



Supporting the chemist decision in small molecule leads discovery through an open and easy access automated HPTLC-MS-ELSD platform .

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(1) :Sanofi-Aventis; Vitry ;France .

(2) :Sedere; SA Alforville ;France .

(3) : Bcp Instruments ; Irigny ; France .

(4):Chromacim-Camag; France .

.



TLC-MS-ELDS with Open Access mode.

a) Off line TLC (HPTLC) method :

- cutting/scratching CCM Spots separated via TIC .
- in solution in solvents

(DMSO, MeOH; chloroform; dichloromethane;..)

▪ filtration of the suspension by seringue filter (0,2 µm) or Vial filter Whatman Uniprep (0,2 µm)...

▪ The solution is analyzed by MS: EI ;MALDI;APCI ; FAB ; Electrospray...

(N.B: Off Line TLC-MS has no limitation on the ionisation MS mode..)

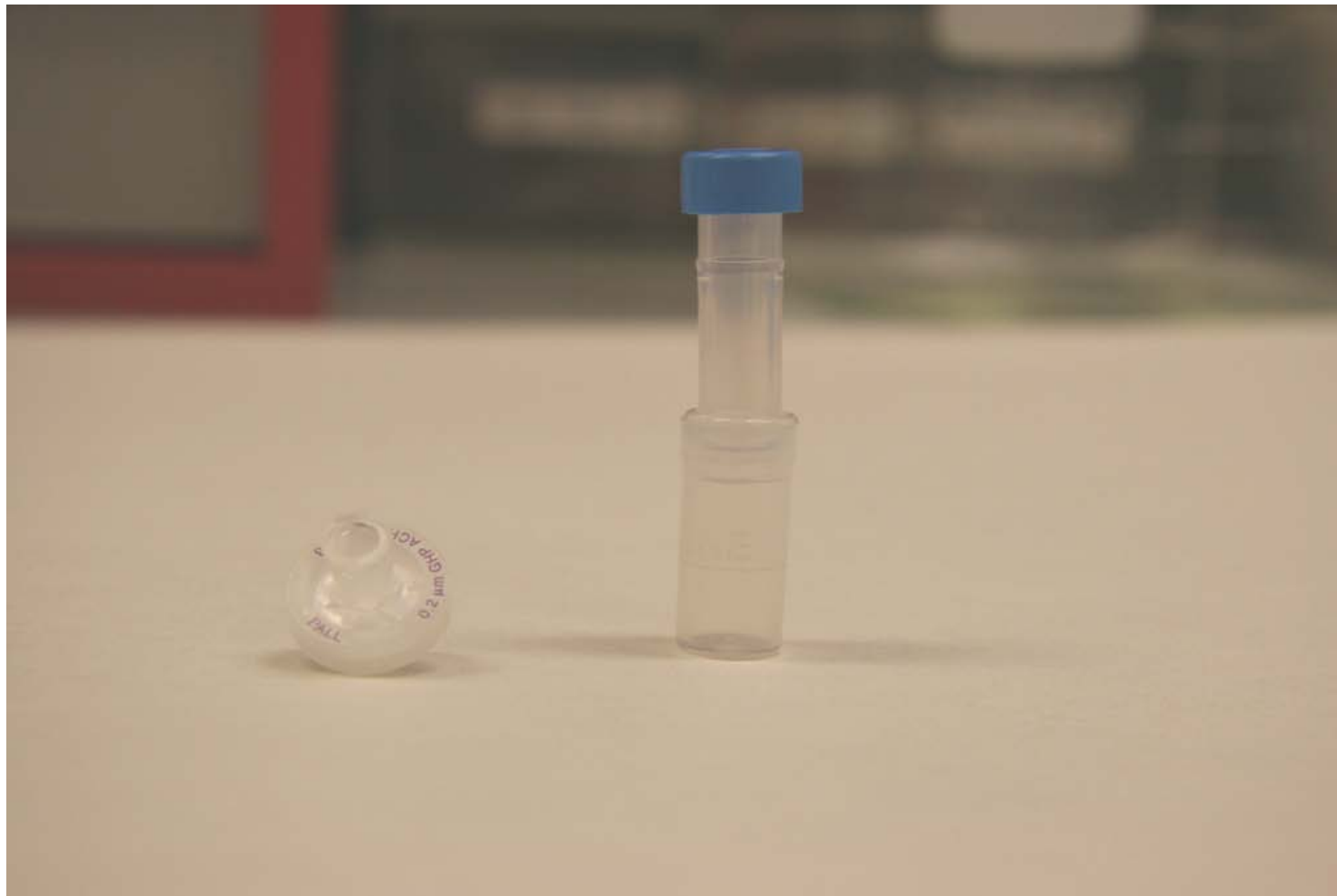


TLC-MS-ELSD with Open Access mode .





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TLC-MS-ELSD with Open Access mode .

b) On line TLC-MS method : TLC-MS coupling has been introduced in years 80 : for a complete presentation see : Thin-Layer Chromatography with Ultraviolet and Mass Spectrometric detection : From Preparative-Layer to Miniaturized Ultra-Thin-Layer Technique ; P Salo ; Academic Dissertation ; Helsinki ; 2007 .

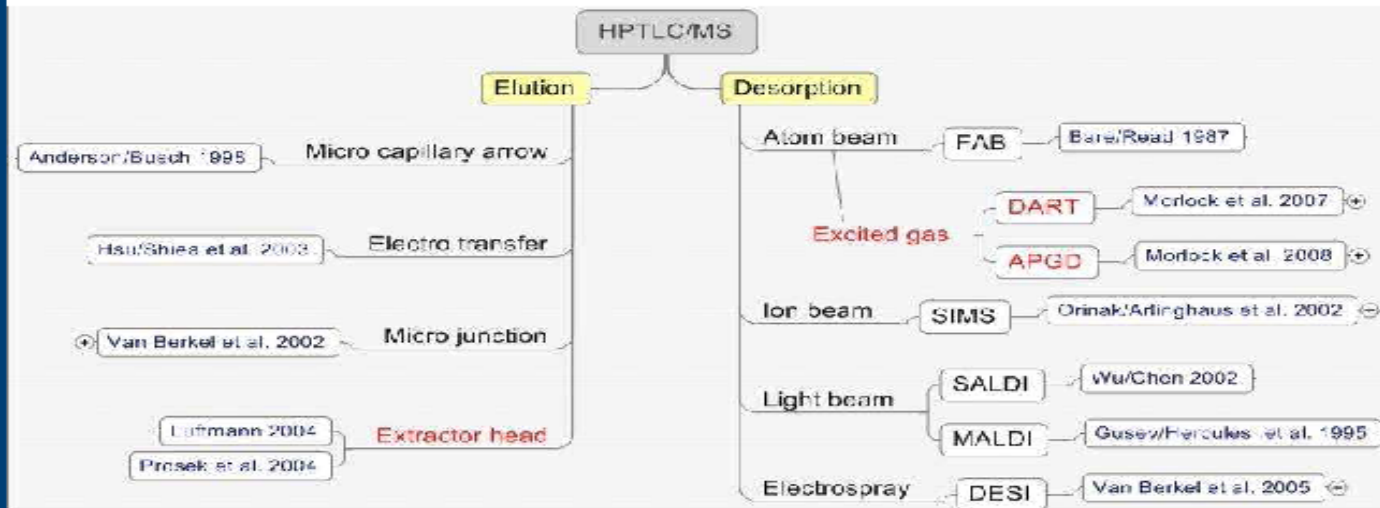


TLC-MS-ELSD with Open Access mode .



