non-destructive • Fast • Perform under atmospheric pressure • No special sample preparation • Sensitive • Moderate risk of impact or contamination	• Product leak clogging can lead to incorrect results • Design of vacuum chamber is critical to determine sensitivity • Humidity can affect measurement • Vacuum equipments require maintenance and routine check	5 µm
Head Space Analysis	Product headspace is analyzed by TDMS laser technology. Variations in pressure or composition is a sign of leakage	• Non-destructive • Fast • No special sample preparation • Highly Sensitive • No risk of impact or contamination	• Limited to transparent container • Time bound process for smaller leak sizes • Different laser wavelength based on headspace composition • Not applicable to atmospheric air pressure headspace • Risk of false results in case of components permeation • Sufficient headspace clearance	2 µm

There isn't a technology able to work in every pharmaceutical product's condition at the moment.

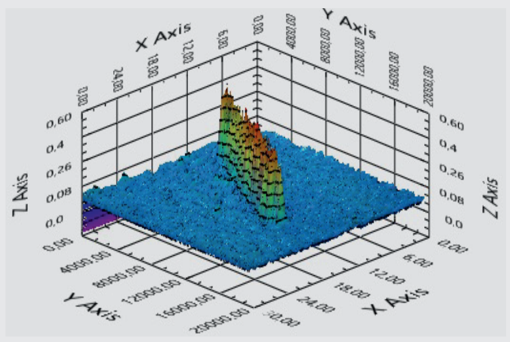
CORRELATION BETWEEN mCCI AND pCCI

Reference	Medium	Bath condition	Leak Type	Conditioning cycle	Smallest leak size of microbial ingress	He Leak rate acceptance criteria
Kirsch (1997)	10^8-10^{10} cfu/ml Escherichia coli	Immersion at 37°C for 24 hours	Micropipettes 0.1-10µm	Airlock elimination	0.3 µm (orifice)	6.3 x 10^{-6} mbar l/s
Moll (1998)	10^8 cfu/ml Pseudomonas diminuta	Immersion	Laser microholes 5-20 µm	30 min. at vacuum and 1 hour at 1 atm.	5 µm	5 x 10^{-6} mbar l/s
Keller (1998)	10^9 cfu/ml Pseudomonas fragi	Aerosol	Microtubes 2-50µm	-210/+210 mbar	2 µm	4.2 x 10^{-6} mbar l/s
Buller (2000)	10^8 cfu/ml Escherichia coli	Immersion at 30-35°C for 7 days	Microtubes 2-75um	n.a.	10 µm	2 x 10^{-5} mbar l/s
Gibney (2000)	10^9 cfu/ml Pseudomonas fragi	Aerosol		-350 mbar	5 µm	5 x 10^{-6} mbar l/s
Morrical et alt (2007)	10^9 cfu/ml Serratia marcescence	Immersion at 30-35°C for 14 days	Laser microholes	-400/+400 mbar for 1 hour each	2 µm	1.4 x 10^{-3} mbar l/s
			Copper wire		15 µm (wire)	1.3 x 10^{-5} mbar l/s
Mathaes (2016)	n.a.	n.a.	Copper wire	n.a.	n.a.	1 x 10^{-7} mbar l/s
Langlois (2018)	Liquid (SUS)	n.a.	Laser microholes	-250/300 mbar	40 µm	1 x 10^{-6} mbar l/s
USP (2014)			Orefice ID		0.3 µm	6 x 10^{-6} mbar l/s

Microbial ingress requires a wet path; HVLD works on the same requirement.
Liquid surface tension reduces the microbial ingress probability, it means that the physical current flow or gas ingress represents a worst-case scenario.

