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Microfluidic devices applications to micro & nanoencapsulation

Mário Ricardo Góngora-Rubio

Slides do trabalho apresentado no South-American Symposium Microencapsulation, Limeira, 2012 e Workshop em Microfluída, 2., 2012, Campinas

South-American Symposium on Microencapsulation

MICROFLUIDIC DEVICES APPLICATIONS TO MICRO & NANOENCAPSULATION

Mário Ricardo Gongora-Rubio – gongoram@ipt.br

Center for Process and Product Technology
Chemical Processes and particle technology laboratory
CTPP-LPP

SUMMARY

- Introduction
- Micro Technology
- Micro Fluidics
- Microfluidic Devices in Micro & Nanoencapsulation
- Conclusion

Bioencapsulation Thematic Workshop

INTRODUCTION

ipt

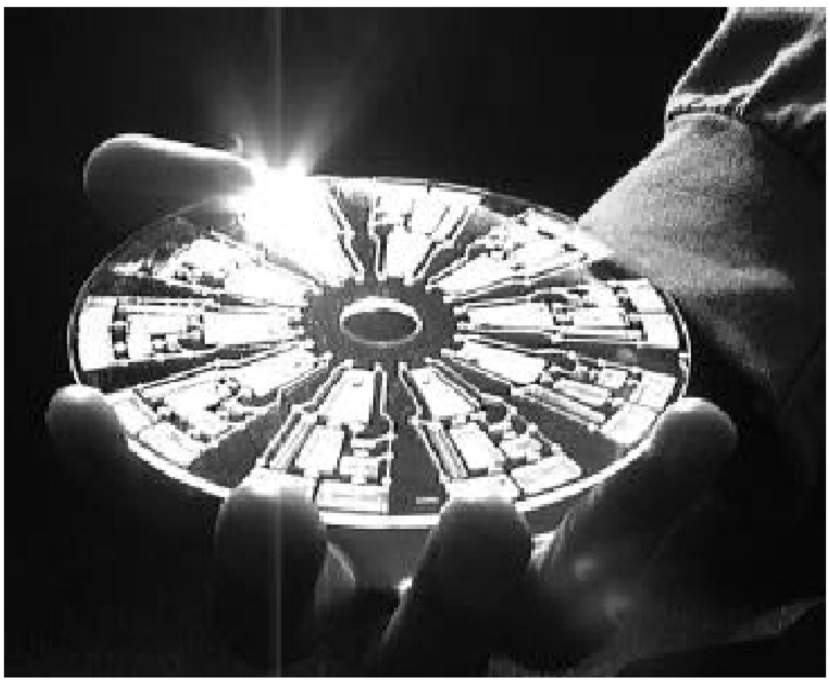
IPT

- Institute for Technological Research of the State of São Paulo S.A.
- One of the first applied R&D&I institutions in Brazil and the largest applied multipurpose R&D&I institution in Latin America
- Linked to the Secretariat of Development of the State of São Paulo
- IPT provides technological solutions to public and private companies and institutions

MICROTECHNOLOGY

WHAT IS MICROTECHNOLOGY?

Is an outstanding strategy for miniaturization and integration where the same principles as in microelectronics, are applied to Mechanical, Acoustic, Optical, Magnetic, Thermal, Chemical or Biotechnical components and systems.



VALUE OF MICROTECHNOLOGY

MICROSYSTEM PLATFORMS

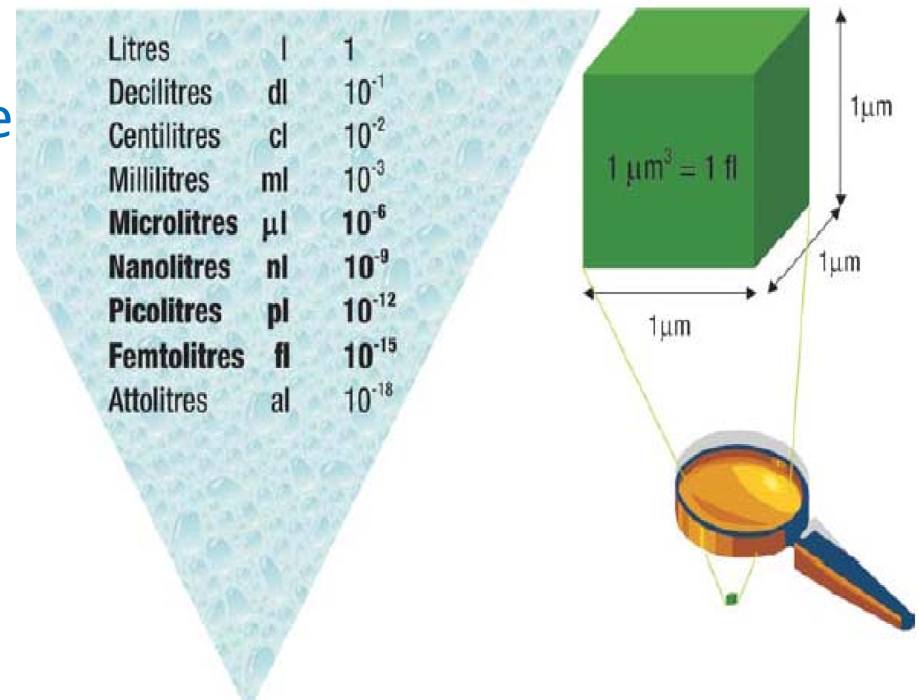
Parameter	ICs	MEMS	µTAS	MECS
Function	Signal processing	Signal acquisition & Control	'Lab on chip'	Process intensification
Primary Materials	Semiconductors	Silicon, Ceramics, glass & polymers	Silicon, Ceramics, glass & polymers	Metals, Silicon, LTCC Ceramics, Glass & polymers
Key Element	Transistors	Transducers & actuators	Microfluidic pumps and valves	Microchannel arrays
Characteristic Feature Size	100 nm	µm	tens of µm	1 to 500 µm
System Size	mm to cm	mm to cm	mm to cm	mm to meters

MICROFLUIDICS

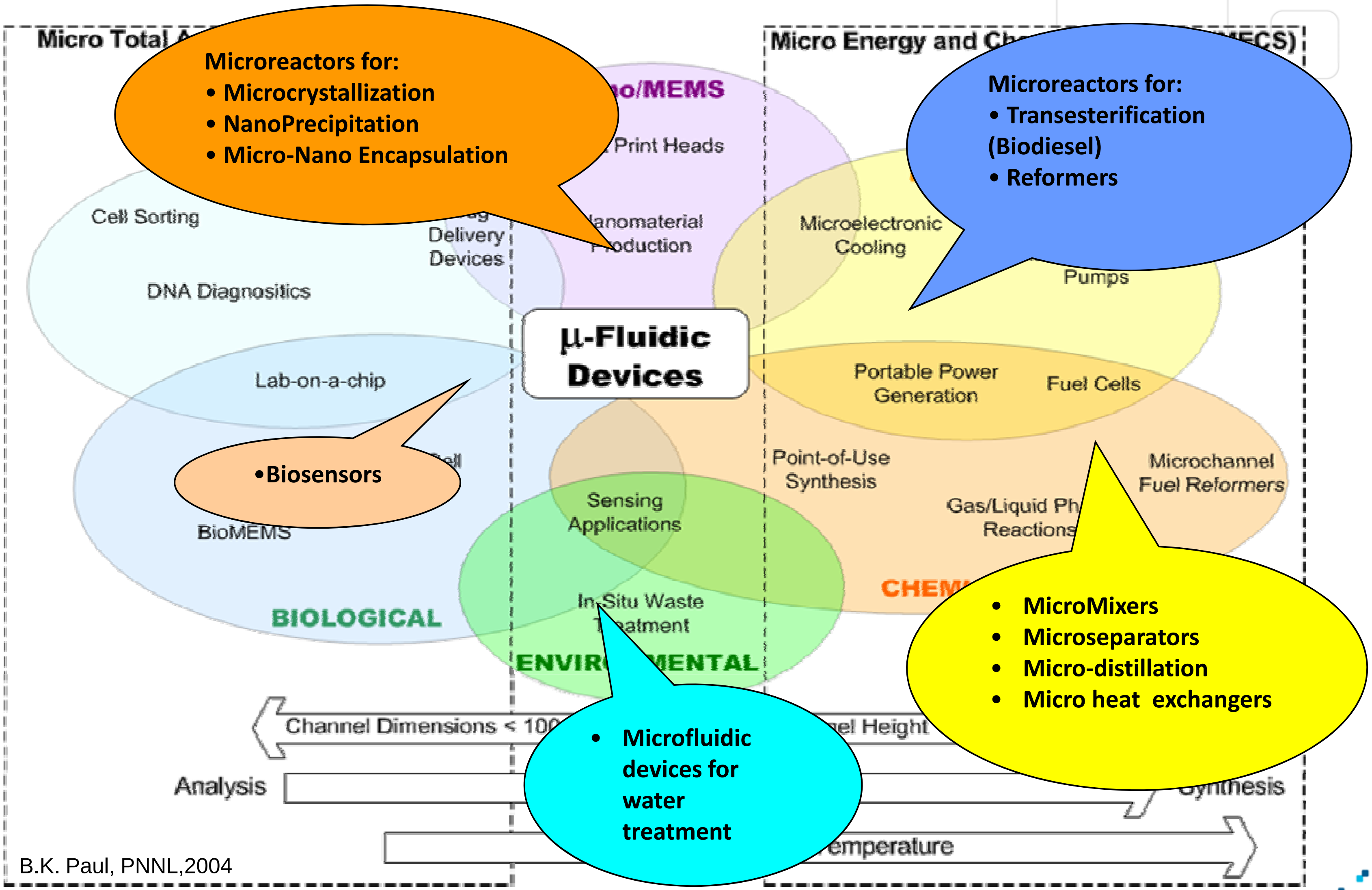
MICROFLUIDICS

Microfluidics is a technology which refers to the research and development of micro-scale devices which handle small volumes of fluids (as small as micro-, nano-, pico and even femtolitre volumes)

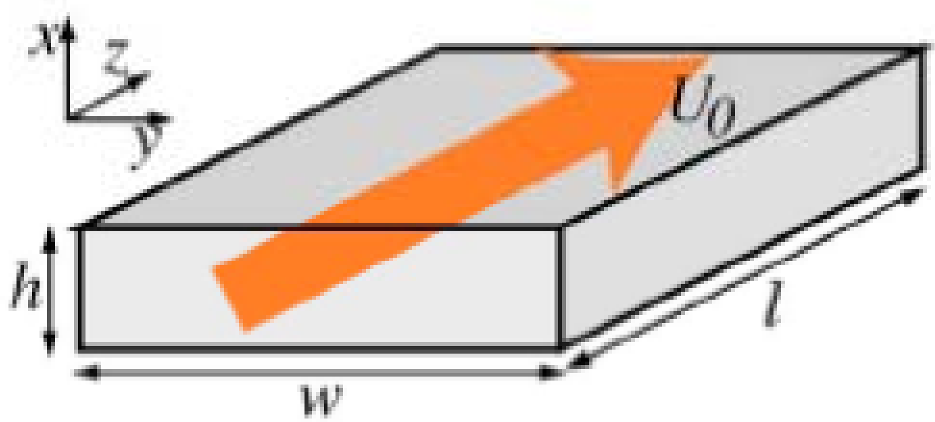
- Behavior of fluids in Micro scale
  - Control of small fluid volumes,
  - Fast response time,
  - Reaction condition well controlled,
  - Low energy consumption,
  - Small systems size,
  - Continuous processes
  - Low raw materials waste