Institute of Food Chemistry
University of Hohenheim, Stuttgart

Approaches of HPTLC/MS coupling



TLC-MS-ELSD with Open Access mode .

 Camag AG (Switzeland) have developped since 2 years a TLS-MS interface : Camag-TLC-MS Interface .

This interface have been developped with Camag Swizerland and Dr Gerda Morlock (University of Hohenheim ;Institut of food Chemistry ; Stuttgart; Germany).

See also Camag web site : www.camag.com .



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TLC-MS-ELSD with Open Access mode .

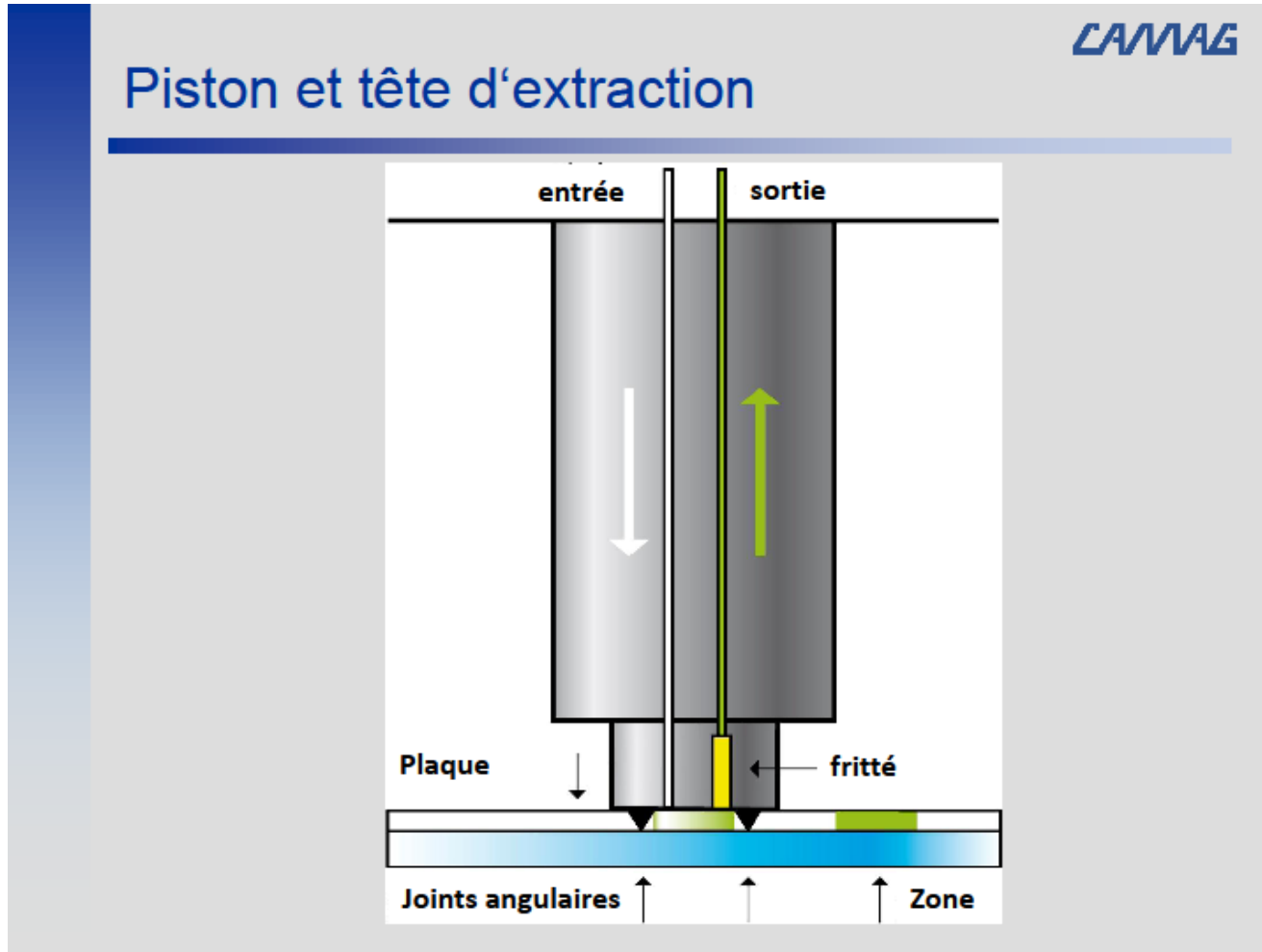
List of additional spare parts (IDEX-Upchurch) for improving day by day used of TLC Camag Interface (for more details see Chromacim-Camag) .

	A	B
1	1561XL	tube peek 1/16"x100µm noir le metre
2	A-327	coupe tube peek & plastique 1/16" et 1/8 " OD
3	A-355-01	filter body precolumn biocomp
4	A-355-02	filter cap precolumn biocomp
5	A-501	fritté Ti red 0.2 µm φ .062 x .065 x φ .2485
6	F-113	fingertight microferrule 1/32in
7	F-130X	raccord long 10-32 peek naturel pour tube 1/16" OD par 10
8	F-330-01	long fingertight nut peek
9	MXP7900000	commutateur de vanne Rheodyne MXP serie II 6w/2p inox stator 0.30 mm inox 400 Bar maxi

10: plate support with positioning system (ref 022.8411) .



TLC-MS-ELSD with Open Access mode .





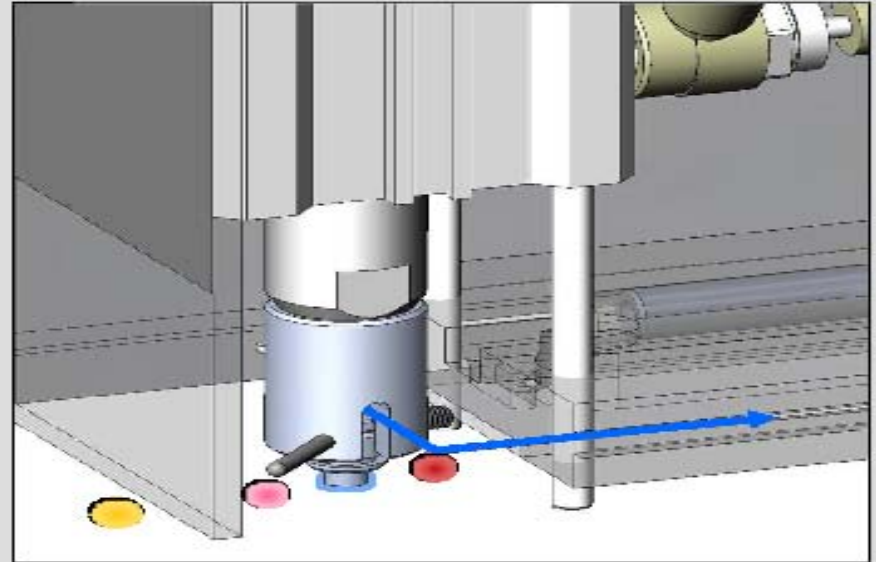
TLC-MS-ELSD with Open Access mode .