HVLD «microscope»

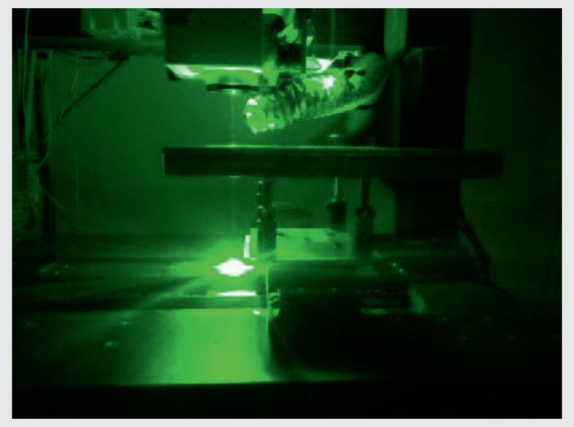
To verify the capabilities of the HVLD method, we designed an HV microscope to scan the container surface in a controlled manner with high spatial resolution.



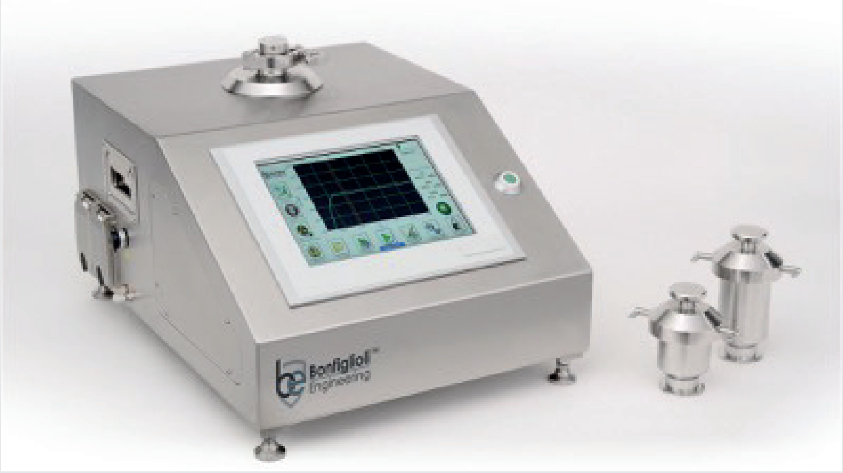
- X-axis, horizontal scan: max res 10 µm
- Y-axis, axial rotation: max res 2.5 µm
- Z-axis, elettrode distance: max res 10 µm
- HV generator: 5-30 KV pkpk at 20KHz

Samples preparation by KIRANA s.r.l.

We prepared three sets of vials: 2R, 10R, and 30R with laser-drilled micro holes of sizes from 2 to 20 µm in collaboration with Kirana S.r.l. an Italian company specialized in micromachining.
Each sample was checked by a microscope to measure the hole entrance aperture.



The channel is not cylindrical but tapered; this can justify the difference between the actual flow and the nominal one.