MICROFLUIDICS & MICROREACTORS



NAVIER STOKES EQUATION



- The velocity field for a Newtonian fluid comply the Navier-Stokes equations, which essentially represent the continuum version of F = ma on a per unit volume basis:
- Inertial acceleration terms appear on the left and forces on the right.
- Here f represents external body force densities and $\vec{\sigma}$ forces per unit area
- When inertial forces are small when compared to viscous forces, which is usually the case in microfluidic devices, the nonlinear term can be neglected, leaving the Stokes equation
- In both cases, mass conservation requires

$$\rho\left(\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\cdot\nabla\mathbf{u}\right) = \nabla\cdot\vec{\sigma} + \mathbf{f} = -\nabla p + \eta\nabla^2\mathbf{u} + \mathbf{f},$$

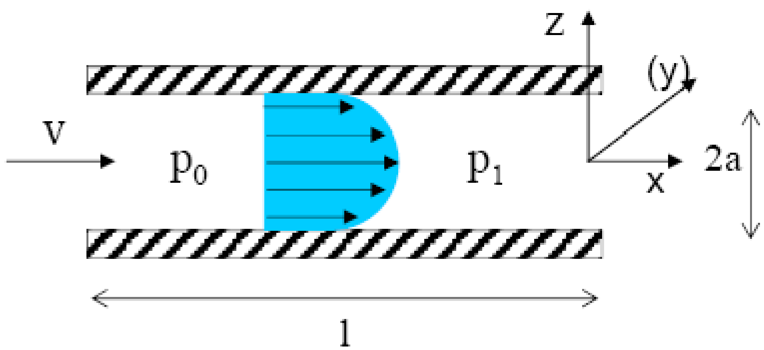
$$\rho\frac{\partial \mathbf{u}}{\partial t} = \nabla\cdot\boldsymbol{\sigma} + \mathbf{f} = -\nabla p + \eta\nabla^2\mathbf{u} + \mathbf{f}.$$

$$\frac{\partial \rho}{\partial t} + \nabla\cdot(\rho\mathbf{u}) = 0,$$

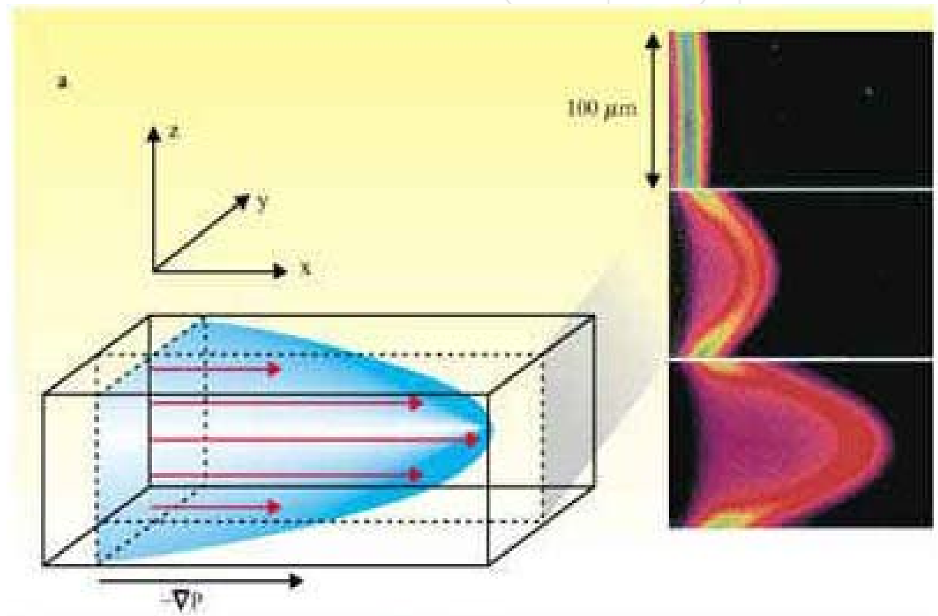
T. M. Squires, S. R. Quake
Rev. Mod. Phys., Vol. 77, No. 3, 2005

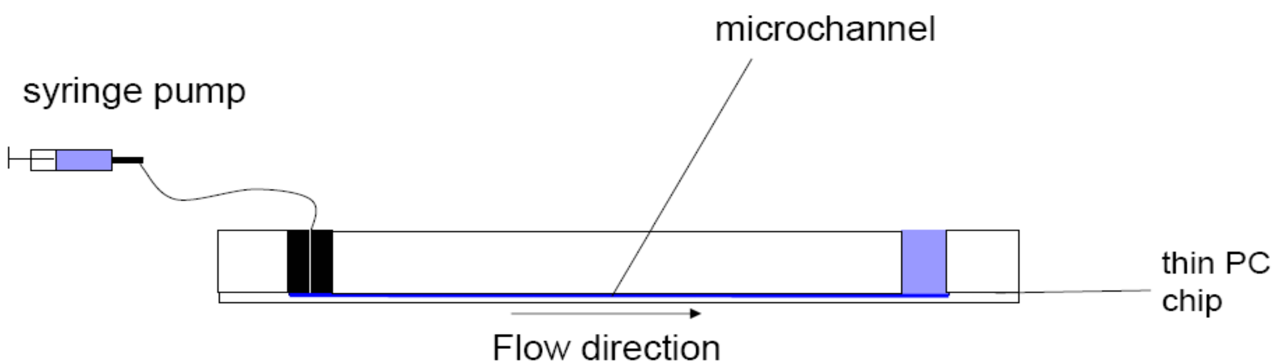
PRESSURE-DRIVEN FLOW

- **Poiseuille flow** – fully developed pressure driven



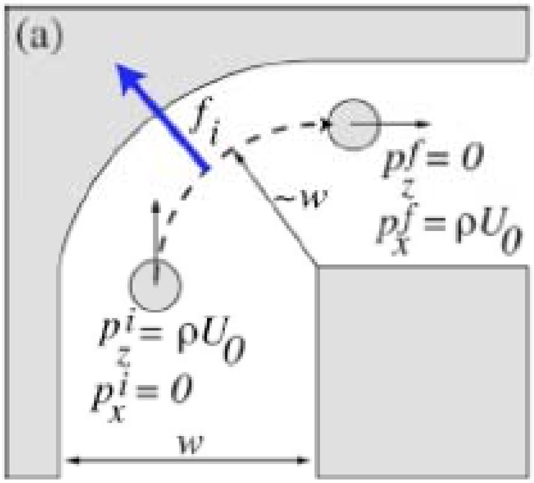
$$v_x(y,z) = \frac{y^2 - a^2 - z^2}{4\eta}\frac{\Delta p}{L}$$

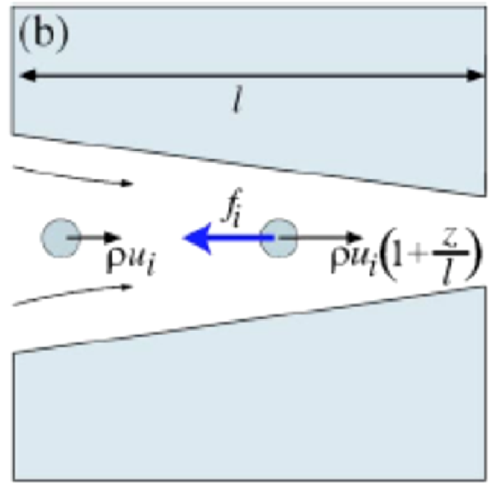




INERTIAL FORCES IN MICROFLOWS

Microflow Rounding a Corner





Flow Through a Channel Contraction

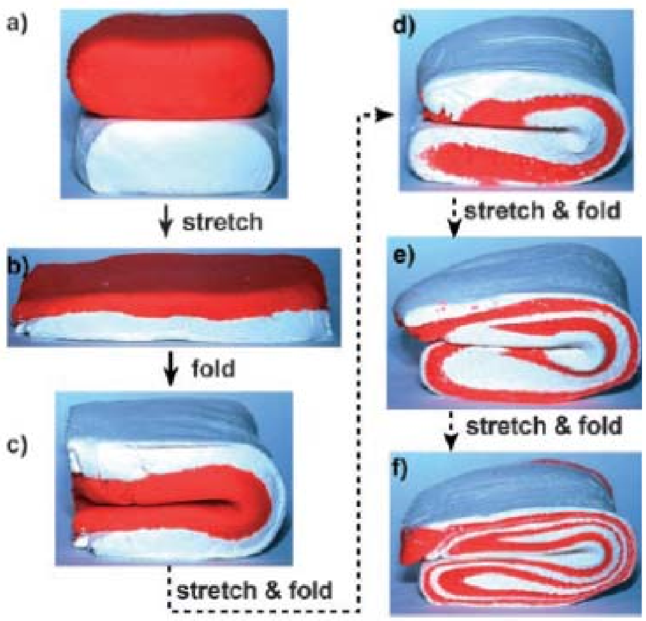
- A fluid that flows with velocity U_o through a microchannel of width w that makes a sudden right turn. During the turn time $\tau_o \approx w/U_o$, a fluid element rounding the corner loses momentum density ρU_o by exerting an inertial centrifugal force density $fi \approx U_o / \tau_o = \rho U_o{}^2 / w$.
- Thus the force on the fluid due to a curved streamline points outwards centrifugally.
- By mass conservation, the velocity increases as u ≈ Uo(1+z/ l), causing a fluid element to gain momentum at a rate:

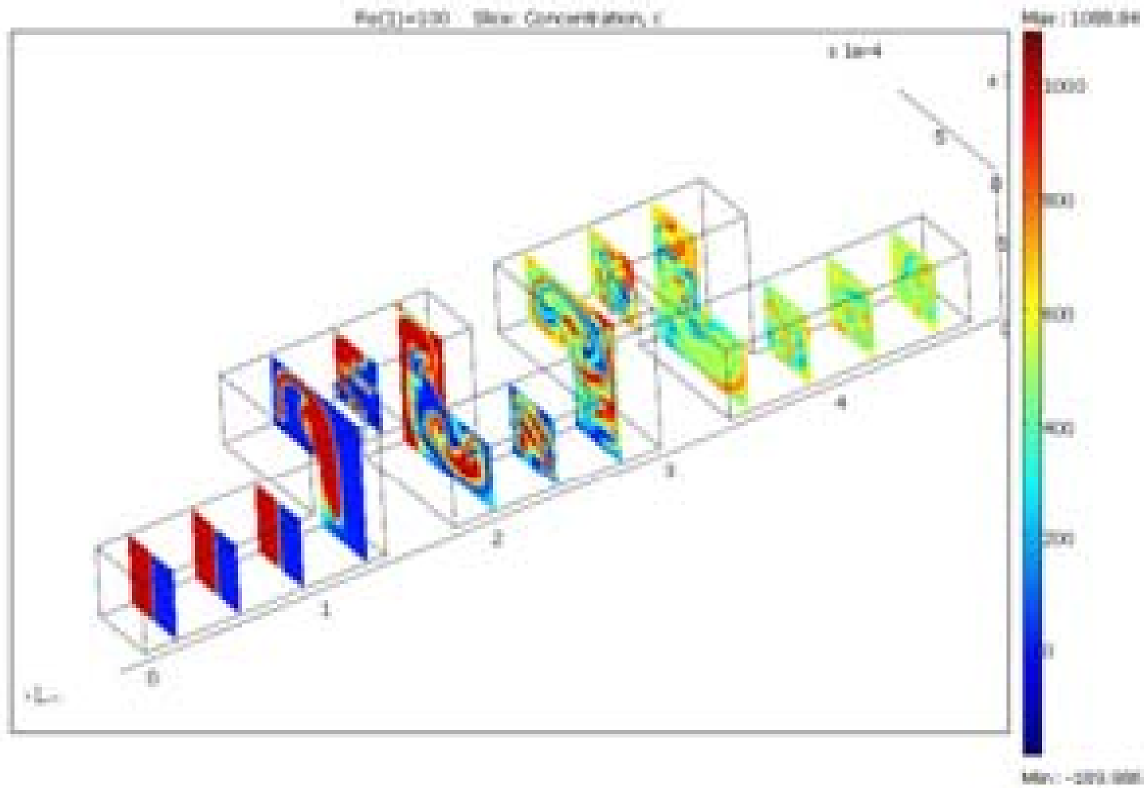
$$f_i \sim \rho \frac{du}{dt} = \rho U_0 \frac{du}{dz} \sim \frac{\rho U_0^2}{l}.$$

- In both cases, the inertial force exerted on the fluid is equal and opposite to the force required to accelerate each fluid element, and is the same for flows in either direction.

T. M. Squires, S. R. Quake
Rev. Mod. Phys., Vol. 77, No. 3, 2005

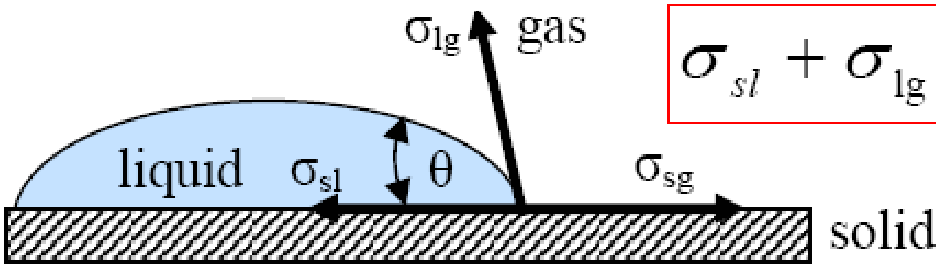
CHAOTIC ADVECTION MIXING





Chaotic advection mixing simulation in a 3D serpentine micromixer

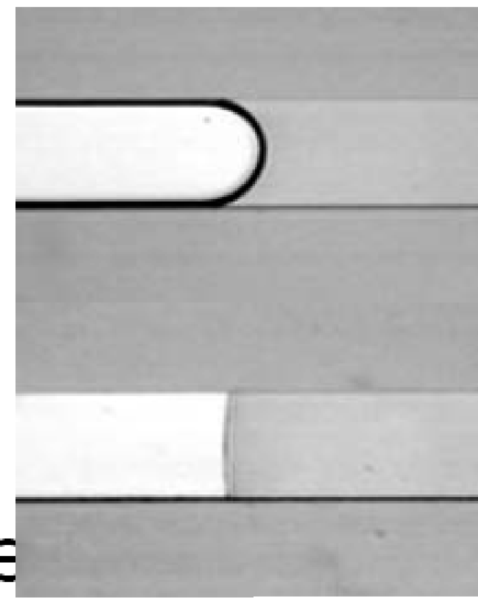
SURFACE TENSION



$$\sigma_{sl} + \sigma_{lg} \cos\theta = \sigma_{sg}$$

θ … contact angle
interfacial tensions:
σ_{sl}… solid-liquid
σ_{lg}… liquid-gas
σ_{sg}…solid-gas
p pressure
R radii of curvature of the interface surface

- θ < 90o → *wetting* (**hydrophilic**) surface
- θ > 90o → *nonwetting* (**hydrophobic**) surface



$$\Delta p = \sigma\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

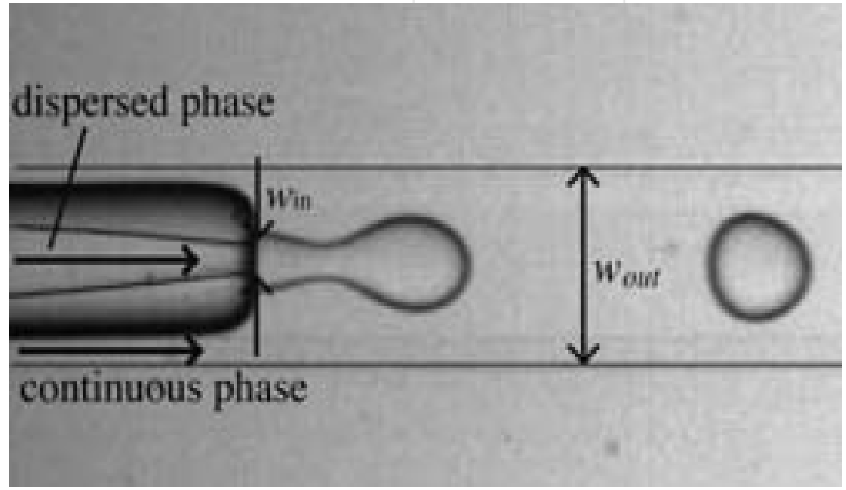
DROP GENERATION

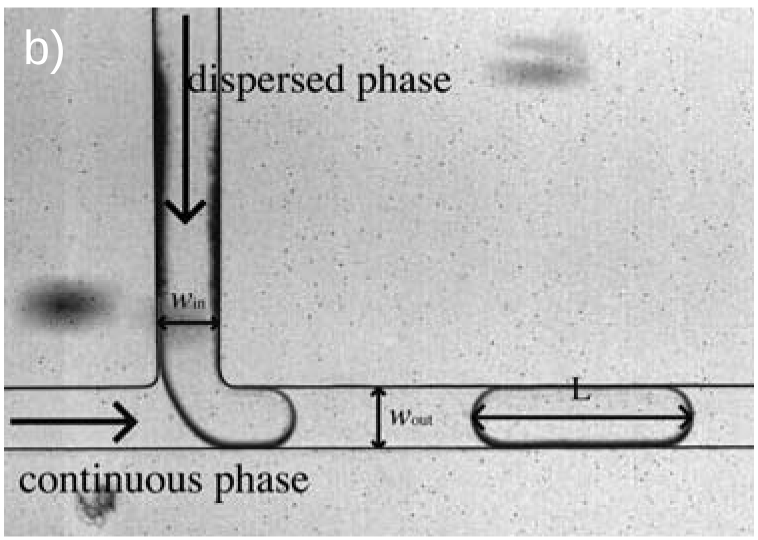
Three main approaches for drop generation based on different physical mechanisms are:

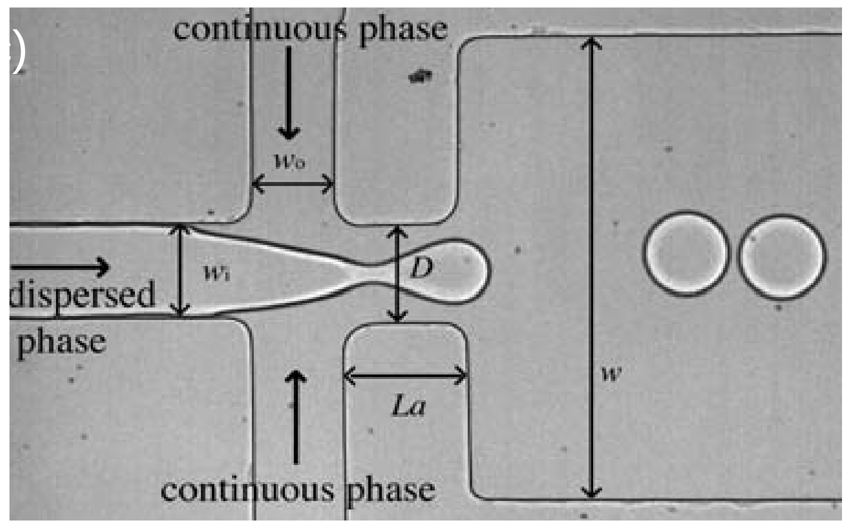
a) breakup in co-flowing streams

b) breakup in cross-flowing streams

c) breakup in elongational strained flows





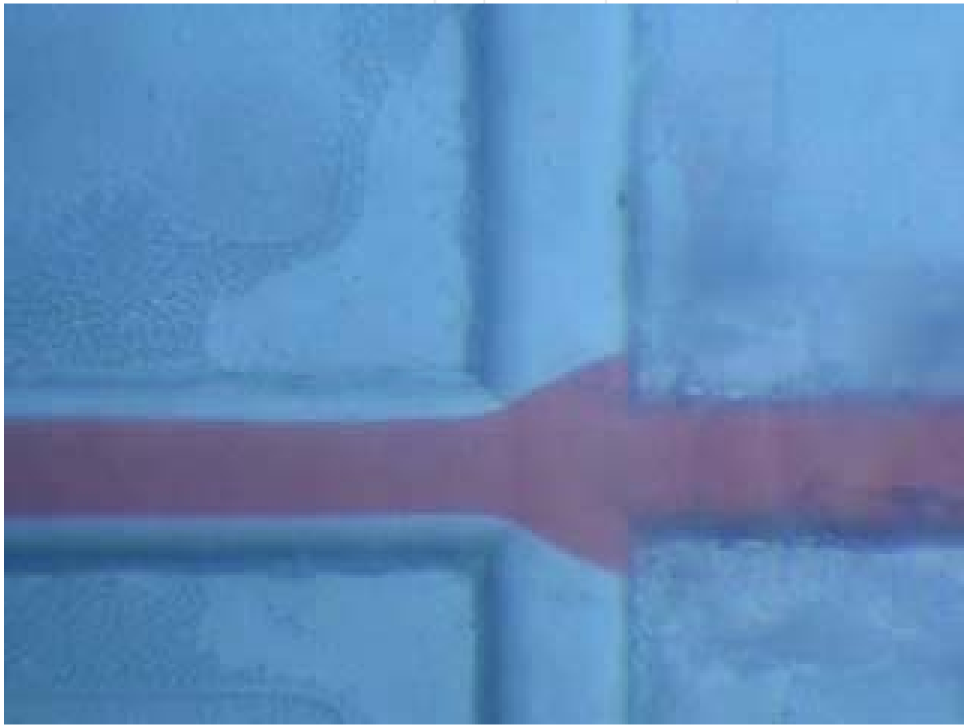


C. N. Baroud, F. Gallaire and R. Dangla
Lab Chip, 2010, 10, 2032–2045

HYDRODYNAMIC FLOW FOCUSING

Hydrodynamic flow focusing can be used as drop generator allowing drop control of frequency and size.