CAMVAG

Principe de fonctionnement



Positionnement de la plaque en face du spot à éluer (échelle x/y et laser)



Le piston descend sur la plaque avec une pression de 4 bars et l'extraction peut commencer



TLC-MS-ELSD with Open Access mode .

- This TLC Camag interface is fully compatible with all MS instruments (Quad;triple quad;Tof ; Ion Trap;Hybrid;...) working with electrospray mode (+/-);....
- This TLC –Camag Interface is compatible with all TLC(HPTLC) material and support: cellulose;silica gel/ kieselgurhr ,... with plastic, aluminium sheet,glass plate. .. and analytical and preparative plate...
(also interesting to test new Merck plate : LuxPlate silica gel 60 F 254;Concentrating zone plateTLC/HPTLC..)



TLC-MS-ELSD with Open Access mode .

Two additional developments could be done on this interface :

- a) Automatisations of the TLC plate : expensive ; not easy monitoring via MS software: see Camag Dried blood spot analysis = DBS-MS 500=see presentation made by CEO R .Rolli –Camag AG –Basel-7 Jul 2011 .**

- b) Automatisations of the analysis/acquisition of TLC spot selected via a chemist (: Self service TLC-MS)... In collaboration with Camag-Chromacim/Sedere/BCP Instruments we made this adaptation by adding a automated Rheodyne valve MXP7900-000 .**



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MX Series II™ - High Pressure

Brand: Rheodyne
Product #: MX Series II™

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Part Number	Name	Material	Differential Pressure, Max	Valve Type	Positions	Ports	Price (USD)
MXP7900-000	MX Series II	DuraLife®	6000 psig	Switching	2	6	📞
MXP7920-000	MX Series II	DuraLife®	6000 psig	Vertical Port	2	6	📞
MXP7960-000	MX Series II	DuraLife®	6000 psig	Switching	2	10	📞
MXP7970-000	MX Series II II	DuraLife®	6000 psig	Selector	6	7	📞
MXP7980-000	MX Series II II	DuraLife®	5000 psig	Switching Nano M4	2	6	📞
MXP7986-000	MX Series II II	DuraLife®	5000 psig	Switching Nano M4	2	10	📞
MXP9900-000	MX Series II	PEEK	5000 psig	Switching	2	6	📞
MXP9960-000	MX Series II	PEEK	5000 psig	Switching	2	10	📞

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TLC-MS-ELSD with Open Access mode .

