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Microfluidics for Biomedical Applications

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Greenland
Iceland
Suomi (Finland)
Sverige (Sweden)
Norge (Norway)
Россия (Russia)
United Kingdom
Polska (Poland)
Deutschland (Germany)
Україна (Ukraine)
Canada
France
España (Spain)
Italia (Italy)
Kazakhstan
Mongolia
Türkiye (Turkey)
中国 (China)
North Pacific Ocean
United States
North Atlantic Ocean
Iraq
Iran
Afghanistan
Pakistan
Algeria
Libya
(Egypt)
Saudi Arabia
India
México
Mauritania
Mali
Niger
Chad
Sudan
Nigeria
Ethiopia
Venezuela
Colombia
Kenya
DR Congo
Tanzania
Indonesia
Brasil (Brazil)
Perú
Bolivia
Angola
Namibia
Botswana
Madagascar
Indian Ocean
2000 mi
2000 km
©2011 Google

Microfluidics

Involves the use of microtechnologies to get networks of microscopic channels for chemical processing.

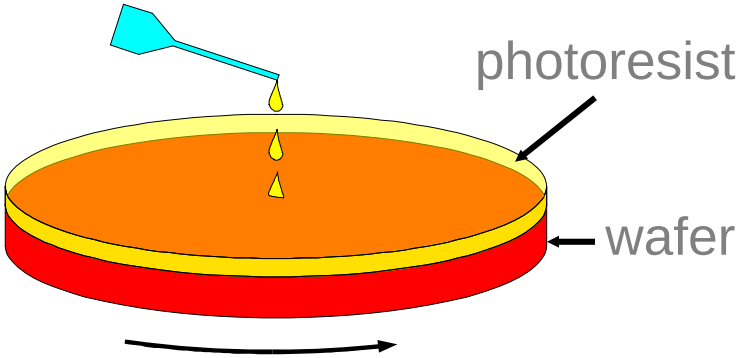
- control of small volumes of liquid (fL to μL),
- reduction of chemicals consumption,
- cheaper process

Available materials

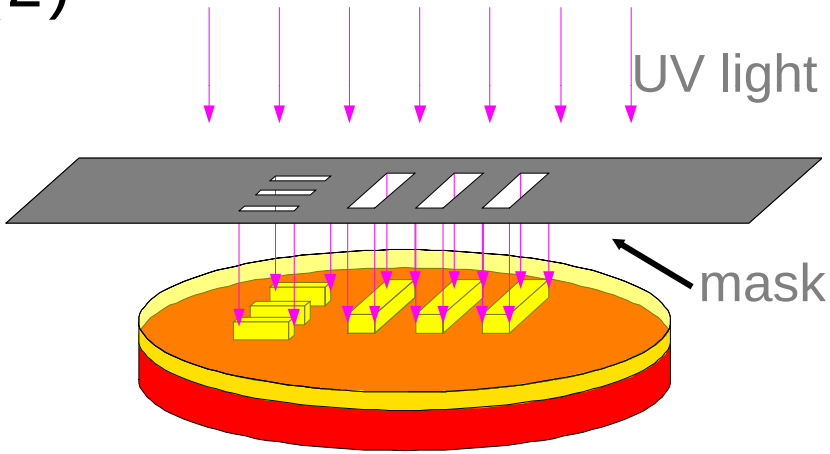
- **Silicon**
- **Glass** (e.g. Pyrex, borofloat)
- **Polymers** (e.g. PMMA, PC, PDMS, etc.)

Device Fabrication

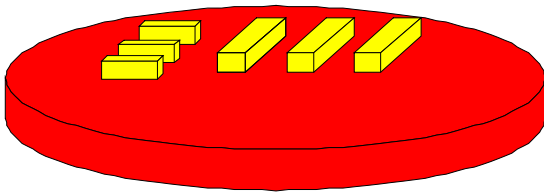
(1) resist deposition by spin-coating



(2)



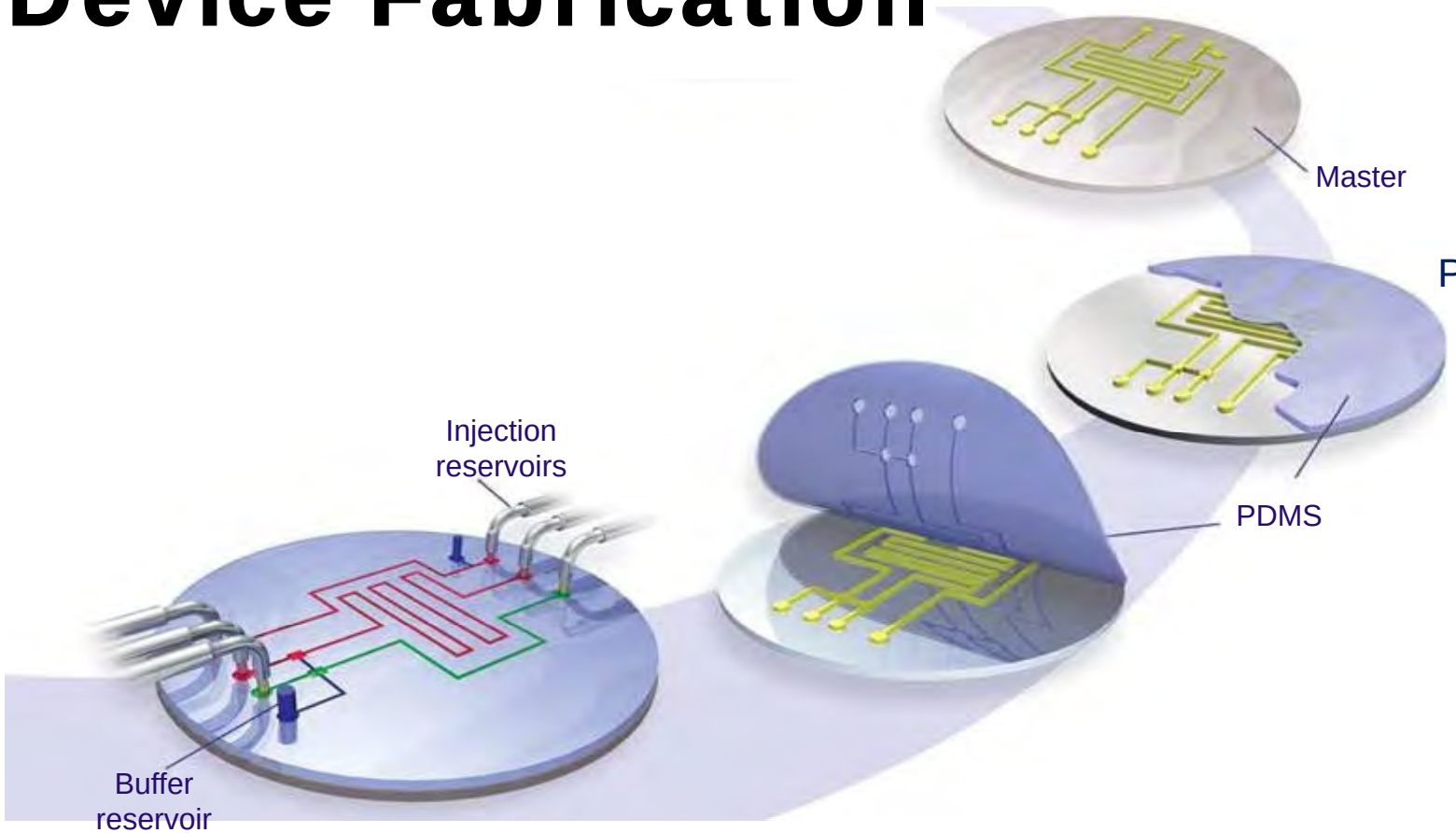
(3) development



negative

Source: U. Staufer (SAMLAB)