Can be used as well in diffusion based processes or reactions

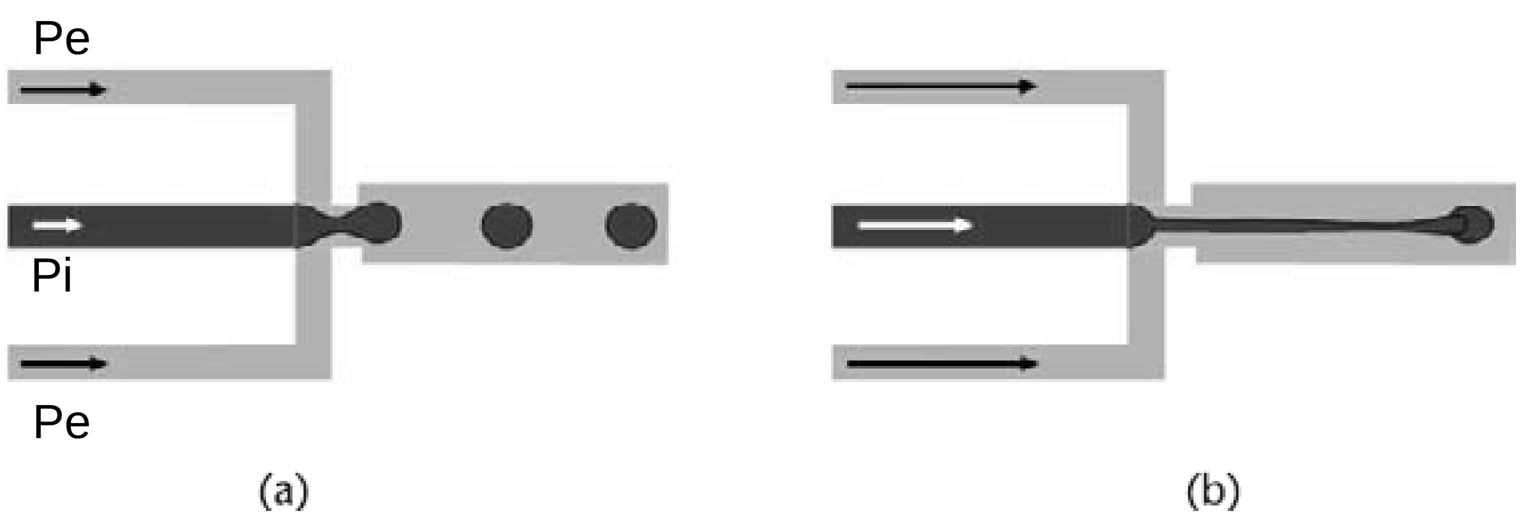


FLOW REGIMES IN FLOW FOCUSING DEVICES

The two principal flow regimes in flow focusing devices are:

DRIPPING AND JETTING.

In the **dripping** regime, the flow rates are small enough so that the droplet forms immediately after the nozzle. In the **jetting** regime, a thread or filament stretches far into the outlet channel

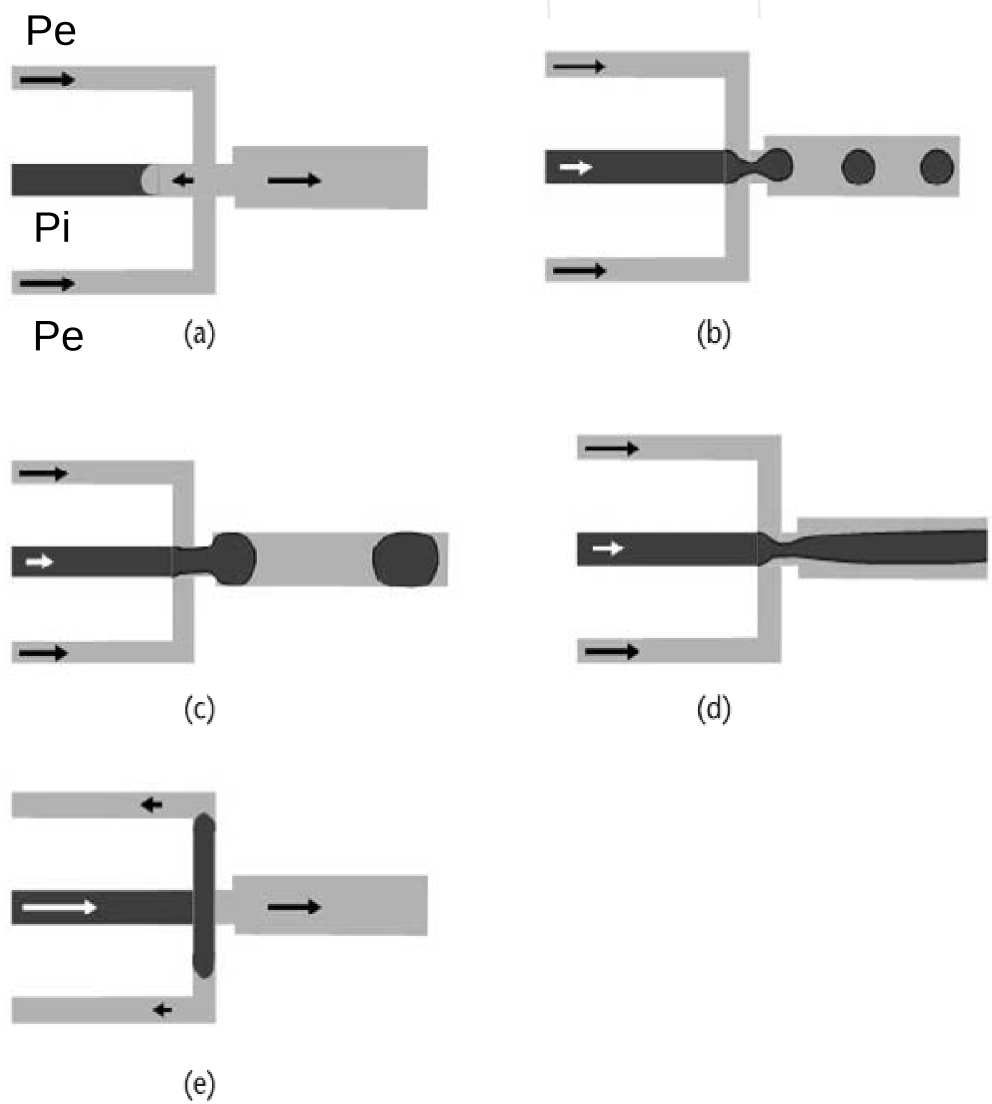


J. Berthier & P. Silberzan, Microfluidics for Biotechnology, 2ED, Artech House, 2010.

DRIPPING MODES IN MICROFLUIDIC FFD

Depending on the relatives values of the driving pressures Pi and Pe, different operating modes appear:

- (a) a flow reversal in the central channel if Pe >> Pi;
- (b) a droplet mode;
- (c) a plug mode — large droplets touching the walls;
- (d) annular flow mode — dispersed phase flowing inside the continuous phase;
- (e) reversal of the flow in the external channels if Pi >> Pe



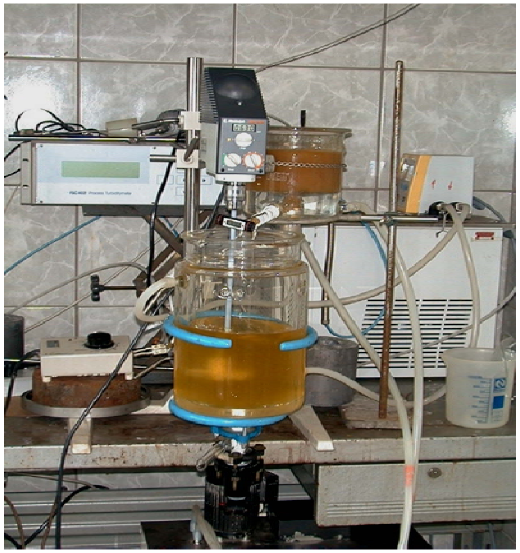
J. Berthier & P. Silberzan, Microfluidics for Biotechnology, 2ED, Artech House, 2010.

MICROFLUIDIC DEVICES IN MICRO & NANOENCAPSULATION

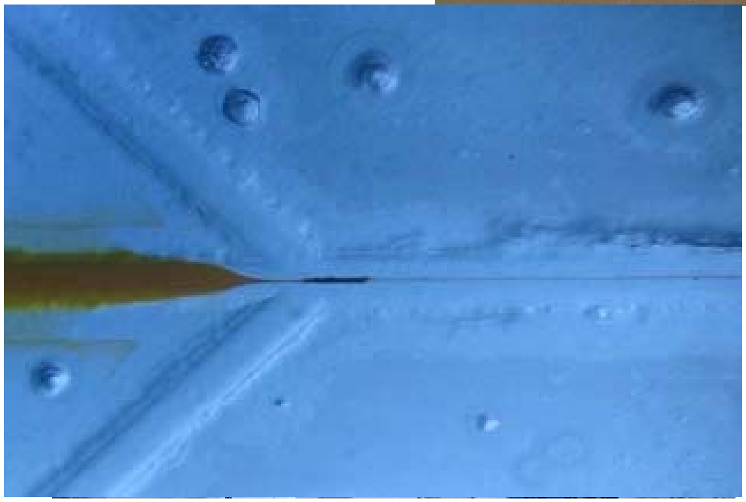
MICRO-NANOENCAPSULATION AT IPT

Technologies

- ❑ Spray drying
- ❑ Coacervation
- ❑ Emulsion/solvent extraction
- ❑ Gelification
- ❑ Polymerisation
- ❑ Electrospinning



Microfluidics



CONTINUOUS MICROFLUIDIC REACTORS

- Functional characteristics of microfluidic continuous reactors relative to conventional batch reactors comprise:
  - A high surface area to volume ratio;
  - Diffusion dominated mass transfer in laminar flow;
  - Intensified surface effects involving rapid heat and mass transfer;
  - Spatial and temporal control of reagents and products;
  - Scaling readiness (numbering-up)
  - The possibility to integrate processes and instrumentation systems on a single technology platform leading to the concept of the FAB ON A CHIP.