Rheodyne TitanMX Control Software

About

Position Control



Configuration

Change Position

1	2	3
4	5	6
7	8	9
10	11	12

Timed Events

Current Position

Valve Homing

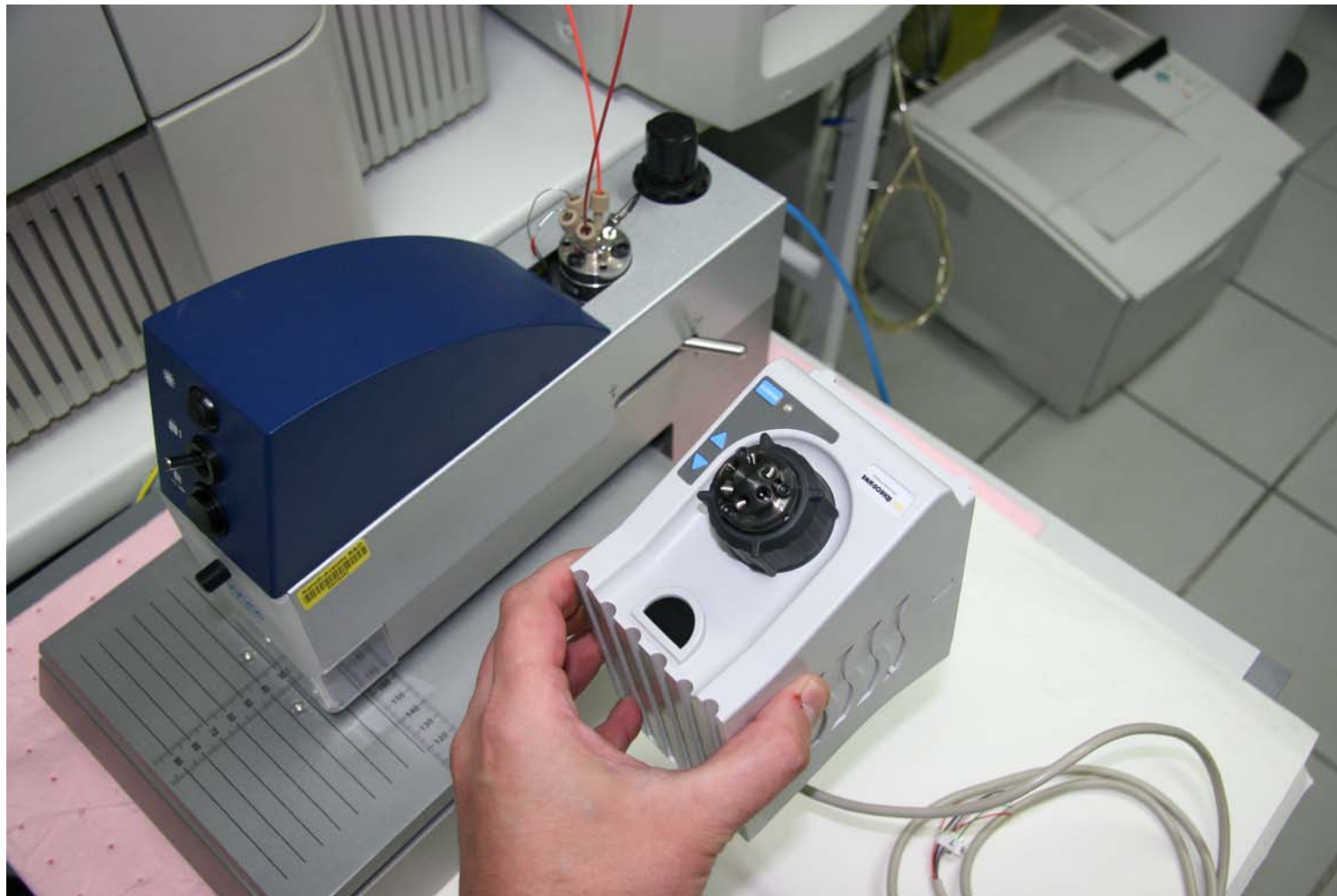
Home the Valve

Events Log

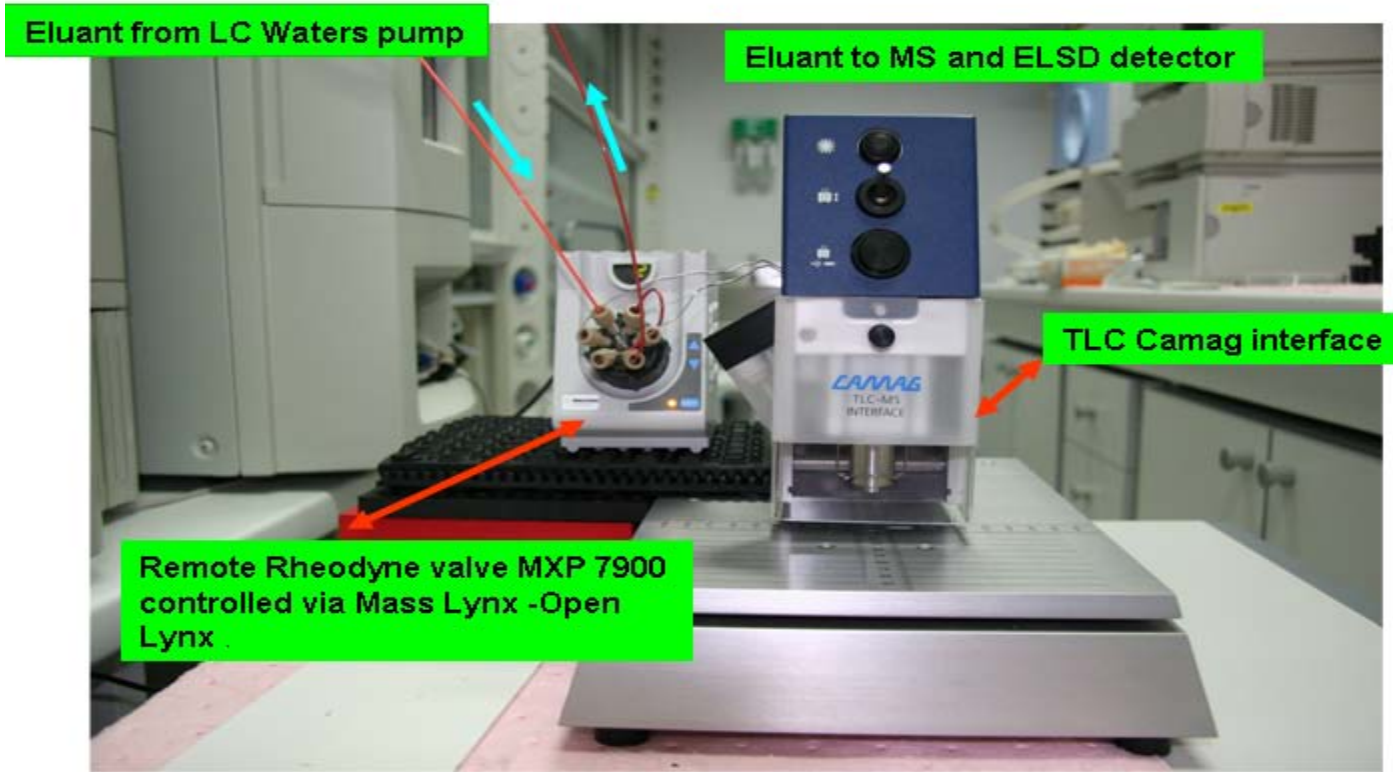
- Found 0 MX II unit through USB
- Error - Could not connect to USB Device
- Could not connect to MX II using USB

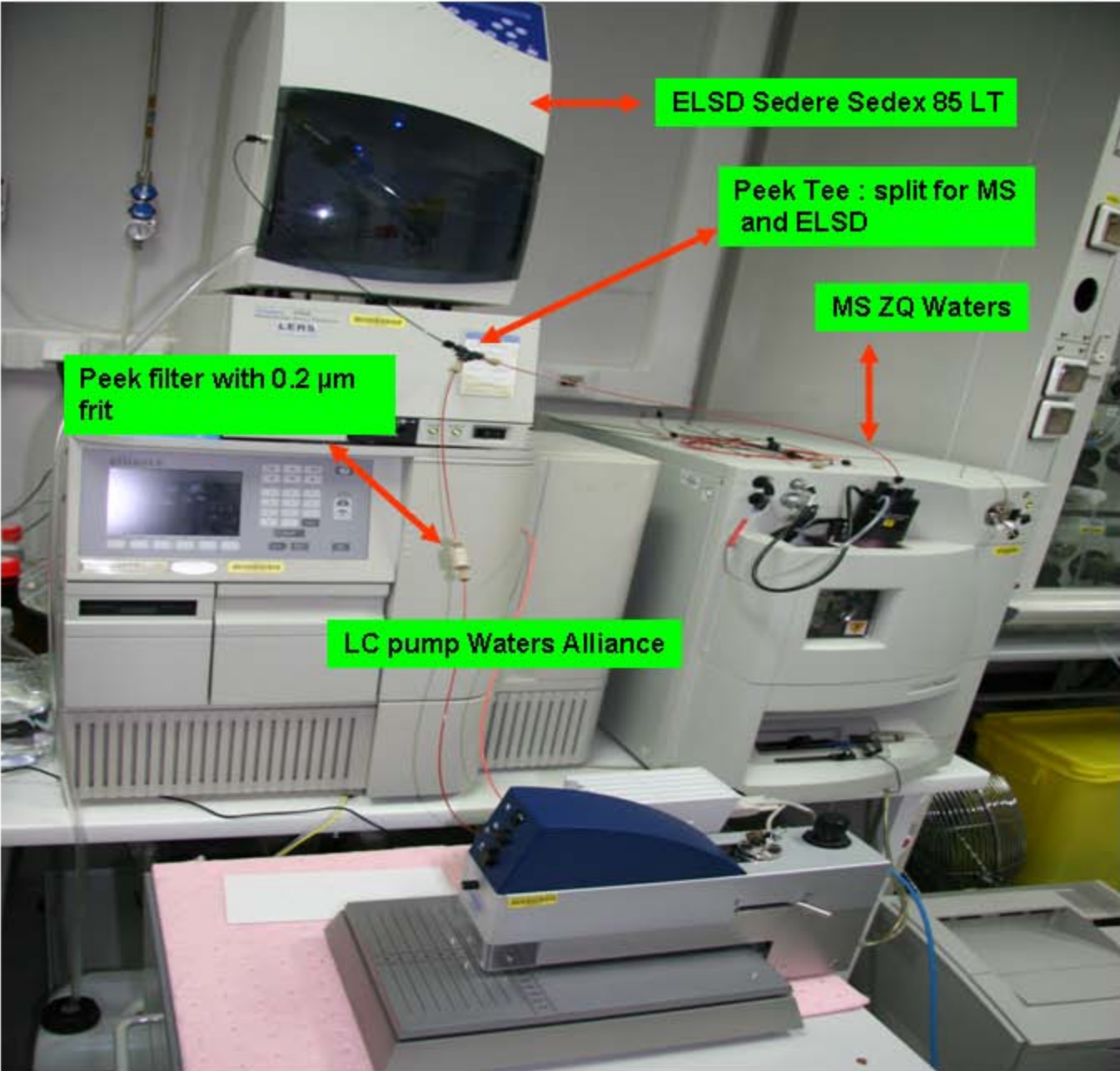


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TLC-MS-ELSD with Open Access mode .