Device Fabrication



Gently peel off the PDMS from the master

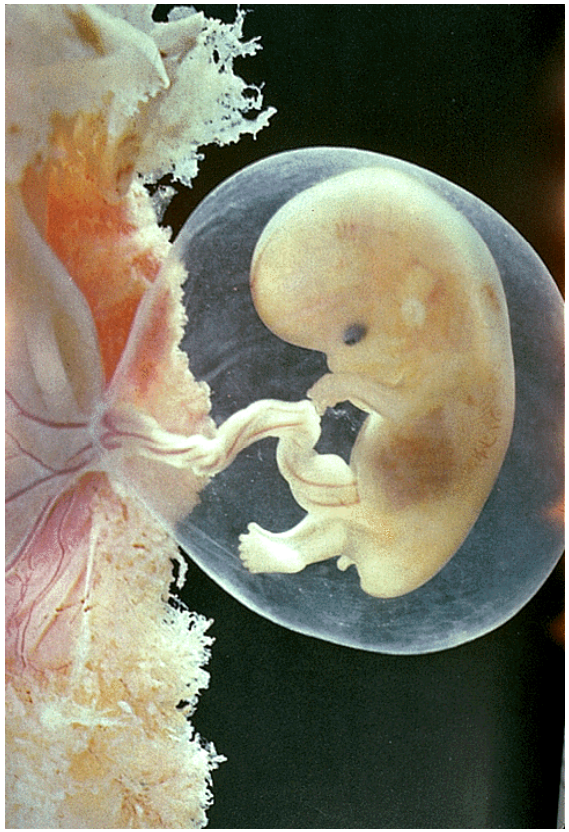
Bond PDMS structure to another flat PDMS layer or to glass and insert tubing

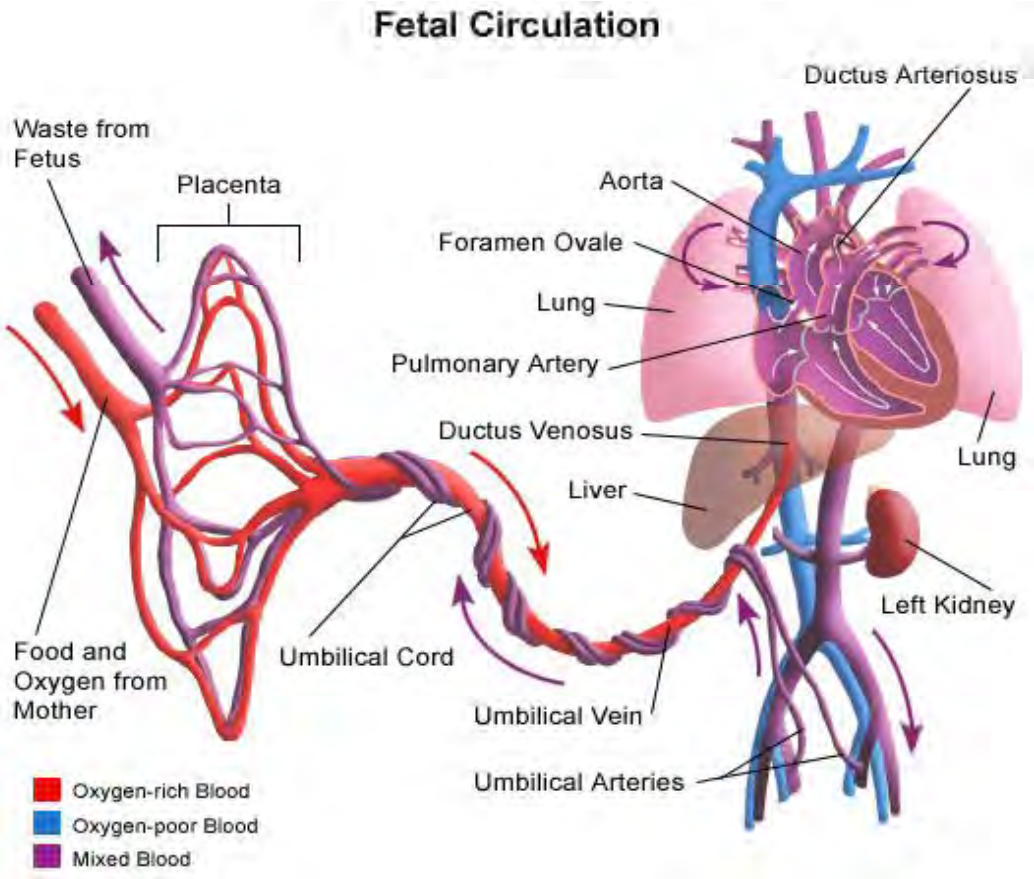
Multiple Internal Reflection Poly(Dimethylsiloxane) Systems for on-line pH Monitoring of Cells

Goal

To develop a method to monitor on-line pH from cell medium, which was in contact with cells.

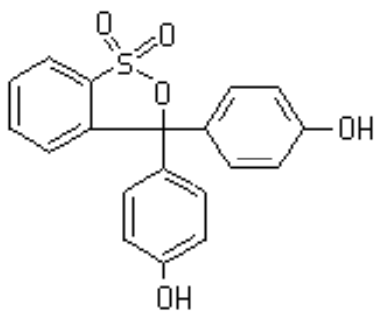
Human Umbilical Vein Endothelial Cells [HUVEC]