MICROFLUIDICS

Microprocesses → Micro & Nanoparticles

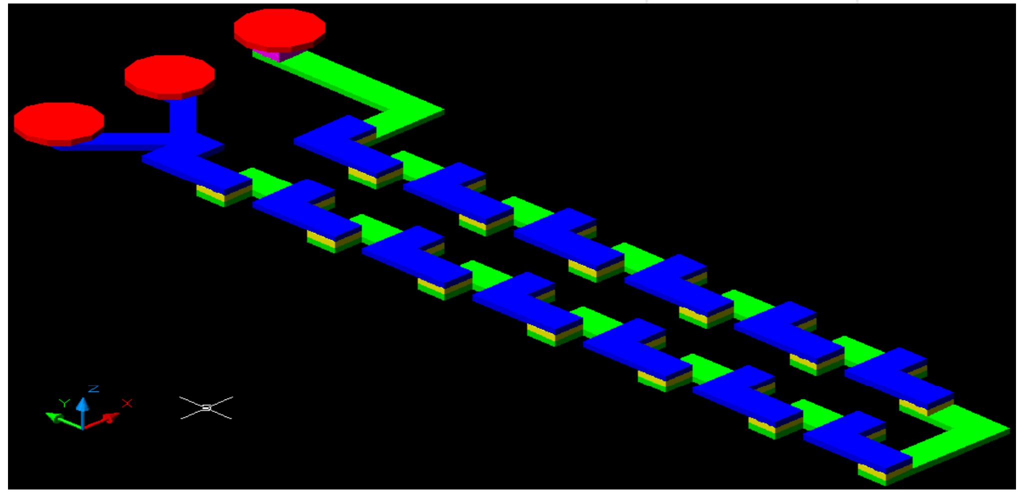
By combining geometry design of microchannels and fluid flow rate is possible to obtain particles with high size control, reproducibility and low polidispersivity.

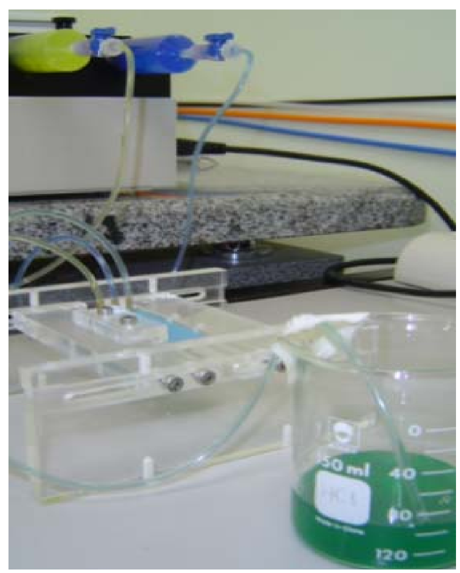
Microfluidics is a powerful tool to obtain particles in micro and nanoscale and for encapsulate drugs based on:

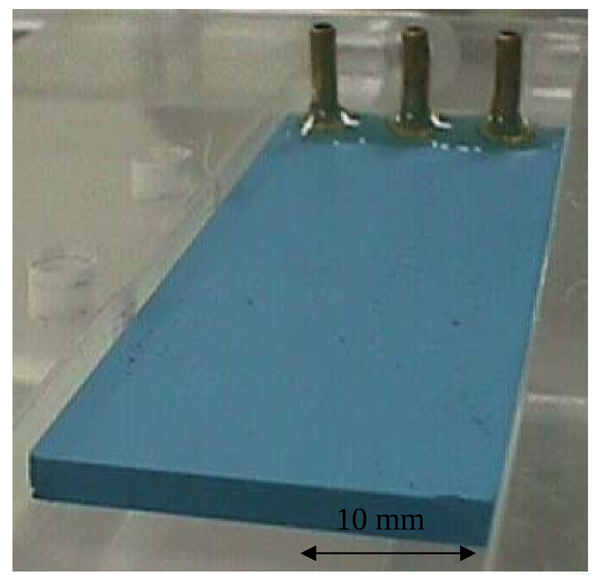
- Emulsions (simple & double)
- Liposomes
- Nanocrystals

3D MICRO MIXERS IN LTCC

- 3D Serpentine Micromixers can be used for chemical Microreactors in order to fabricate emulsions, particle packaging and nanomaterial fabrication

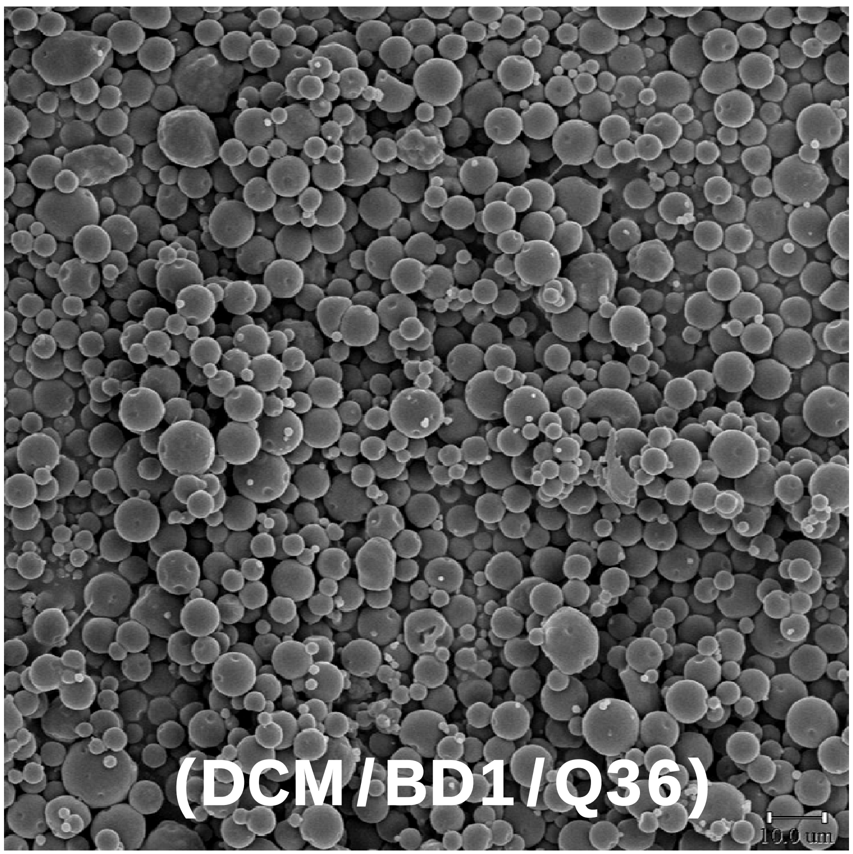




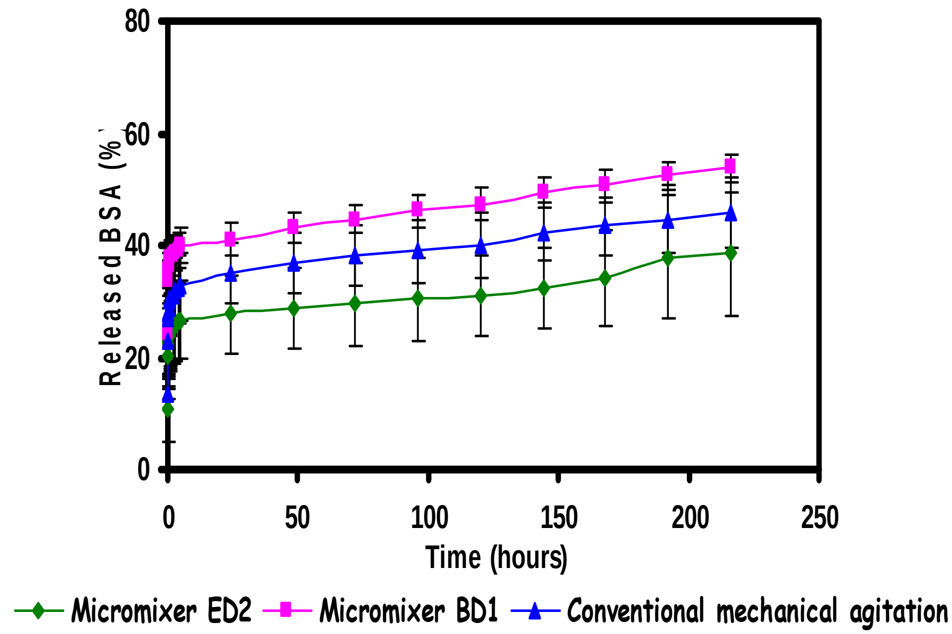


MICRO PARTICLES VIA MICROFLUIDICS

PLGA (Poly (DL-lactide co-glycolide) microspheres loaded with BSA (Bovine serum albumin) (750x)

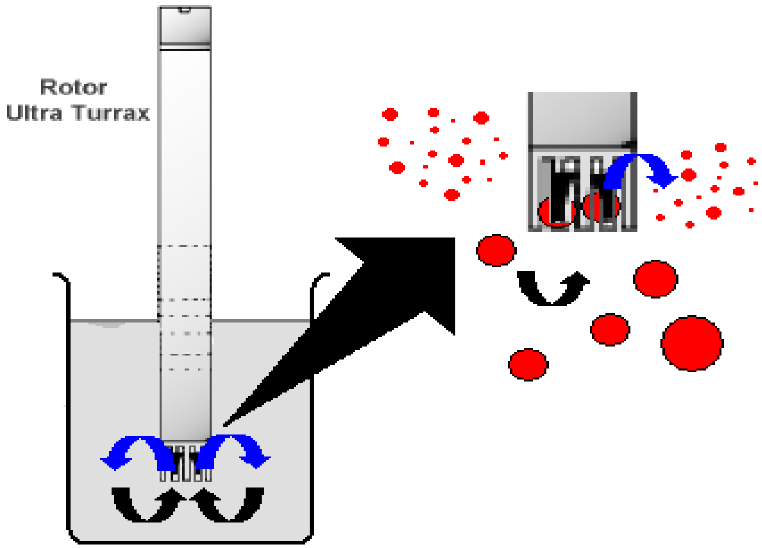


Comparison of particle release obtained with micromixers and standard methods (Turrax agitation)