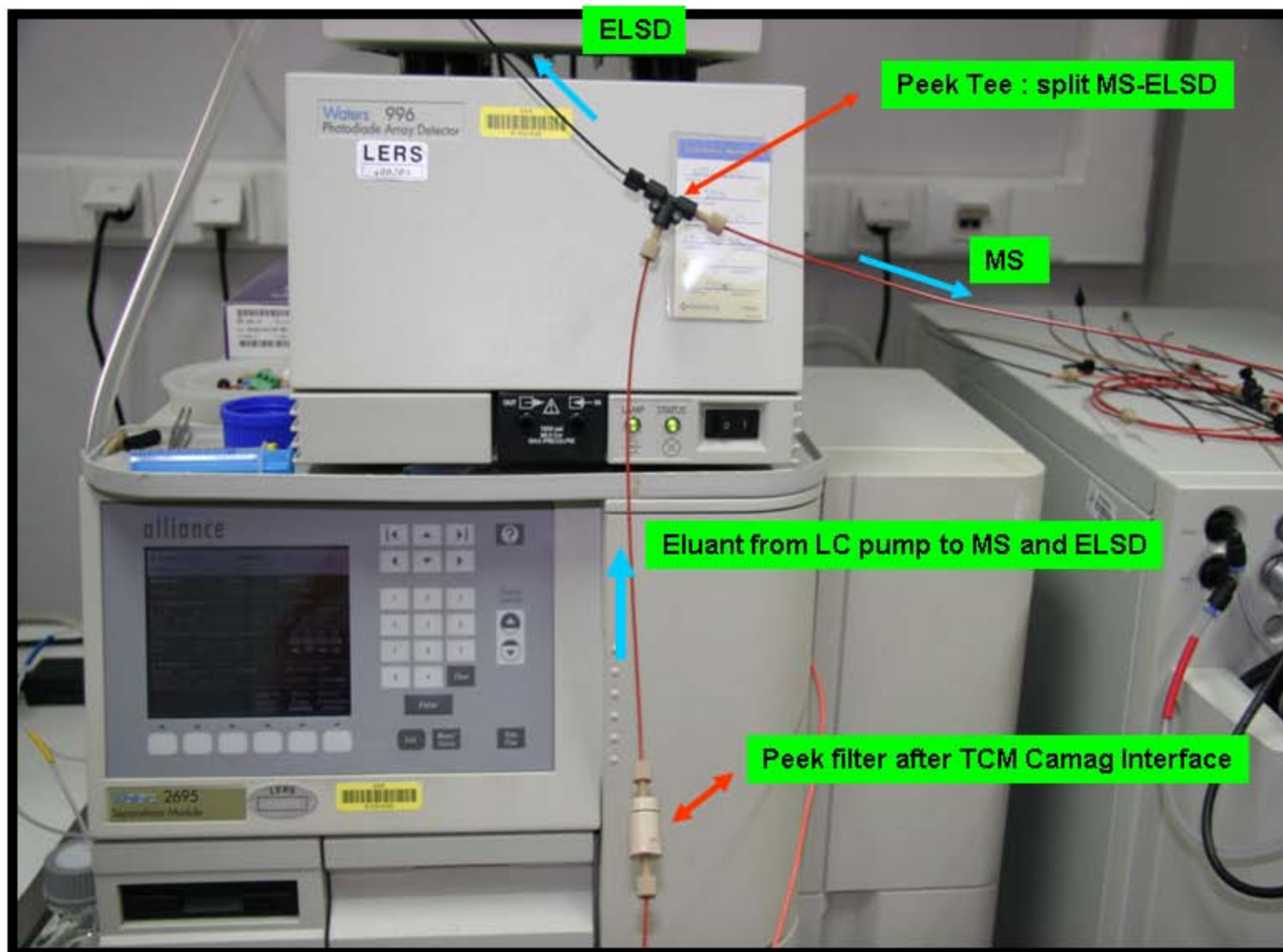
ELSD Sedere Sedex 85 LT

Peek Tee : split for MS and ELSD

MS ZQ Waters

Peek filter with 0.2 μm frit

LC pump Waters Alliance





TLC-MS-ELSD with Open Access mode .

SEDEX LT-ELSD Technology

SEDEX^{LT-ELSD}

ELSD ADVANTAGES

- Nearly Universal (Ideal for Unexpected Analyte Detection).
- Compatible with Gradients (vs. RID).
- Mass Response Detector.
- Simple and Robust (Ideal for Method Development).
- Optimized for U-HPLC: Peak widths < 1s (SEDEX 90LT and 85LT).

LIMITATION

ELSD

- Mobile Phase without Dry Residue (R.A.E. Preferably below 1ppm).
- Sample Volatility.

UV

- Mobile Phase without UV Chromophore (Cut-Off).
- Sample Chromophore.



SEDERE S.A.S.

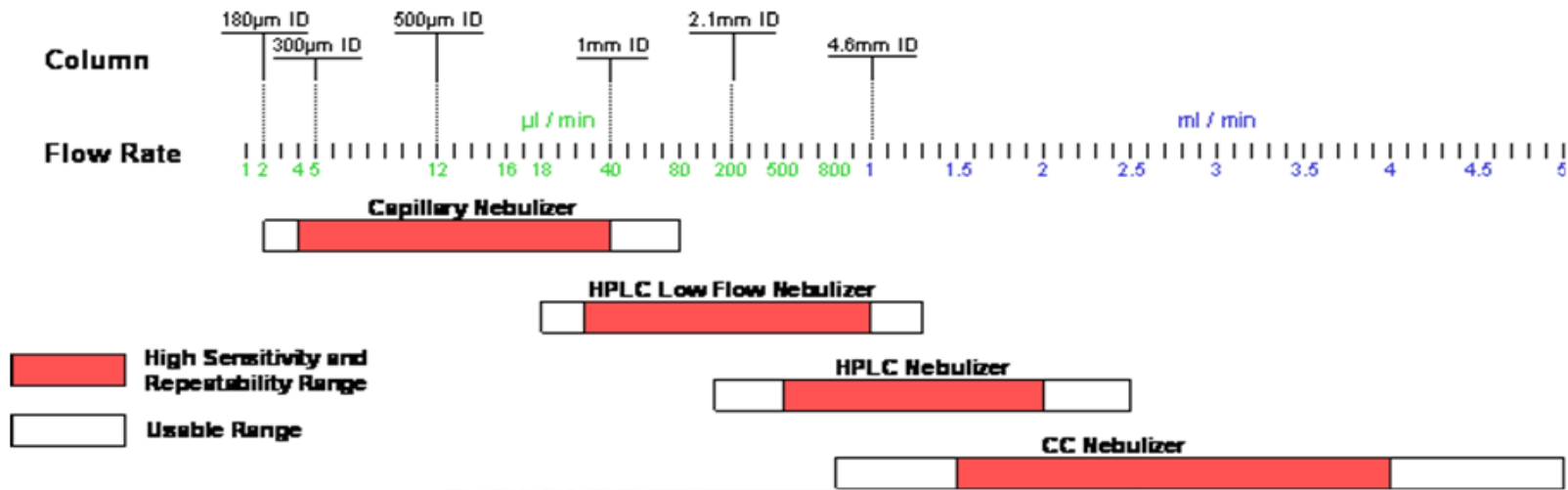
9 rue parmentier – Parc Volta - BP 27

Eric VERETTE, Ph.D.
+33 (0)2 38 66 84 47

TLC-MS-ELSD with Open Access mode .

Four Nebulizers 04-75XXX for the 75 & 85

SEDEX_{LT}-ELSD



4 nebulizers covering the range from 5 $\mu\text{L}/\text{min}$ to 4-5 ml/min are available

Maximum sensitivity and the best peak shape for specific applications

SEDEX 90LT Light Source

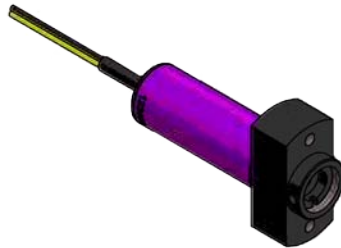


Laser Advantages:

- The beam is focused.
- The output light power is higher than LED or power LED.

Why 405nm?