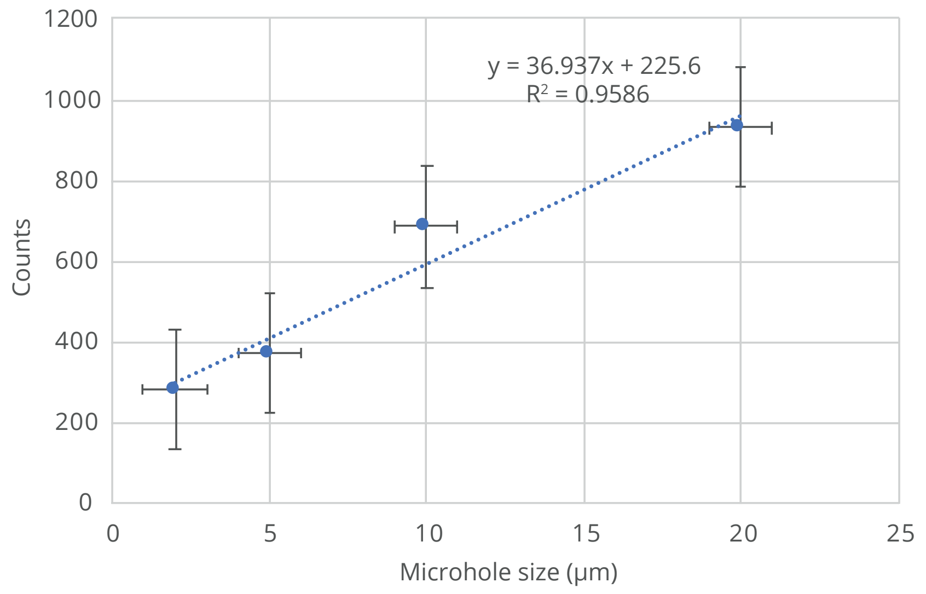
Flow determination by Vacuum Decay

To establish the correspondence between the geometrical appearance of the micro-holes and the real flow through them, we used a benchtop vacuum decay unit LF-S by Bonfiglioli with a custom holder to measure the flow of the empty vials.

Sensitivity to micro-hole size

We tested the sensitivity of HVLD to different micro-hole sizes to determine the limit of detection (LOD).
As a metric, we used the maximum value of the integral of the current collected by the return electrode during a scan of the container surface.
As we expected, there is a correlation with the leak size. Still, the HV level used to achieve the detection could be different for the different sizes and different product conductivity.

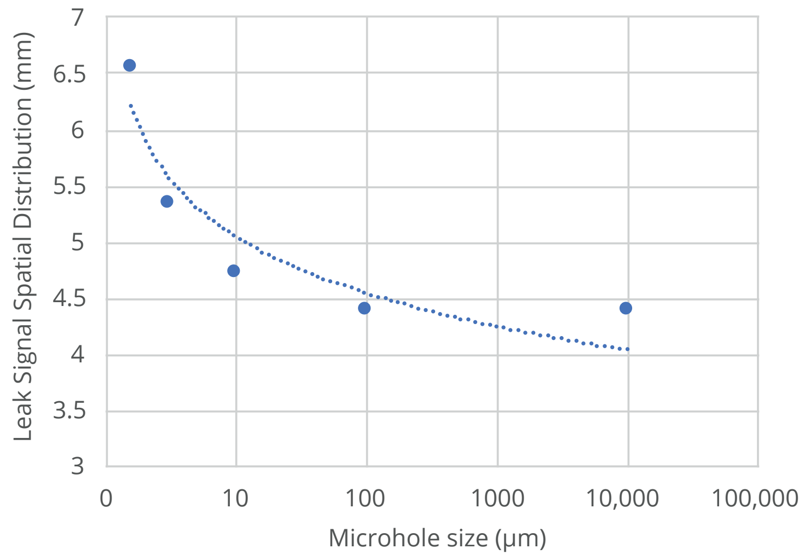
MAX INTEGRAL CURRENT AT 500µS/CM



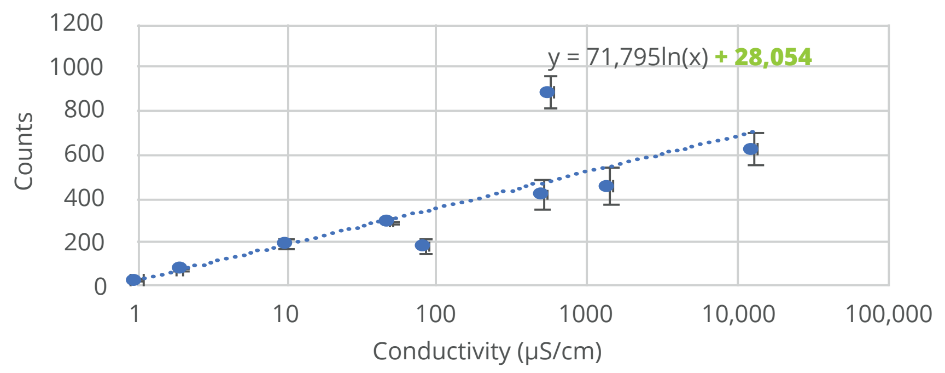
Single pin inference

Another essential characteristic to investigate has been the coverage of a single pin in terms of surface area.
HV and conductivity seem not to influence the coverage of an electrode, while the micro-hole size seems to affect it, but this is probably an artifact due to how we determine the "size" of the HVLD leak.
In general, we can say that a pin can cover a circular area of radius 4.5-5.0 mm.