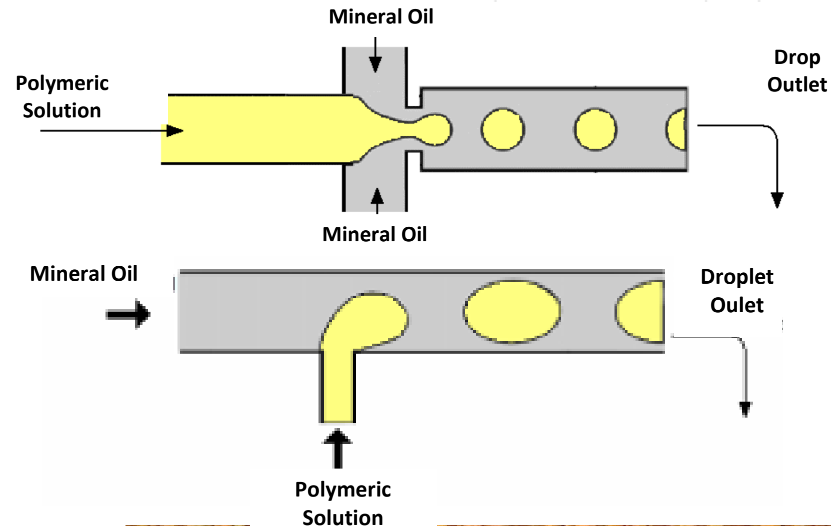


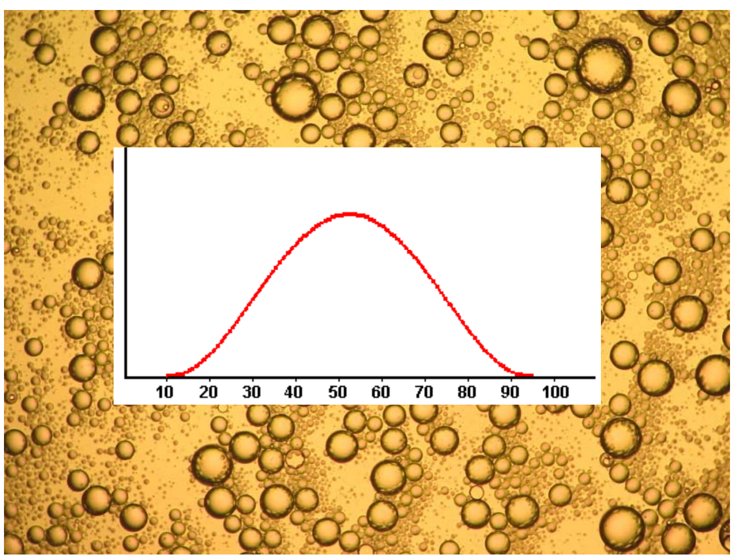
M. Ribeiro-Costa, et al. Preparation of protein-loaded-PLGA microspheres by an emulsion/solvent evaporation process employing LTCC micromixers, Powder Technology Vol-190, p.107–111, (2009)

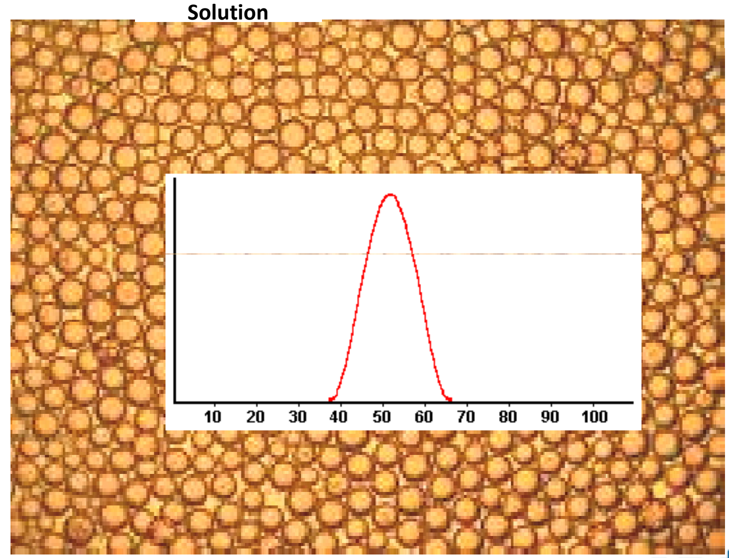
EMULSIONS: BATCH VS CONTINUOUS



Microfluidic Devices







ADVANTAGES OF PRODUCING EMULSION VIA MICROFLUIDICS

In Products

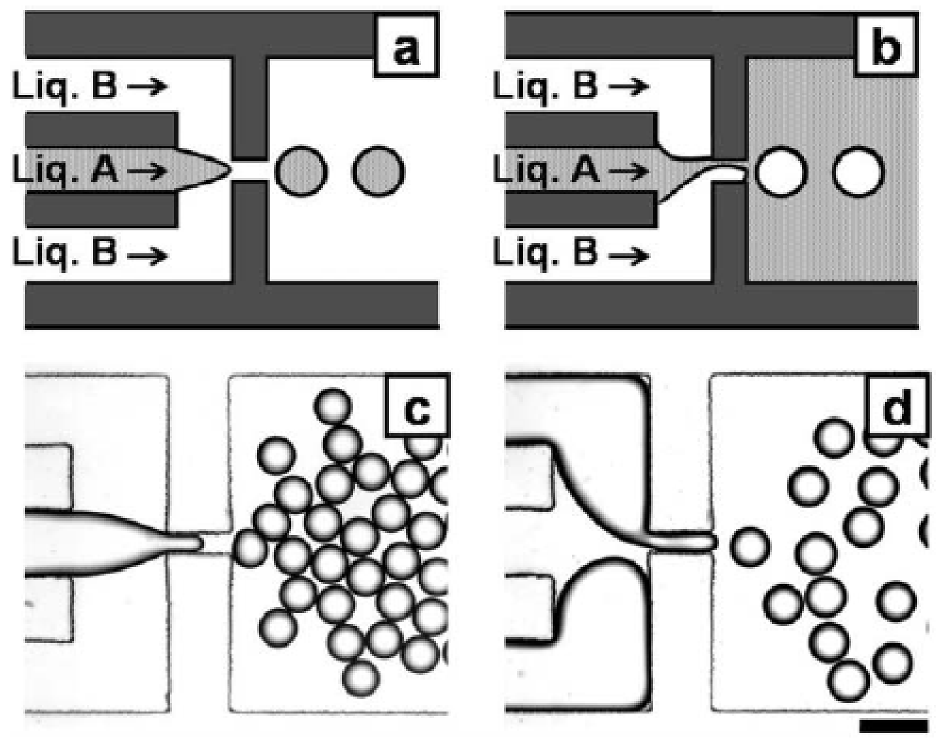
- Formulation flexibility (single & double emulsions)
- Drop distribution control
- Less raw material consumption (less surfactant for emulsion stabilization)
- Emulsion can stand thermal processes
- System free of contamination

In Processes

- Elimination of mixing mechanical forces, emulsions based on microfluidic principles
- More portable equipment with less size and volume
- Less energy consumption
- Scaling possibility (numbering-up)
- Maintenance easiness

MICROFLUIDIC SINGLE EMULSIFICATION

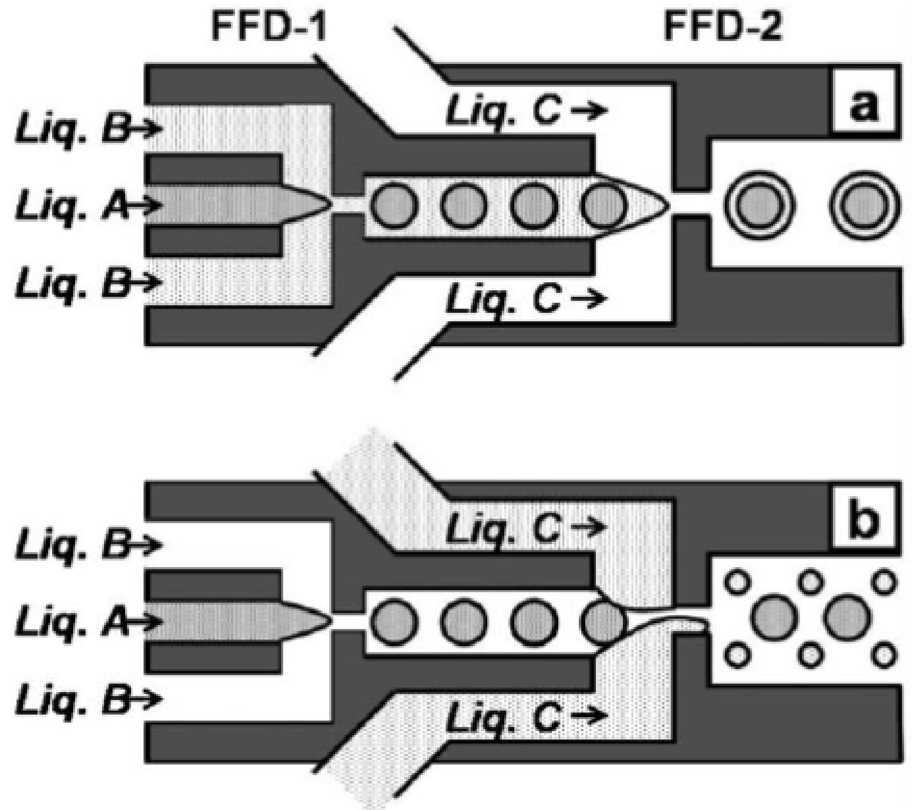
Using one flow focusing device enable us to obtain single emulsions water/oil with controlled characteristics