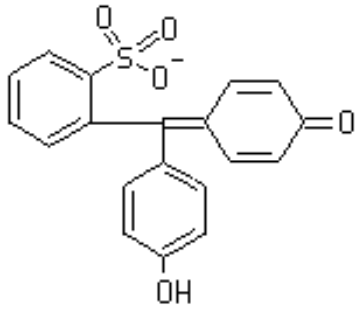


pH monitoring

Phenol red



acid form



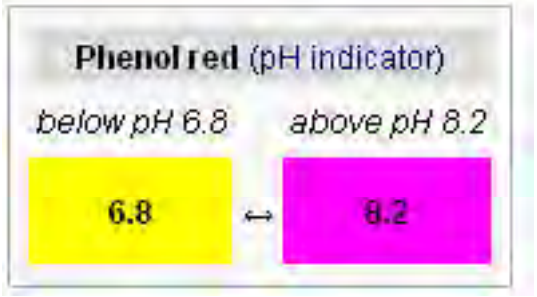
alkaline form

450 nm

560 nm

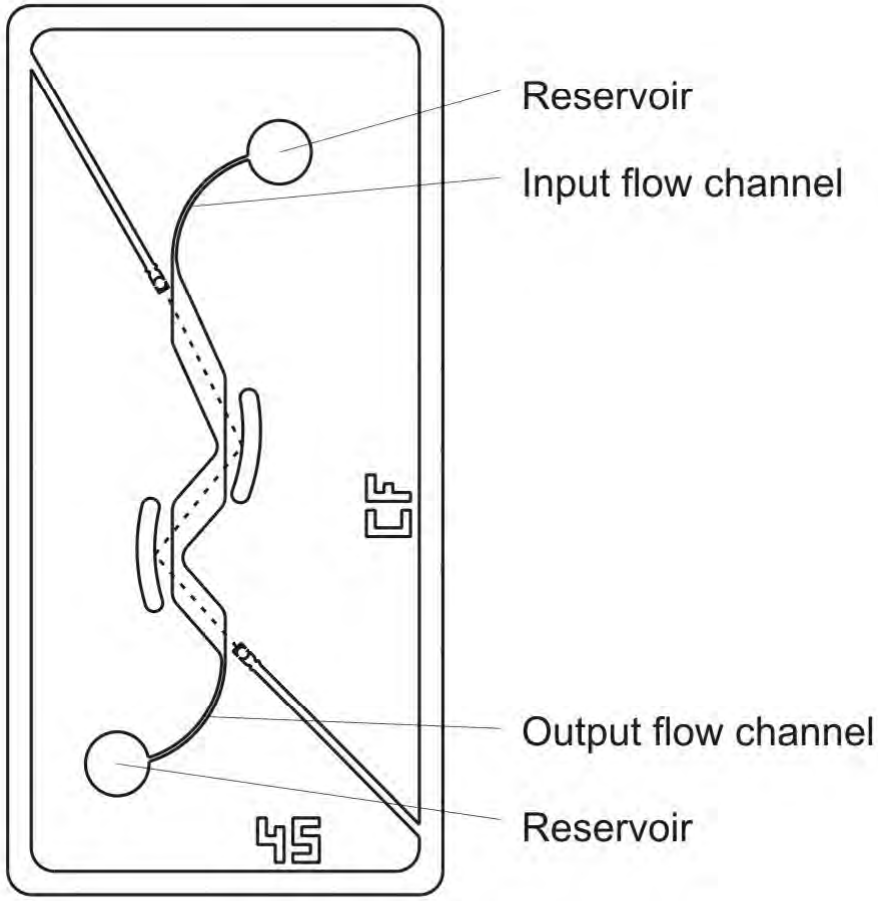
Phenol Red

http://chemistry-1023.wikispaces.com/Acids,+Bases+and+Buffers



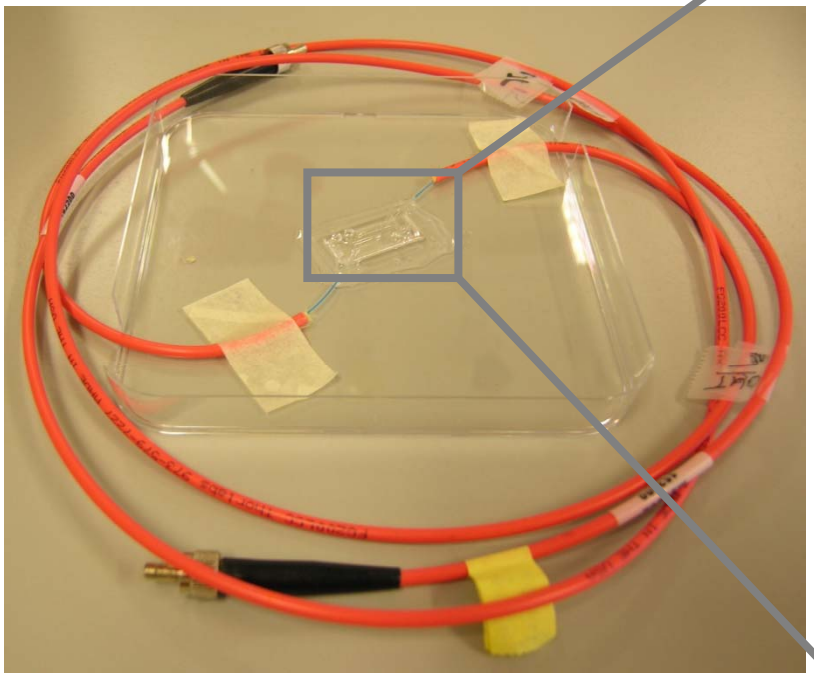
http://en.wikipedia.org/wiki/Phenol_red

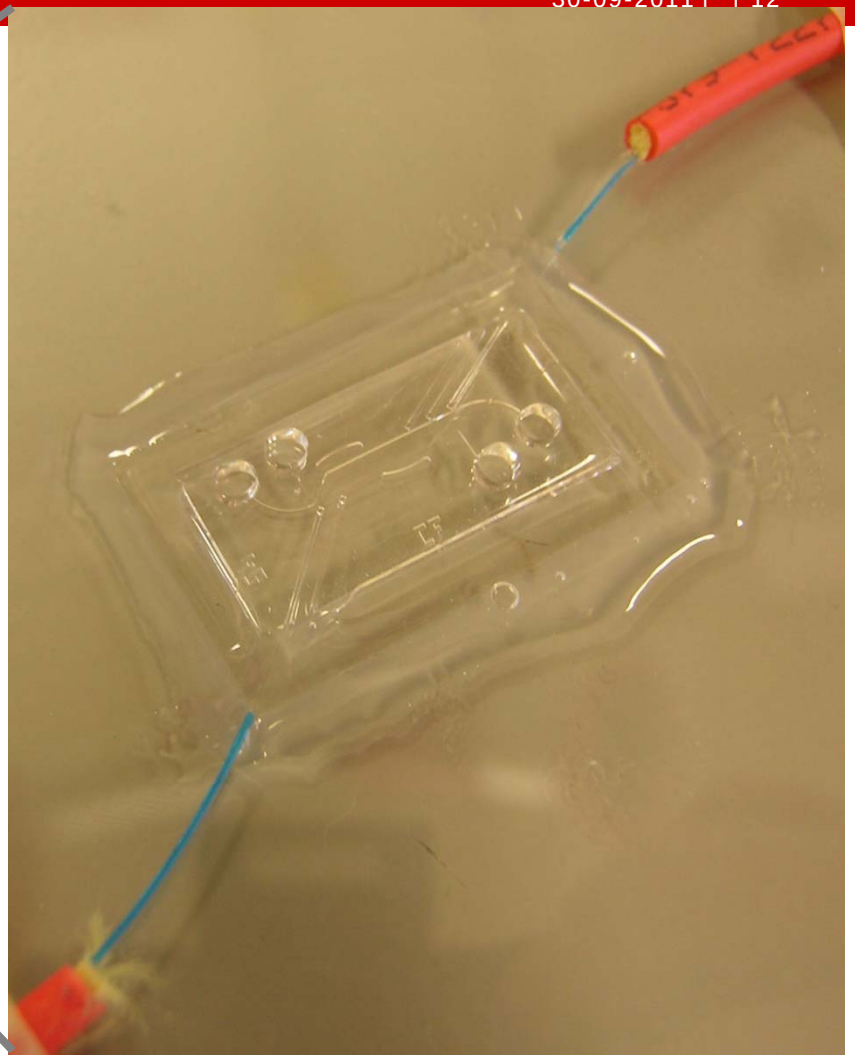
Propagating Multiple Internal Reflection System (PMIR)