- This wavelength corresponds to the maximum sensitivity of the PMT.
- This laser wavelength are now available in production thanks to blu-ray discs.





TLC-MS-ELSD with Open Access mode .

Hyphenation conditions:

Eluant : Methanol/waters ; 95/5 ; v/v Baker LC-MS grade solvent .

Flow rate : 0,4 ml/minute .

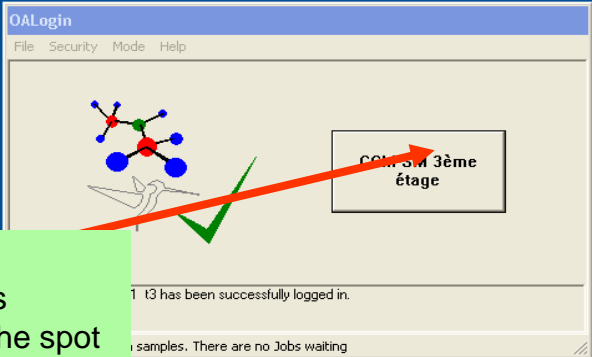
**Split out of the pump(MS/ ELSD) : P-727-Peek Tee Upchurch Idex :
0,2ml/minute to MS / 0,2 ml/minute to ELSD .**

**Solvent Filter After Camag TLC Interface: Upchurch Idex A 356 with
titanium frit A -504 (0,2 μ m).**

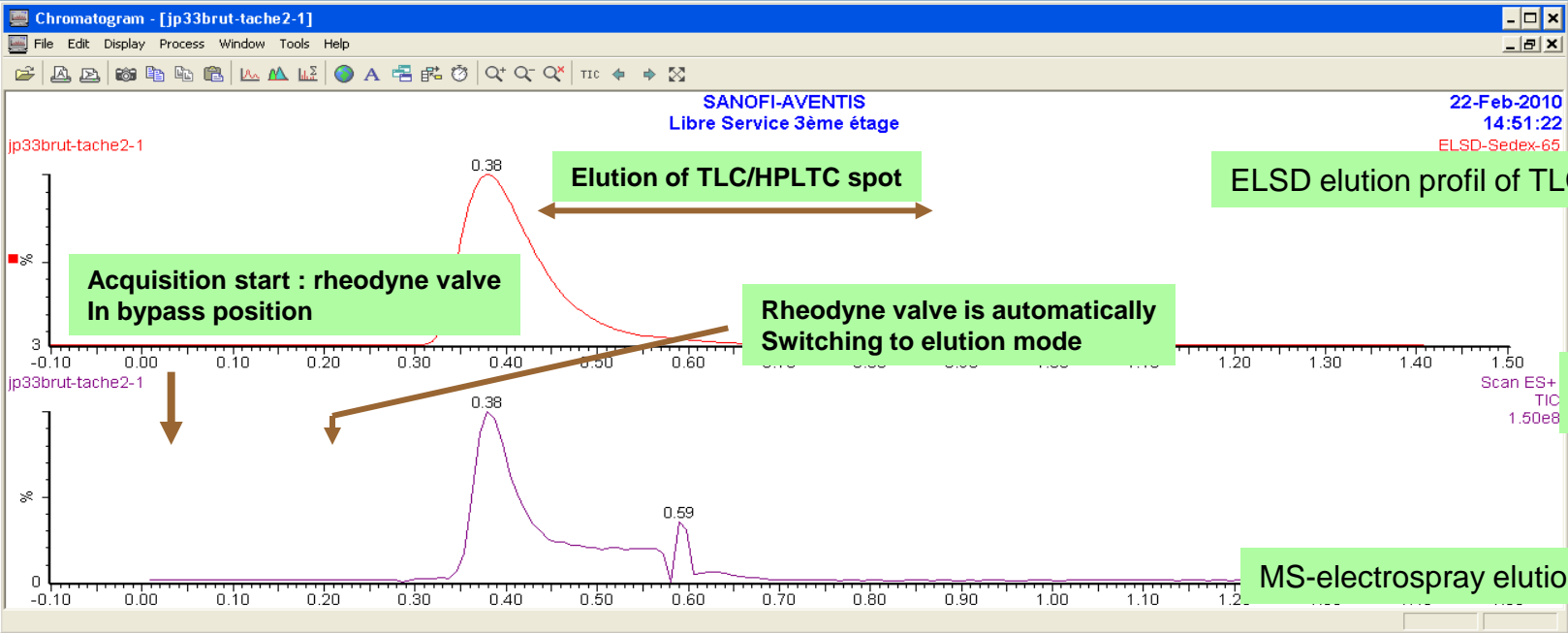
**Contact closure between TLC Camag Interface and MS-Mass Lynx
Open Lynx via Rheodyne MXP 7900-000.**

**ELSD- Sedere 85 LT : Nitrogen gas ; nebuliseur temperature 32°C;gas
pressure=3,8 bars; signal gain : x5 (very intense !! gain limite x12
!!).**

ccm en cours.txt - Notepad
 Ce Self est actuellement en mode CCM-SM .
 Pour LC-MS voir autres etages (0,1,2)



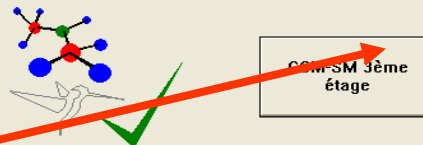
Analyst/chemist will enter Identification /reference of the TLC spot by clicking inside this Window. Then automatic elution/acquisition of the spot will start.



My Computer HP Photo Printing
 My Network Places EZ-Monitor...
 Recycle Bin A00005483
 Internet Explorer zq.ppt Docu...
 Access IBM oalgin en cours.txt
 oalgin setup.ppt

ccm en cours.txt - Notepad
 File Edit Format View Help
 Ce Self est actuellement en mode CCM-SM .
 Pour LC-MS voir autres etages (0,1,2)

Analyst/chemist will enter Identification /reference of the TLC spot by clicking inside this Window. Then automatic elution/acquisition of the spot will start.

OALogin
 File Security Mode Help

 Batch vas-lyv9-066-1 t3 has been successfully logged in.
 Press button to login samples. There are no Jobs waiting

Chromatogram - [jp33brut-tache2-1]
 File Edit Display Process Window Tools Help
 TIC

SANOFI-AVENTIS
 Libre Service 3ème étage
 22-Feb-2010
 14:51:22
 ELSD-Sedex-65
 An1
 6.51e5

jp33brut-tache2-1
 0.38
 Elution of TLC/HPLC spot

Acquisition start : rheodyne valve in bypass position

Rheodyne valve is automatically switching to elution mode

ELSD elution profil of TLC spot

Rheodyne valve return In bypass position

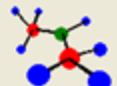
MS-electrospray elution profil of TLC spot