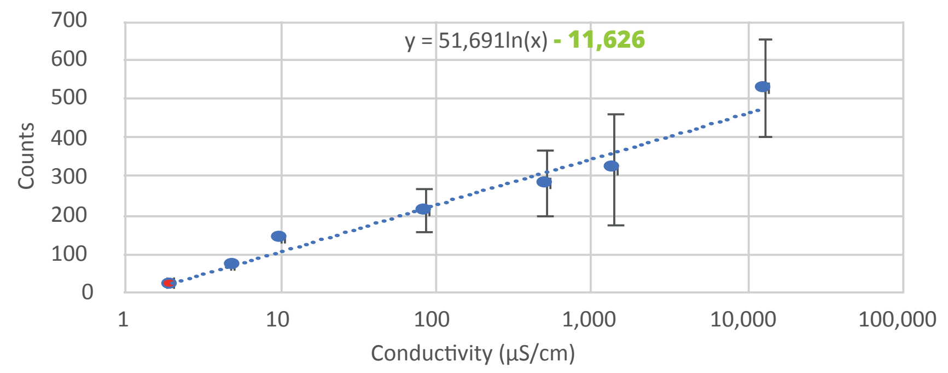
INFERENCE AREA UNDER PIN AT 500µS/cm



MAX INTEGRAL CURRENT AT 10µM VS CONDUCTIVITY



MAX INTEGRAL CURRENT AT 2µm VS CONDUCTIVITY

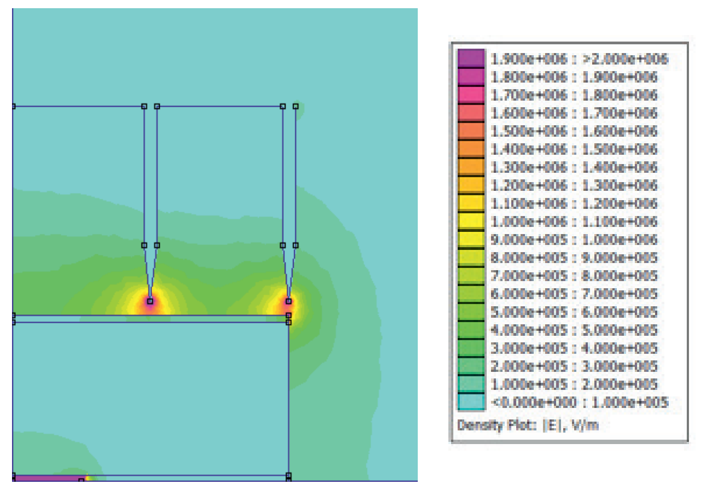


Sensitivity VS product conductivity

We investigated the detection efficiency at different product conductivities for several micro-hole sizes to better characterize LOD.
As shown in the 2nd graph, very low conductivity (<5µS/cm) limits the LOD of very small leaks (≤2µm).
With conductivity >10µS/cm, even leaks of 1µm are detectable with good detection efficiency.
As shown, proteinaceous products seem to increase HVLD sensitivity at the same conductivity (TBI).

Impact of HVLD on product integrity

We have used electromagnetic simulation software to understand the electric field distribution in the presence of a product of known conductivity within the actual measurement geometry.
As shown, most of the electrical field is concentrated out of the product if the return electrode is well-coupled to the liquid: This gives us confidence in the possibility of minimizing the effect of the electrical field by optimizing the electrode geometry.



From Lab to Production

- We have shown that the HVLD method can fulfill the requirement of Pharmacopeia for the vast majority of liquid products and containers. The results are deterministic, and LOD is well-determined.
- The "HV microscope" allows us to optimize electrode geometry, HV generation, and detection scheme for different products and containers and to provide a very reliable feasibility test on customer products.
- The knowledge acquired can be transferred directly to production for the "HV microscope," having been designed around the same concepts used for in-line HVLD machines.

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