Soft Matter, 2007, 3, 986–992

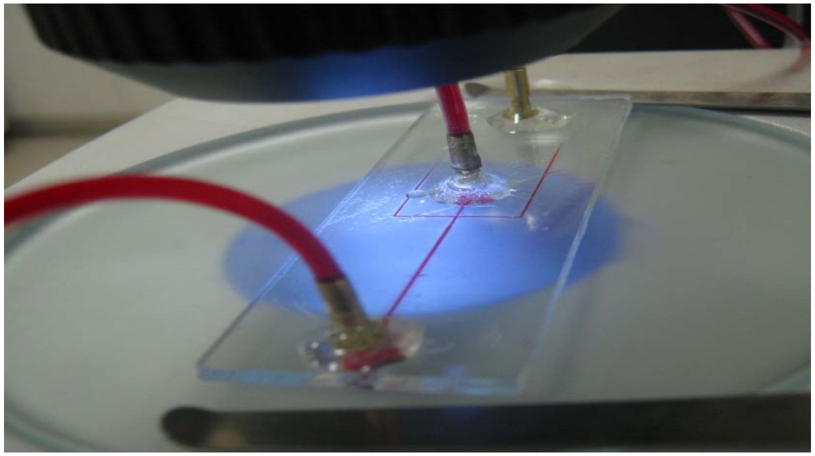
DOUBLE EMULSIFICATION

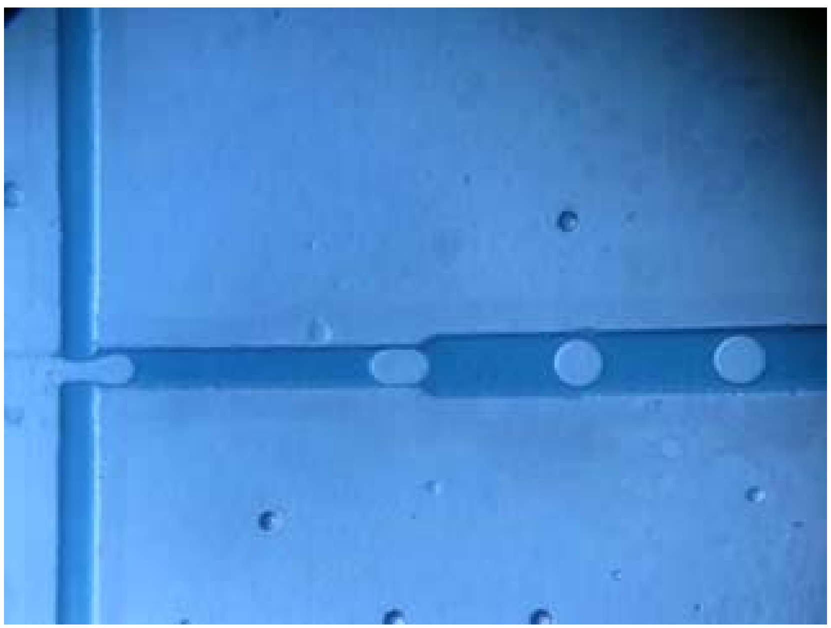
Using two consecutive flow focusing devices enable us to obtain double emulsions oil/ water/oil/ with controlled characteristics



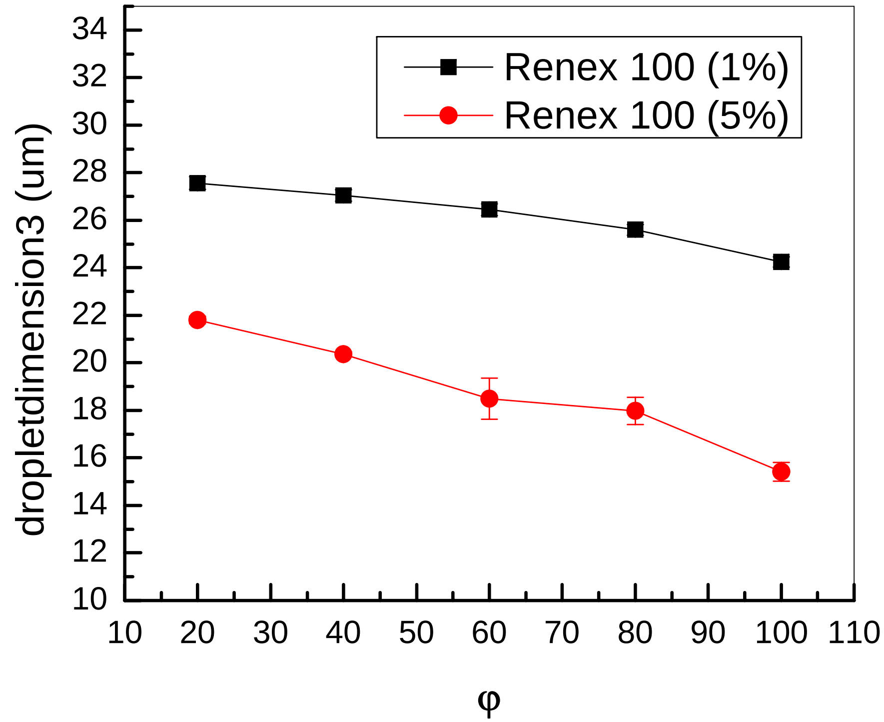
Soft Matter, 2007, 3, 986–992

EMULSIONS USING GLASS DEVICES





Single emulsion production (Water-oil)
Drop size Vs. input fluid ratio



J. N. Schianti, et al. Emulsion production using glass microfluidic devices, Proc: IBERSENSOR 2010

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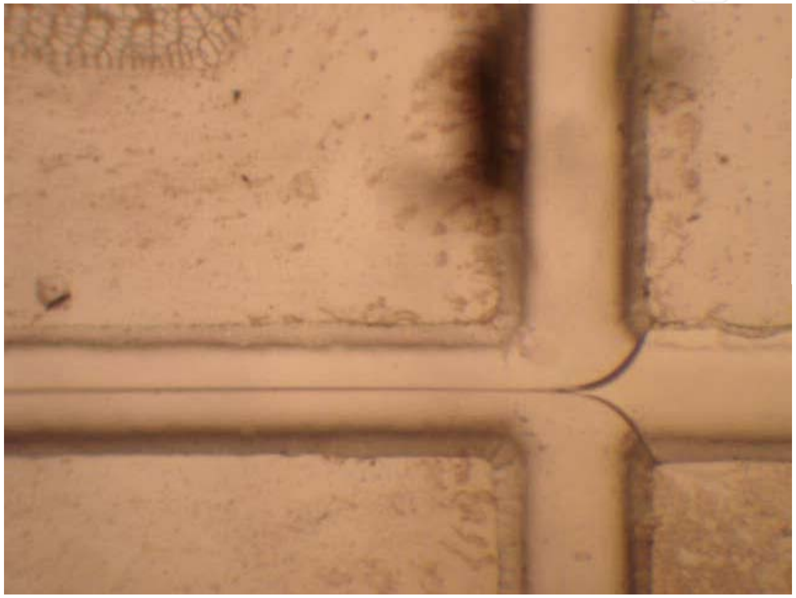
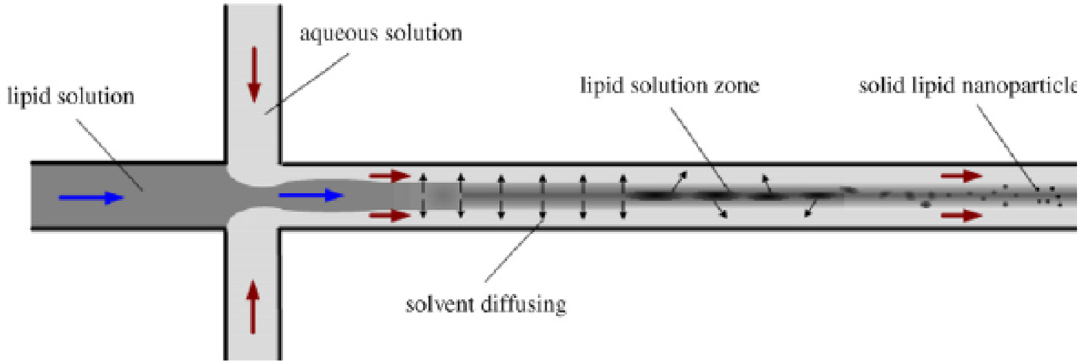
NANOLIPOSOME PRODUCTION VIA MICROFLUIDICS

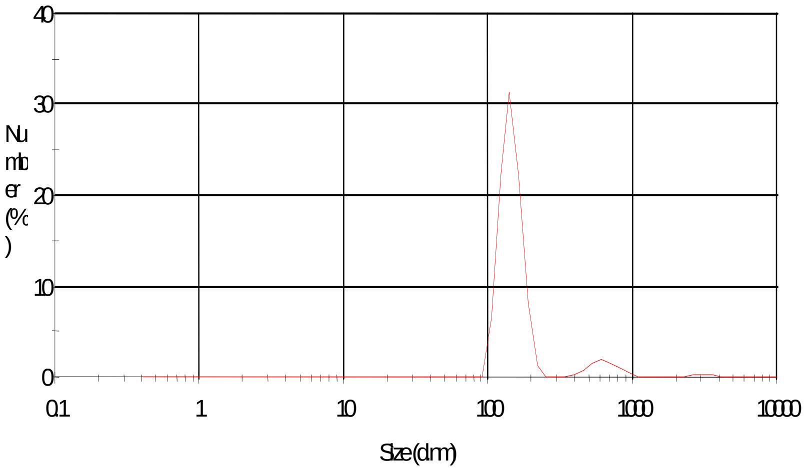
- BOTTOM - UP

Liposome Microfluidic Hydrodynamic Focusing

Glass Microfluidic device in flow focalization regime were used to obtain nanoliposomes