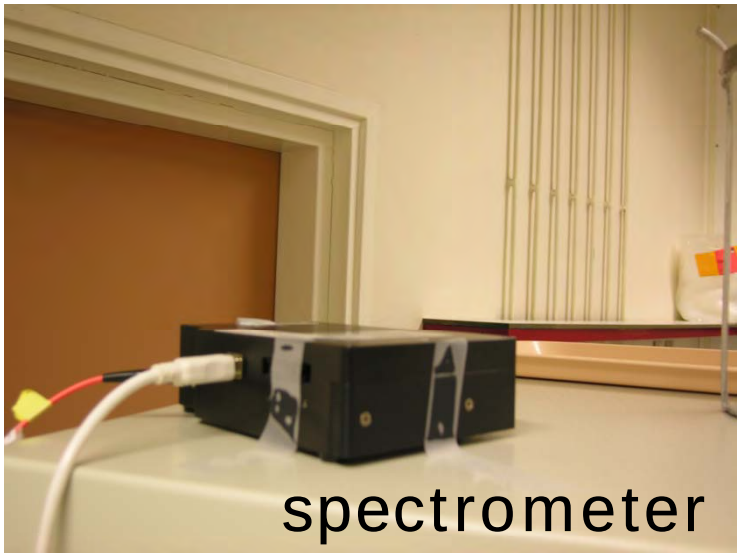
Llobera *et al*., 2007

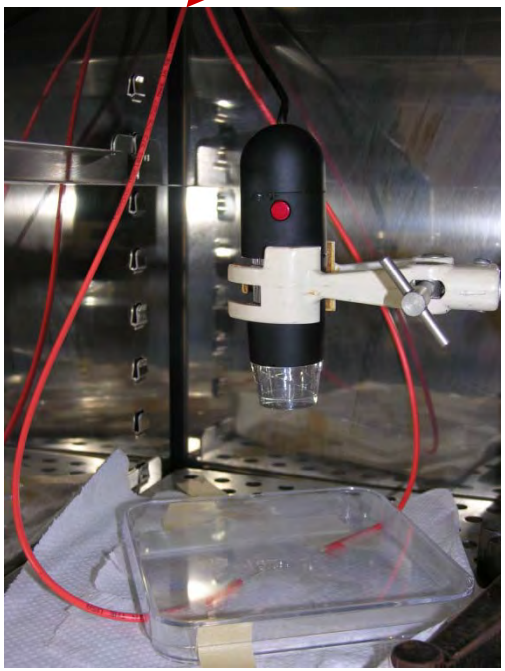
PMIR





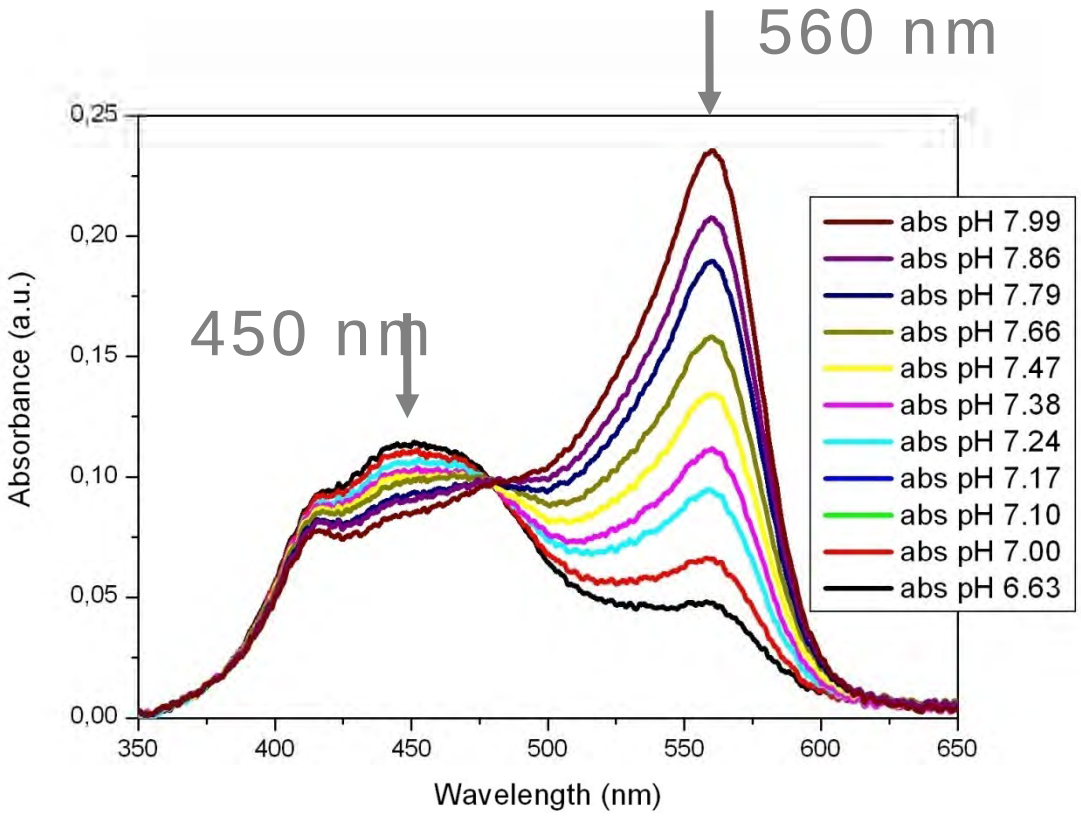
Set-up





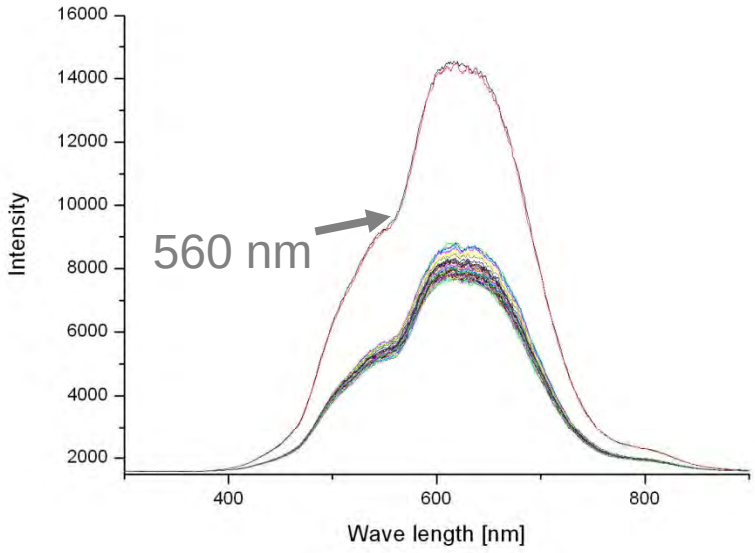
Incubator:
5% CO_2
37° C

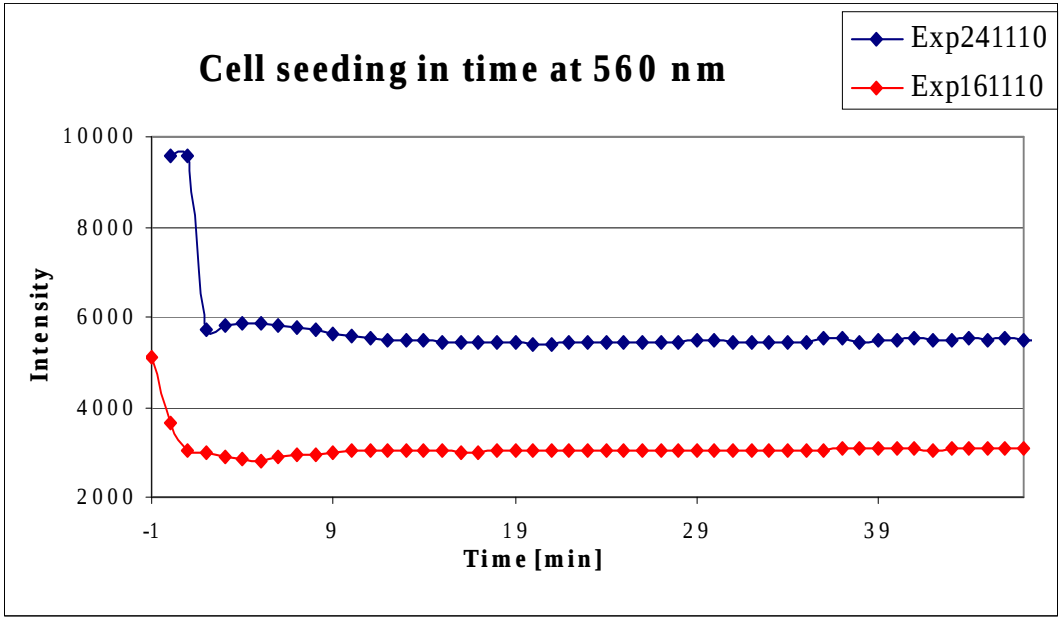
pH monitoring



M.J. Lopez-Martinez *et al.*, MicroTAS 2010

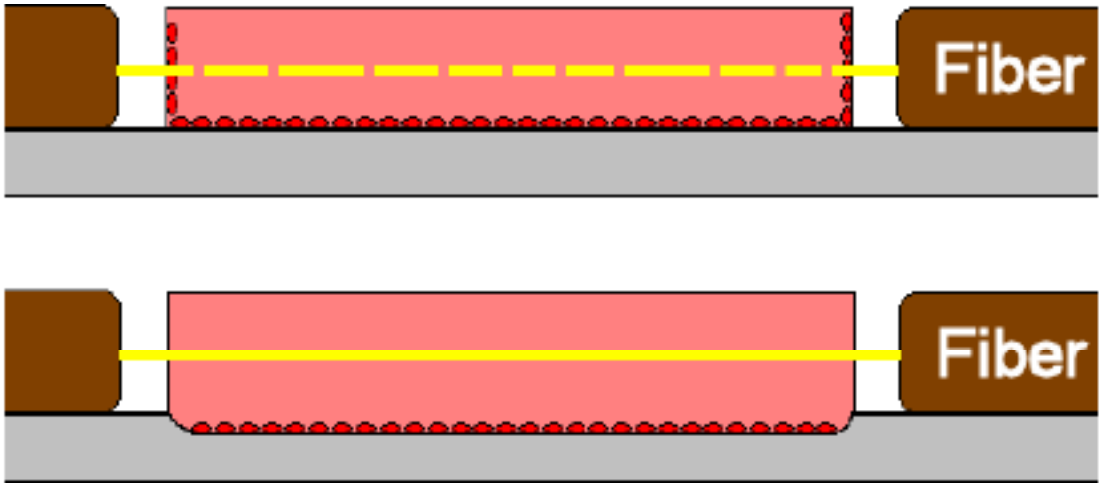
Results



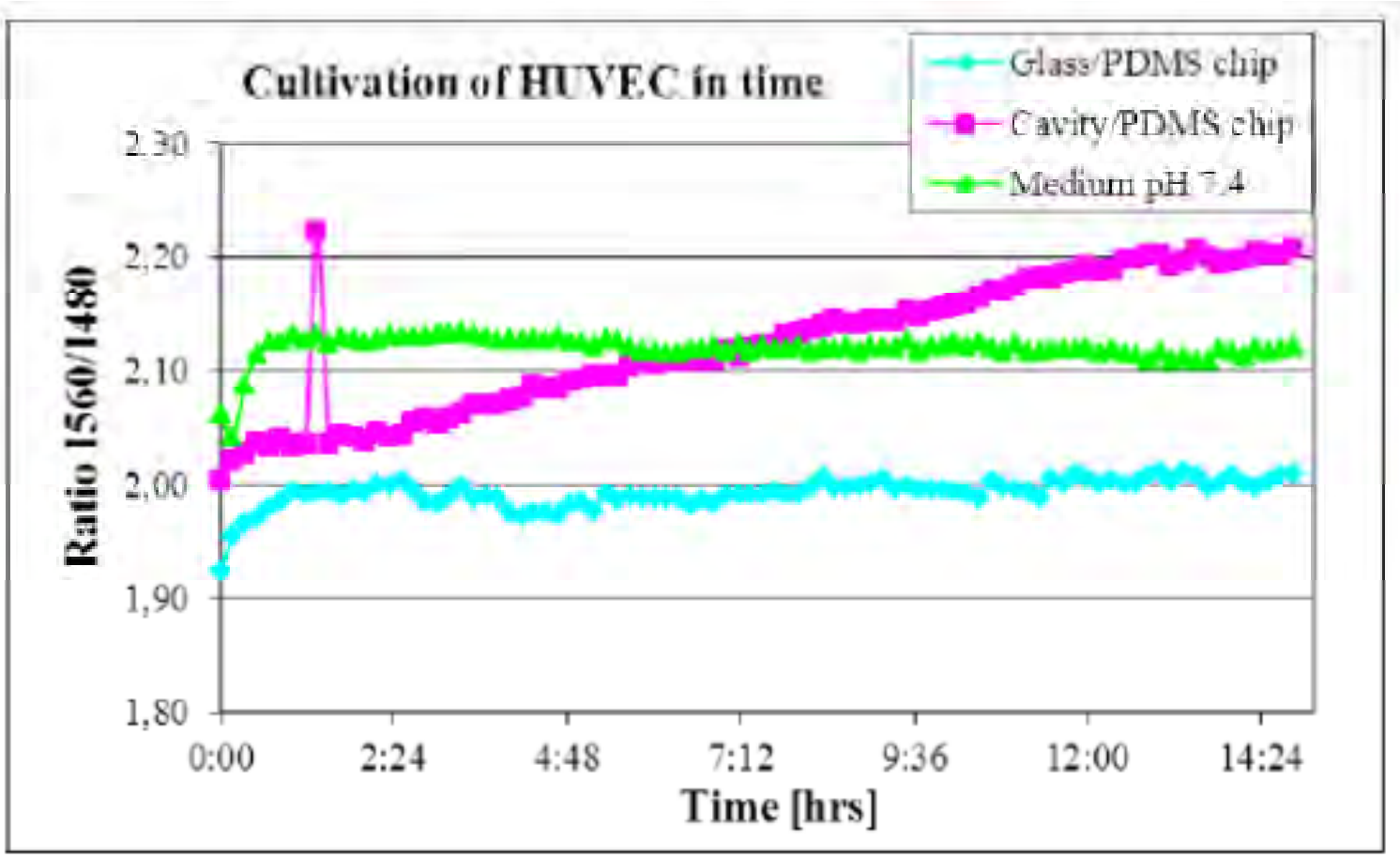


Cells disturb the signal, after introducing them to the chip

- Introduce a cavity in the glass slide using HF treatment.
- Coat only the cavity with gelatin



Results


Cultivation of HUVEC in time
Glass/PDMS chip
Cavity/PDMS chip
Medium pH 7.4
Ratio 1560/1480
2,30
2,20
2,10
2,00
1,90
1,80
0:00
2:24
4:48
7:12
9:36
12:00
14:24
Time [hrs]

Fast Determination of Distribution Coefficients in a Poly(Dimethylsiloxane) Chip

Goal

Calculation of log D at pH = 7.4 for different drugs using a microfluidic device and UV on-line measurements