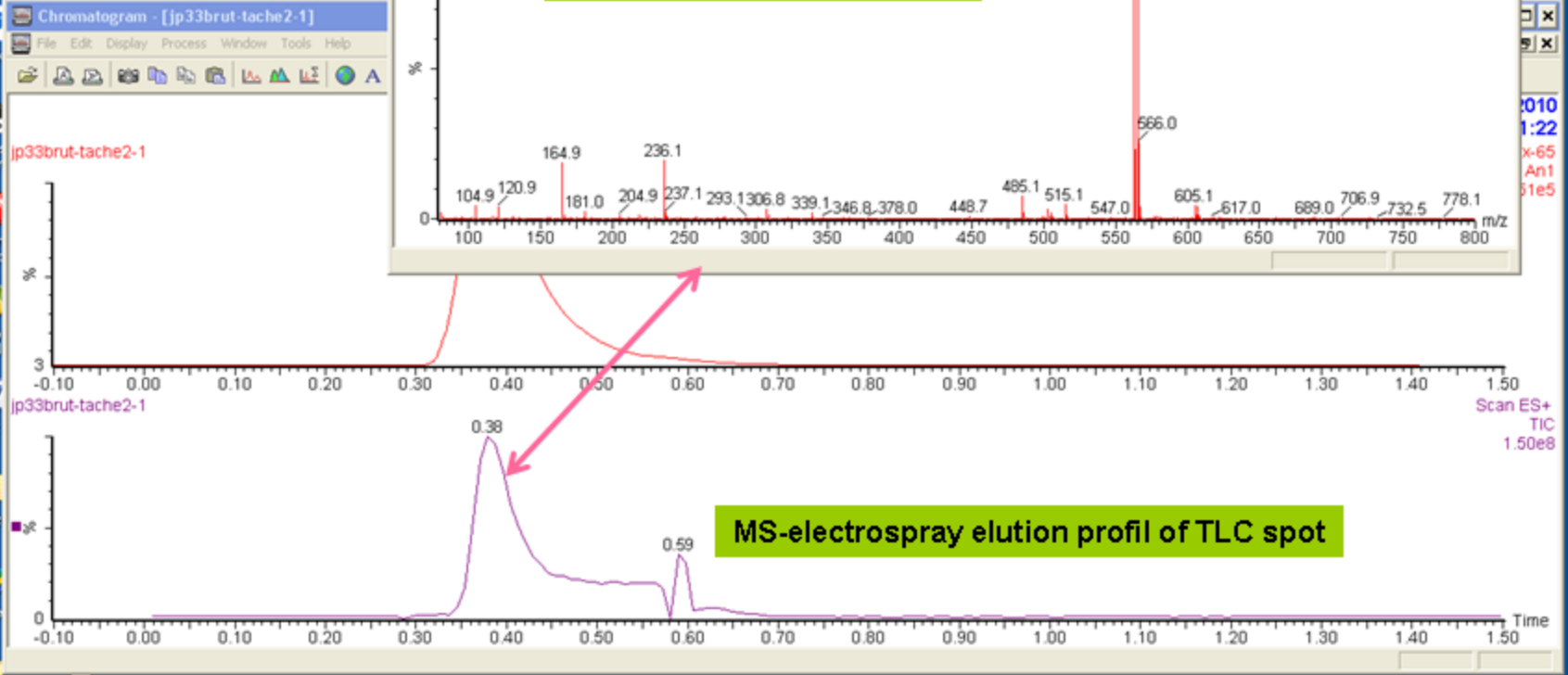
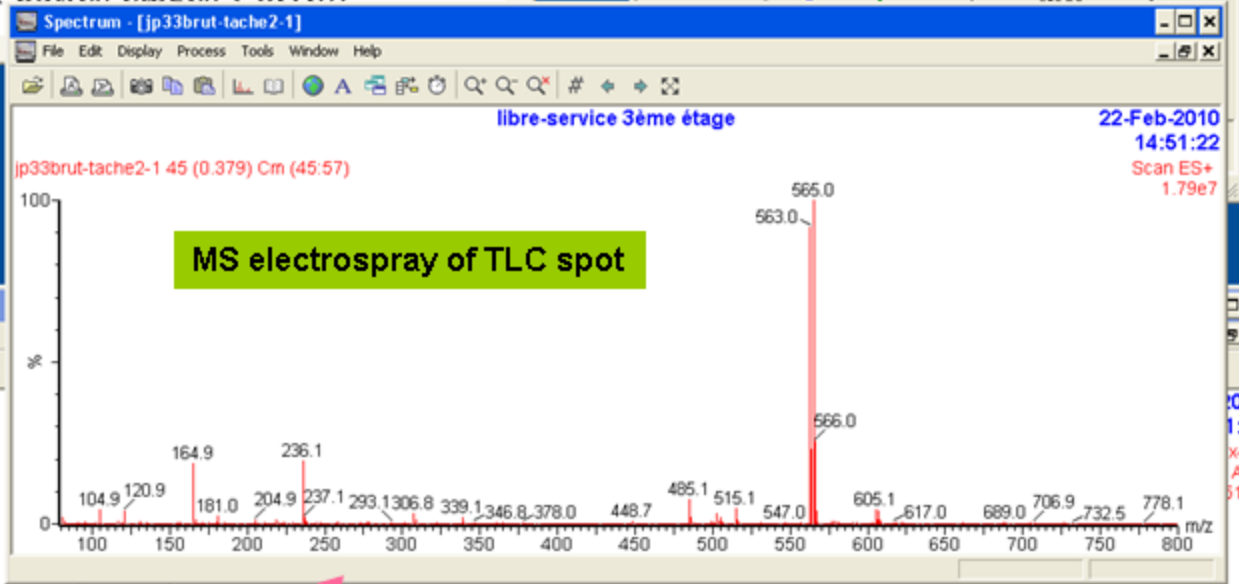
0.59
 1.50e8

Time

Start 3 MassLynx Mo... ZQ - c:\masslynx\... ccm-sm-camag.w... ccm en cours.txt ... OALogin Microsoft PowerP... KINGSTON (E:) KINGSTON (E:) FR << 11:53

ccm en cours.txt - Notepad
Ce Self est actuellement en mode CCM-SM .
Pour LC-MS voir autres etages (0.1.2)

OALogin
File Security Mode Help

CCM-SM 3ème

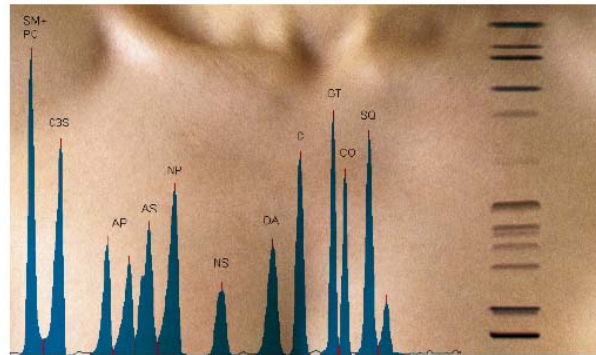




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AMD chromatogram of Stratum corneum lipids

**The versatility of HPTLC –
From Bio Analysis to the Detection
of Pollutants in Water**

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IN THIS ISSUE

Procedures, applications

TLC/HPTLC-ELSD-MS coupling 2-4

Determination of the glycoalkaloids
 α -solanine and α -chaconine
in potatoes at different steps
of potato processing 5-6

1H-Benzotriazole
and tolyltriazole in the
aquatic environment 7-9

Optimization of an
AMD 2 method
for determination of
stratum corneum lipids 10-12

Determination of additives
in plastic foils 13-15

Products featured in this issue

TLC Scanner 4 4

Automated
Multiple Development (AMD 2) 11

TLC-MS Interface 16

Column: Know CAMAG

Seminar, held by CAMAG Berlin
at the University of Zittau/Görlitz 8

CAMAG

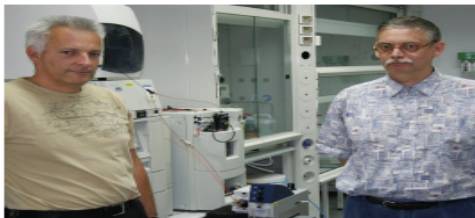
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Planar Chromatography in Practice

TLC/HPTLC-ELSD-MS coupling



Mr. François Bretin and Dr. Francis Maquin (right)

The Lead Generation to Candidate Realization (LGCR) platform identifies small molecule leads and progresses them up to registration. LGCR Analytical Sciences (AnSci) is a new department in Sanofi-Aventis R&D, which is dedicated to support Business Divisions and Therapeutics Units. For LGCR-AnSci, Dr. Maquin[†] and F. Bretin in the research center in Vitry-sur-Seine use various analytical techniques (further locations are in Strasbourg, Chilly-Mazarin, Toulouse and Montpellier).