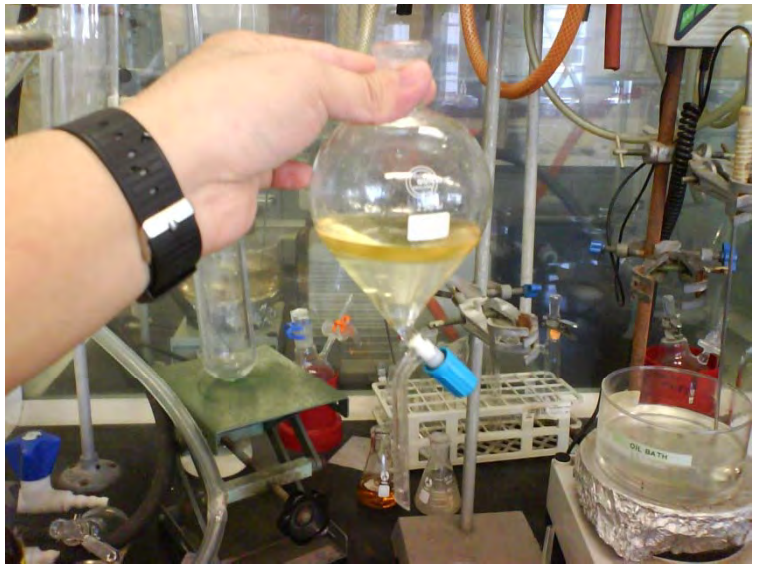
Distribution coefficient

$$LogD = Log \frac{C_0}{C_w}$$

› The distribution coefficient is the ratio between the concentration of the compound in an organic phase (Co), and the concentration in aqueous phase (Ca) at a certain pH.

Standard method

-Liquid-Liquid extraction
-Presaturation of solvents (24h)
-Volume ratio 1:1, 2:1, 1:2

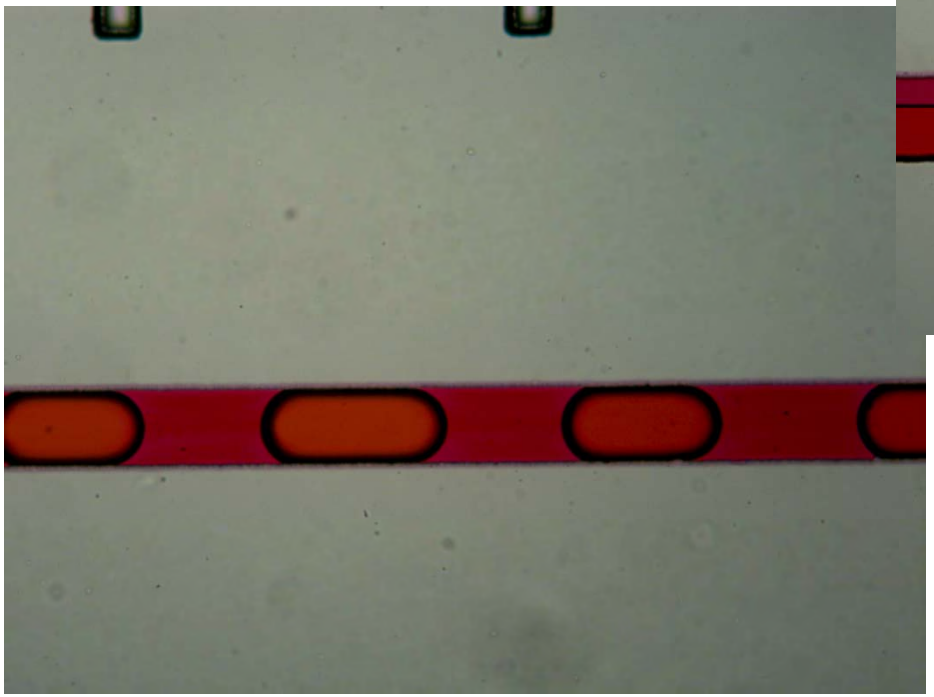


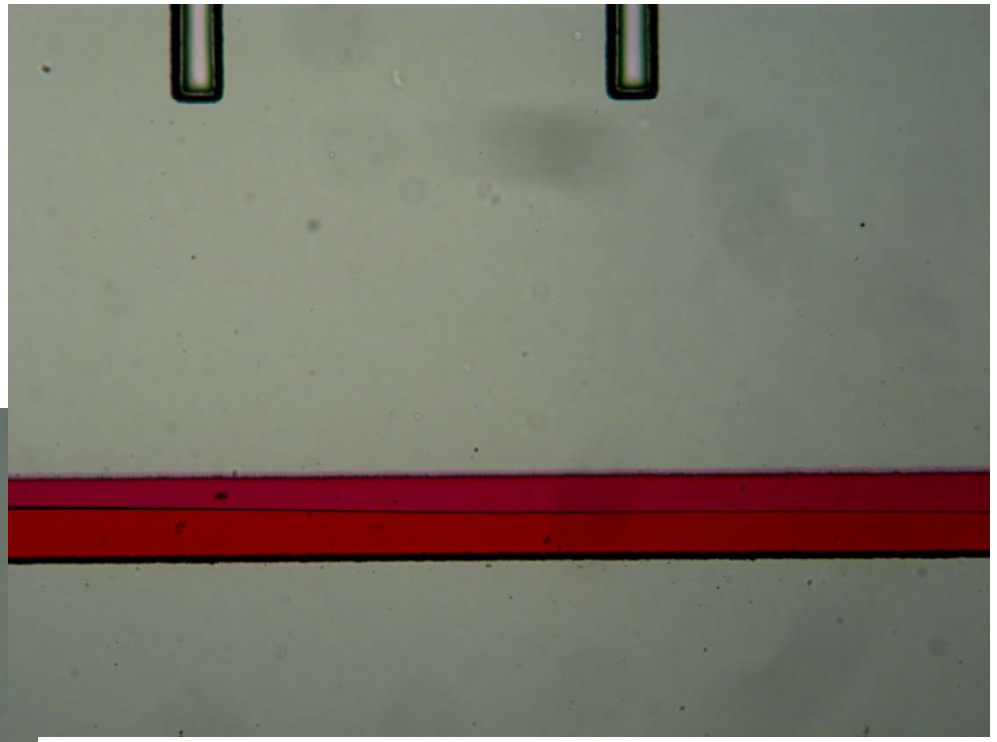
Cons:

- Time consuming (>30 minutes per sample)
- Labour-intensive procedure
- Large amounts of material are required.