Introduction

MS coupled to chromatography supports the chemist's decision for compound identification or follow-up in a synthesis mixture. Therefore, HPLC/UPLC-MS is mainly used, but TLC/HPTLC is also widely applied by the chemists as a rapid and reliable method to follow reaction processes.

This is especially true for cases, when compounds remain on the column, due to high polarity or weak solubility, or when analyte detection is poor (no chromophore). In such cases, the HPTLC/MS platform with the new TLC-MS Interface is ideal for structural analysis. The TLC-MS Interface was complemented by a MS software controlled valve, adding some automation to the process, and by an Evaporative Light Scattering Detector (ELSD). The latter enables the analyst to distinguish between compounds that were not eluted from the plate from those that were not sufficiently ionized for MS detection.

Sample preparation

The samples were taken directly from the reactor and diluted with an appropriate solvent, usually an organic solvent of medium polarity.

Standard preparation

Educts or known intermediate products were dissolved and diluted with an appropriate solvent.



TLC-MS-ELSD with Open Access mode .

Chromatogram layers

TLC and HPTLC plates silica gel 60 F₂₅₄ 10 x 20 and 10 x 10 cm, respectively. If required, the plate size was reduced with the Smartcut.

Sample application

Manually with disposable micropipettes of 5 to 20 μ L volumes.

Note: The Nanomat 4 is recommended to ensure precise positioning without damage of the layer. Especially for polar extracts, small volumes should be applied (<2 μ L to obtain sharp start zones).

Chromatography

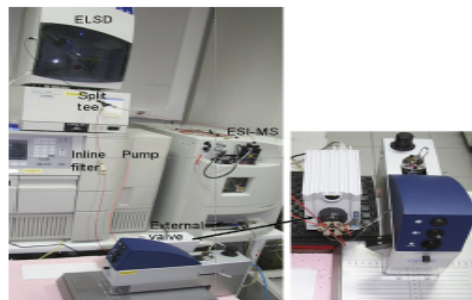
In a twin-through chamber, e.g., with mixtures of methanol and dichloromethane/ethyl acetate, or ethyl acetate and heptane/cyclohexane; the ratios depend on the compound mixtures.

Derivatization

Compounds with neither UV/Vis-activity nor native fluorescence can be derivatized by non-destructive derivatization reagents, e.g., the primuline or berberine reagents for lipophilic compounds, and directly eluted with the TLC-MS interface into the MS. However, for destructive derivatizations, e.g., based on strong acidic carbonization reactions, on both plate sides, the outer track was cut, derivatized, and the respective bands were marked by extrapolation.

Recording of MS spectra

The flow rate of the eluent (methanol – water 95:5, 0.4 mL/min) was split by a tee, and 0.2 mL/min were pumped to the MS (Micromass ZQ, Waters) and 0.2 mL/min to the ELSD (Sedere Sedex 85 LT). The TLC-MS Interface was equipped with either a round or oval elution head and connected via an external automated valve (MXP7900-000, Rheodyne) to the pump (Alliance 2695, Waters) and ESI-MS. In the transfer tube to the detectors, an inline filter was integrated (frit porosity 0.2 μ m, A 356/504, Upchurch IDEX). The recording of mass spectra was performed in the positive/negative electrospray mode; for evaluation the MS software (Mass Lynx V4.0/Open Lynx, Waters) was used.



TLC/HPTLC-ELSD-MS system configuration

Results and discussion

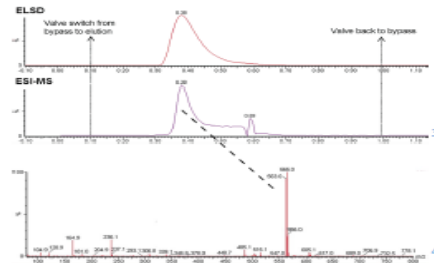
In our experiments, a lot of organic structures were not detected by DAD, so the capability of detection of the TLC/HPTLC-DAD-MS configuration was improved by substituting the DAD with the ELSD. As universal detector, the ELSD confirms more reliably the elution of compounds that are not UV/Vis-active.

Once the elution head was lowered onto the zone of interest and an ID number was entered in the software, valve switching was effected remotely, followed by an automatic acquisition of both the MS and ELSD signal. This minor automation resulted in the zones being eluted into the detector, and then the eluent being subsequently switched back to bypass (waste). The following protocol made cross contamination, which of course is dependent on the substance structure and zone concentration, less likely. For the given connecting tube length and internal diameter, the external valve was set 10 s in bypass, then 1.5 min in elution mode and finally 15 s in bypass. For a high throughput, the elution time was set below one minute.

CBS 105 3



TLC-MS-ELSD with Open Access mode .



Elution profiles obtained by ELSD and ESI-MS (top) and mass spectrum of the eluted zone (bottom)

An intensive use of the TLC/HPTLC-ELSD-MS instrumentation requires frit cleaning twice a week. The requirement of a cleaning cycle is indicated by an increased pump pressure likely from clogging of the inline filter frit (> 10 MPa).

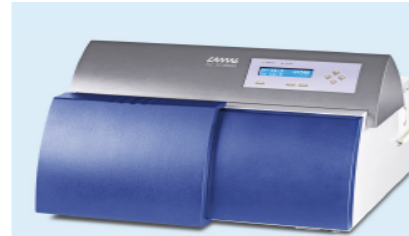
To conclude, our experience underlines the interest in HPTLC/TLC-MS in an advanced analytical environment. The automatization, reliability of the data, and speed were the convincing arguments, which fully comply with our routine analytical needs.

Further information is available on request from the authors.

Contacts

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- Mr. Pierre Bernard-Savary, Chromacim SAS, Pommiers la Placette, France
- Mr. Henri Gangloff, Sedere SA, Alfortville, France
- Mrs. Véronique de Nailly, BCP Instruments, Irigny, France

4 CBS 105



TLC Scanner 4

Classical densitometry uses monochromatic light in the form of a slit of selectable length and width to scan the tracks of a chromatogram, measuring the diffusely reflected light. The TLC Scanner 4 – the successor of TLC Scanner 3 – is the most advanced workstation for densitometric evaluation of Thin-Layer Chromatograms currently available.

Analysts can now benefit from a wider spectral range for measurements from 190 to 900 nm. The optimized positioning stage and its open access allow for robust use.

For the screening of water samples in this application, densitometric determination is performed by the multi-wavelength scan covering the wavelength range between 190 and 300 nm. In combination with AMD the whole polarity range of UV-active compounds is detected. This procedure is proven to be helpful in routine search for potential water contaminants.