Microfluidics

Slug flow





Side-by-side flow

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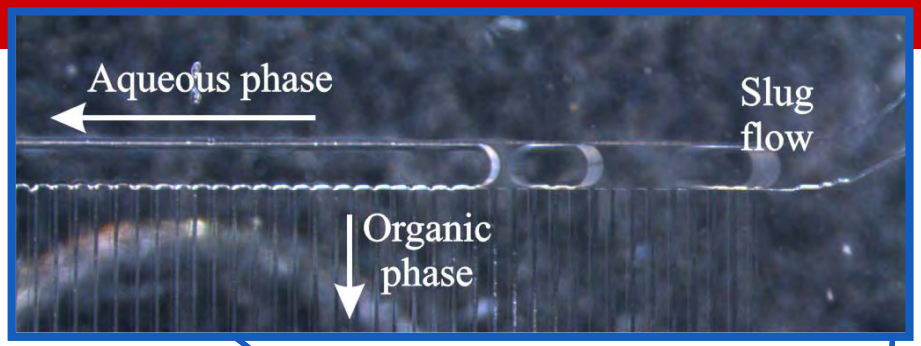
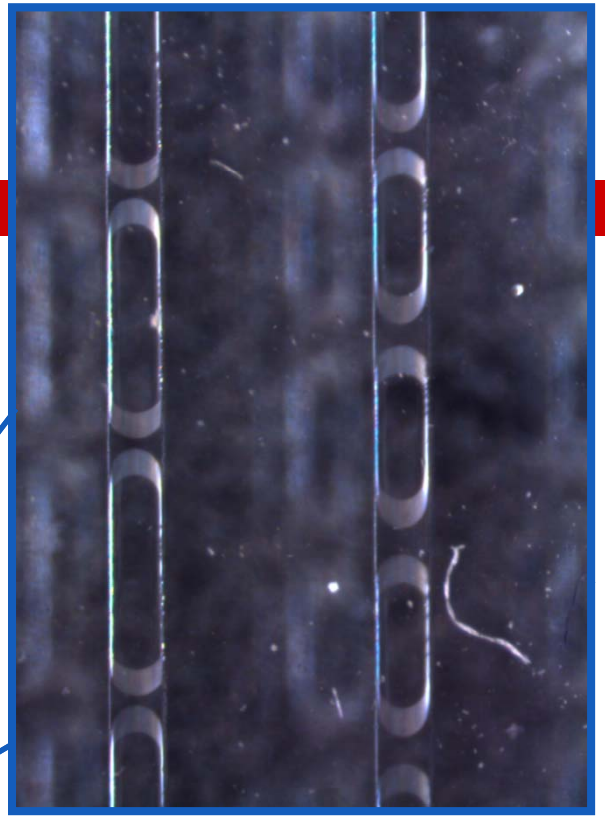
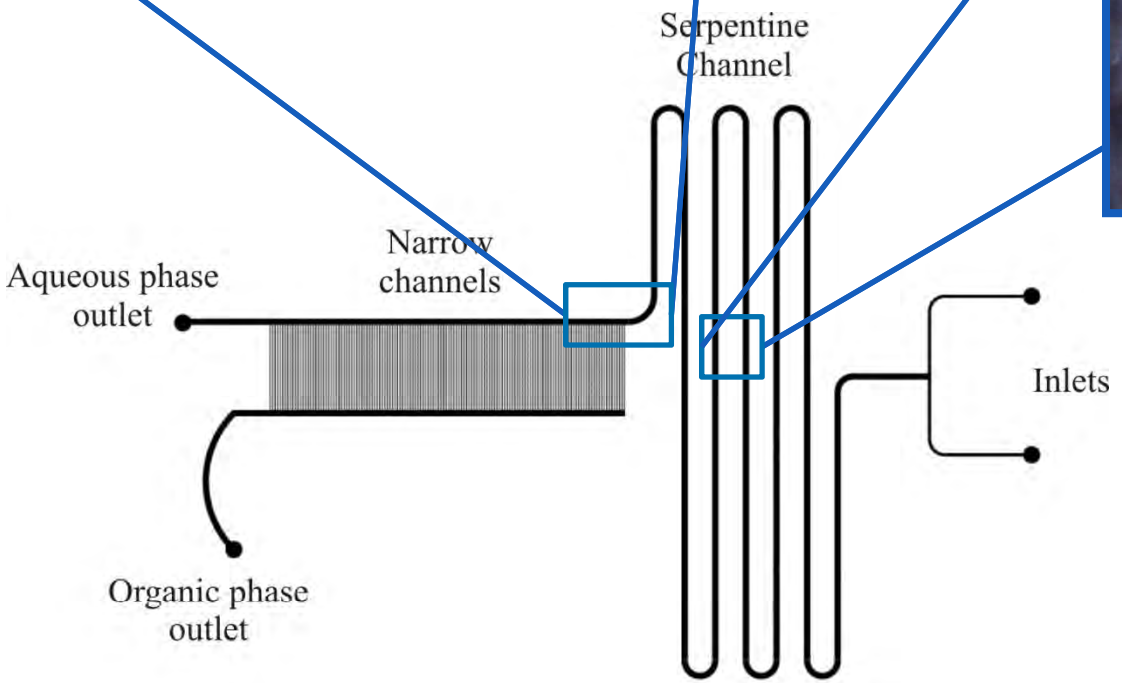


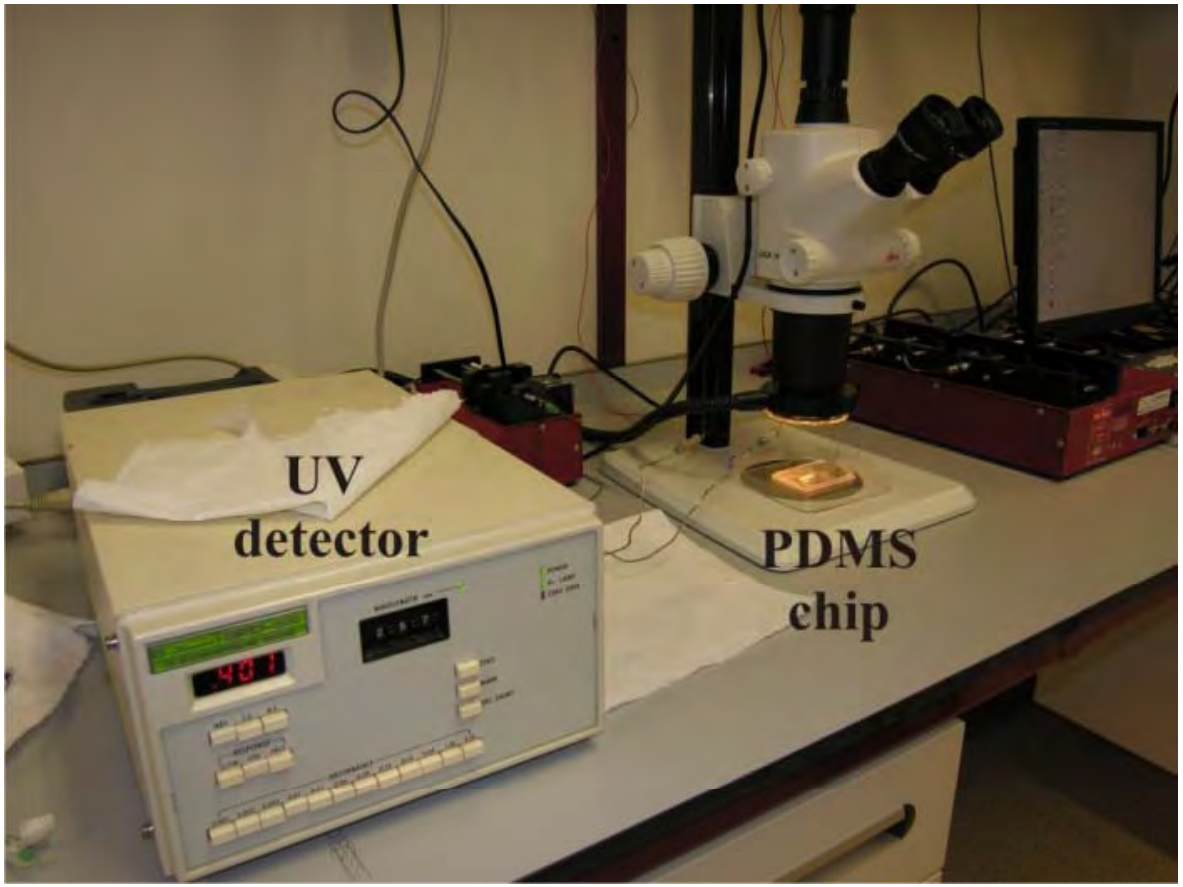


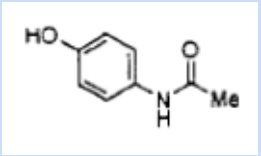
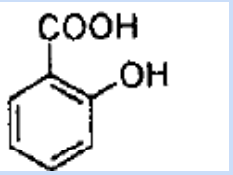
Slug flow



Set up

UV-Detector:
Shimadzu SPD-6A



Compound	λ (nm)*	Structure	pKa
Paracetamol (Mw 151.17 g/mol)	Ac - 245 Alk - 257		9.5 -acid
Salicylic Acid (Mw 138.12 g/mol)	Ac - 236 Alk - 298		2.97-acid

*Moffat, A.C., Osselton, M.D., Widdop, B., Clarke's Analysis of Drugs and Poisons, London: Pharmaceutical Press, 3rd edition (2003), volume 2. Pharmaceutical Press

Standard method

V = 10 mL
t = 2h 30 min

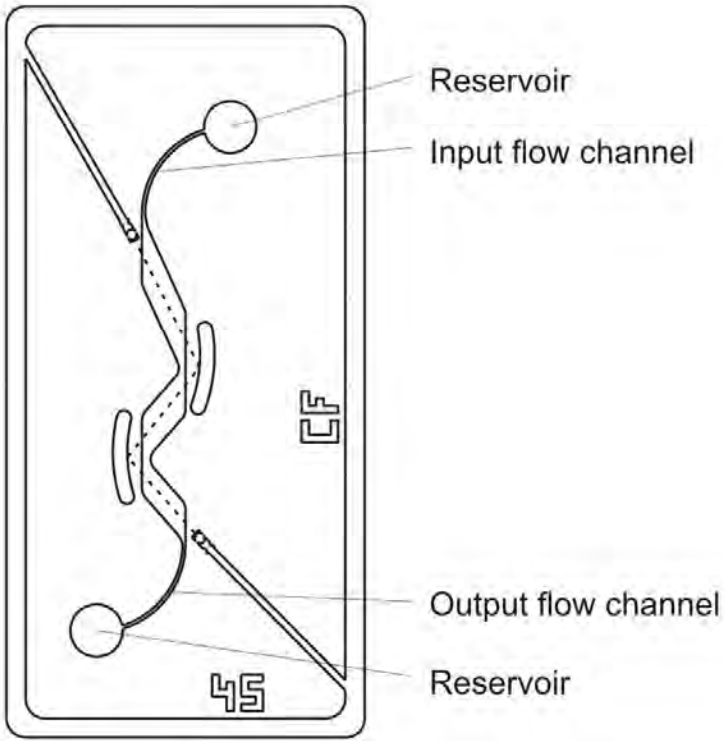
Compound	Log D
Salicylic acid	-1.68 ± 0.01
Paracetamol	0.31 ± 0.01

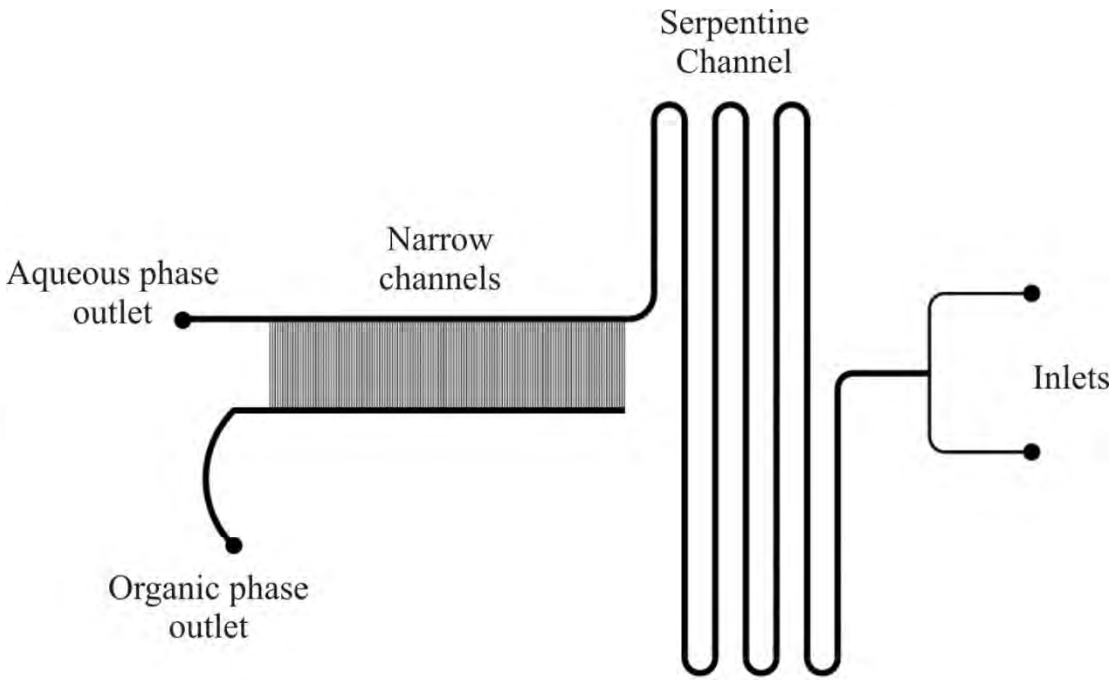
Chip

V = 120 nL
t < 2 min

Compound	Log D
Salicylic acid	-1.69 ± 0.01
Paracetamol	0.36 ± 0.01

Summary


Reservoir
Input flow channel
CF
Output flow channel
45
Reservoir


Serpentine Channel
Narrow channels
Aqueous phase outlet
Inlets
Organic phase outlet

Acknowledgements

Prof. Dr. E.M.J. Verpoorte
P.P.M.F.A. Mulder
M. Van Dijk
W.I. van Leeuwen-Hangyi
M.Lukkien
J. Meindertsma

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Thank you for your attention

Available materials (1)

Silicon

- crystalline
- semiconductor
- transparent at λ > 1.1 mm
- high mechanical strength

- technology well developed (integrated circuits, early 60's)
- bulk etching (3-D structures)
- surface micromachining (2-D structures)
- dry or wet processing

Glass (e.g. Pyrex, borofloat)

- amorphous
- electrical insulator

- bulk etching (like silicon)
- large research lab

Available materials (2)

Polymers

- wide variety (PMMA, PC, PDMS, etc.)
- choice of optical / chemical properties

- *Replication techniques*
  - hot embossing
  - injection molding
  - casting

- resolution: μm to nm

pH monitoring

Cell Medium contains 2 buffer systems:

- hepes buffer
- carbonate buffer

- Measurements will take place in a 5% CO_2 incubator at 37^{o} C

Medium has a pH indicator: phenol red

[*] production information sheet from Sigma-Aldrich

Compound	λ (nm)	pH	Log D
Paracetamol	254 (HPLC)	7.4 (35mM phosphate buffer)	-0.62
Caffeine	254 (HPLC)	7.4 (35mM phosphate buffer)	-0.76
Salicylic Acid	254 (HPLC)	7.4 (35mM phosphate buffer)	-1.31

Hanna et al, Anal. Chem. 70 (1998) 2092-2099

Compound	λ (nm)	pH	Log D	
			Flow system	Batch method
Paracetamol	245	7.4 (20mM phosphate buffer)	0.42	0.38
Caffeine	272	7.4 (20mM phosphate buffer)	-0.08	-0.32
Salicylic Acid	296	7.4 (20mM phosphate buffer)	-1.41	-1.44

Carlsson et al, Analytica Chimica Acta 423 (2000) 137-144