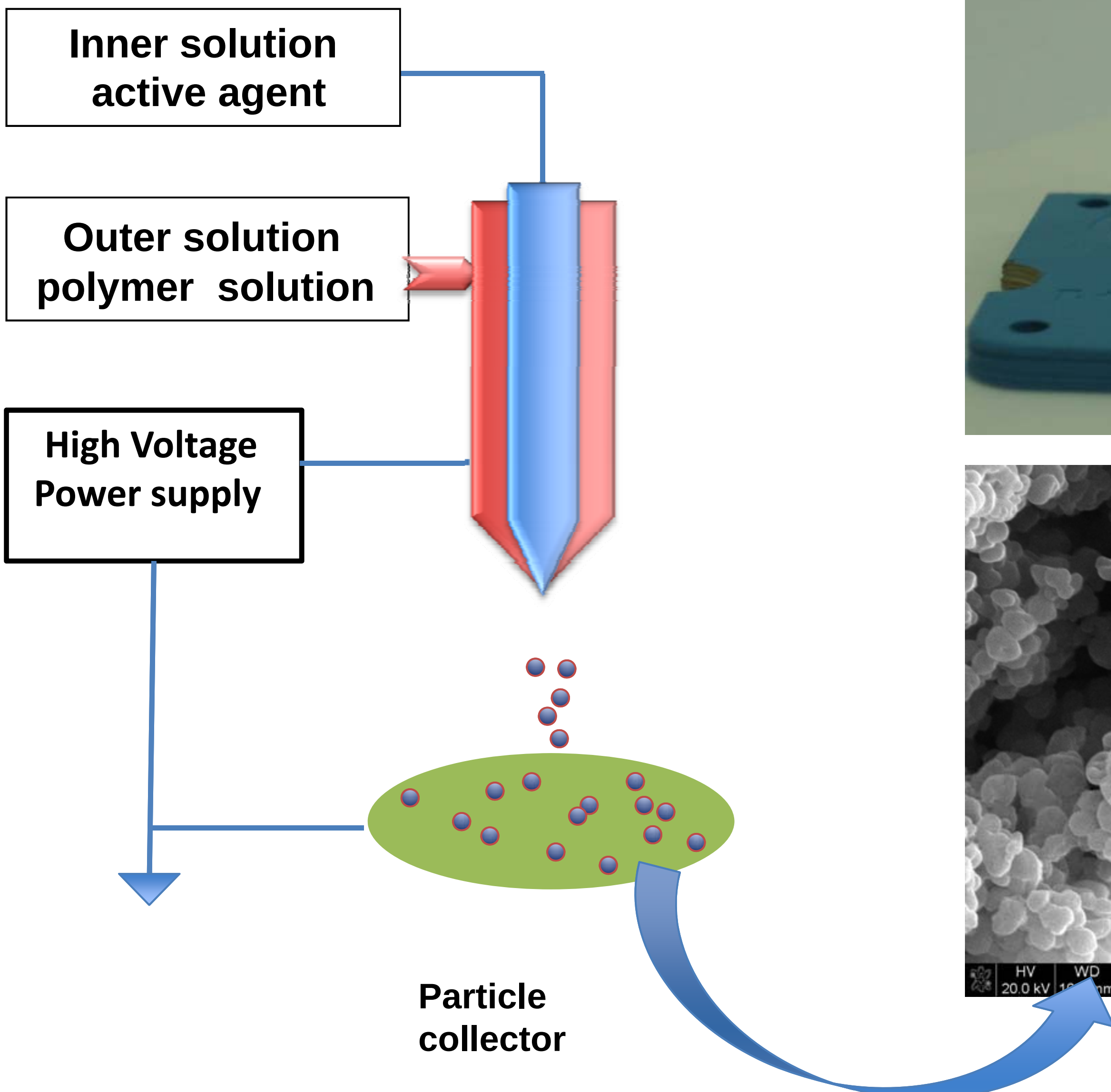


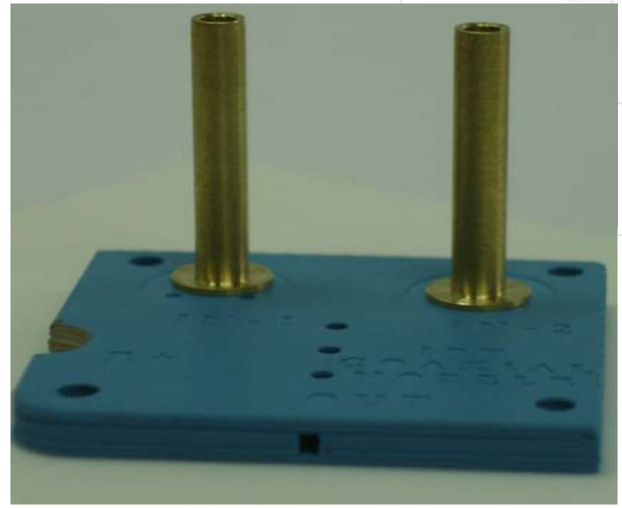


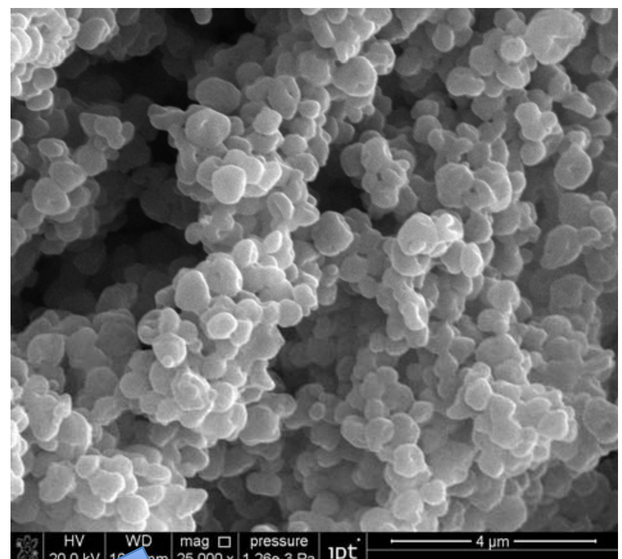


J. N. Schianti, et al. Glass flow focusing microfluidic device for nanoliposome production, Proc: IBERSENSOR 2010

ELECTROSPRAY MICRODEVICES





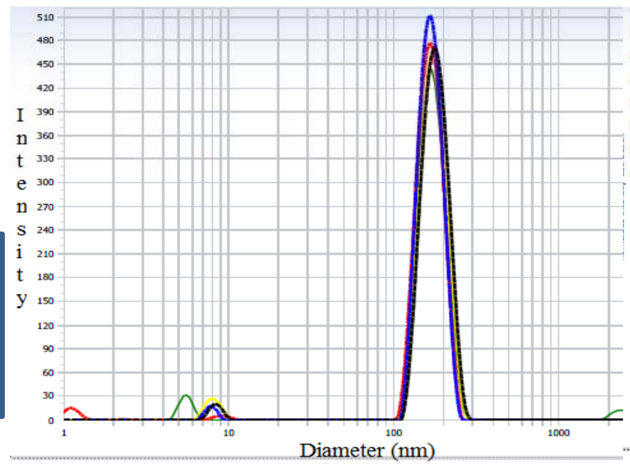


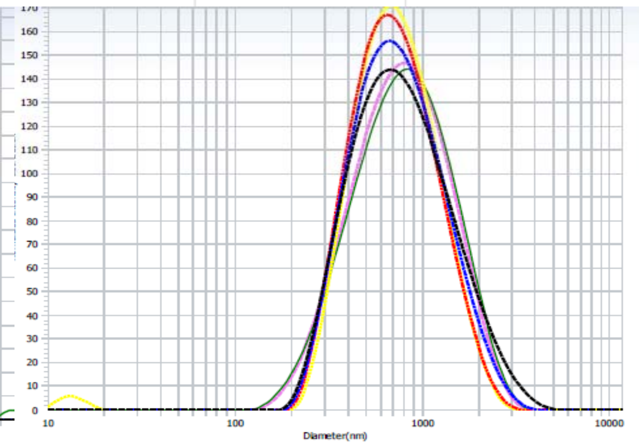
MICROFLUIDIC PROCESS FOR MICRO AND NANO CRYSTALS

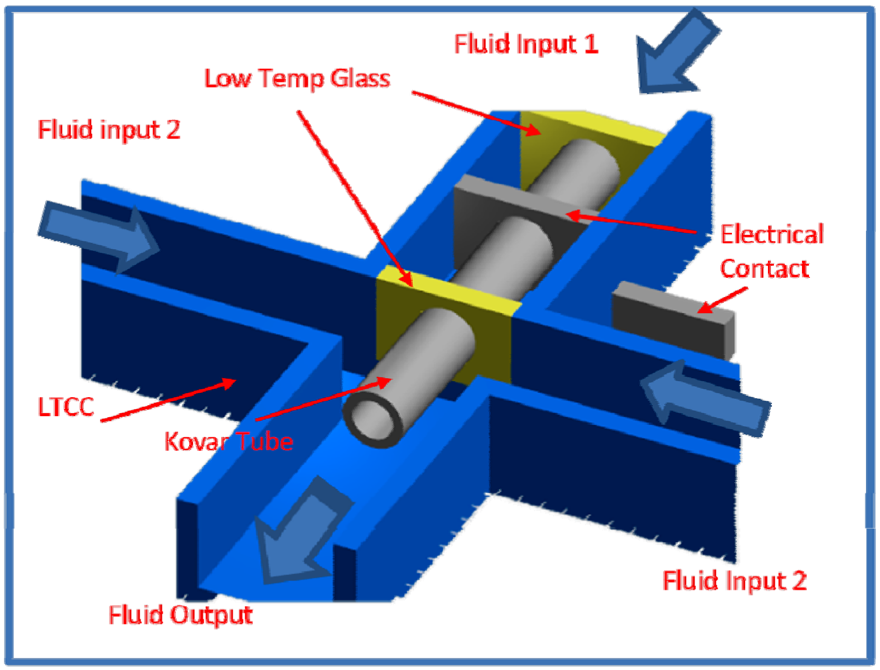
CRYSTALLIZATION PROCESS TO OBTAIN RIFAMPICIN AMORPHOUS NP's

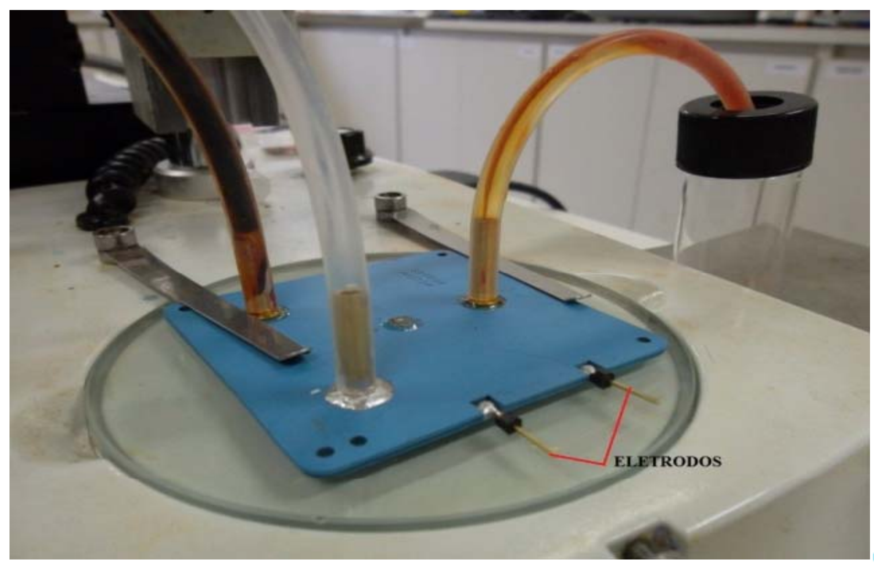
BOTTOM - UP

Nanocrystals
Microfluidic 3D Flow Focusing
+ HV size tuning



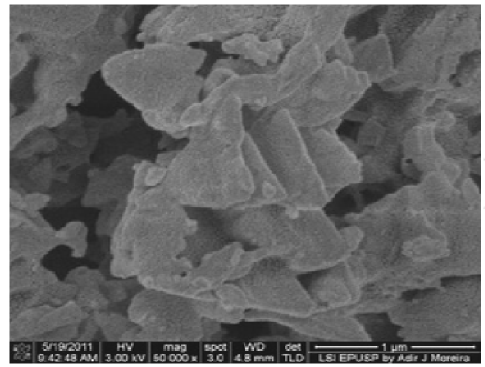




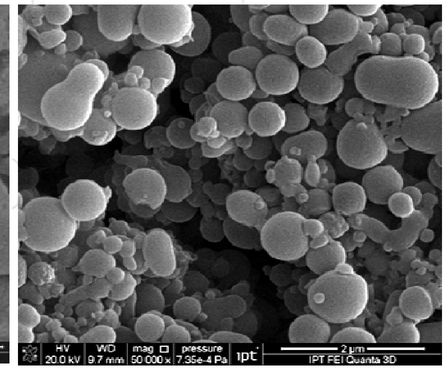


DEVICE FOR MICROPARTICLES

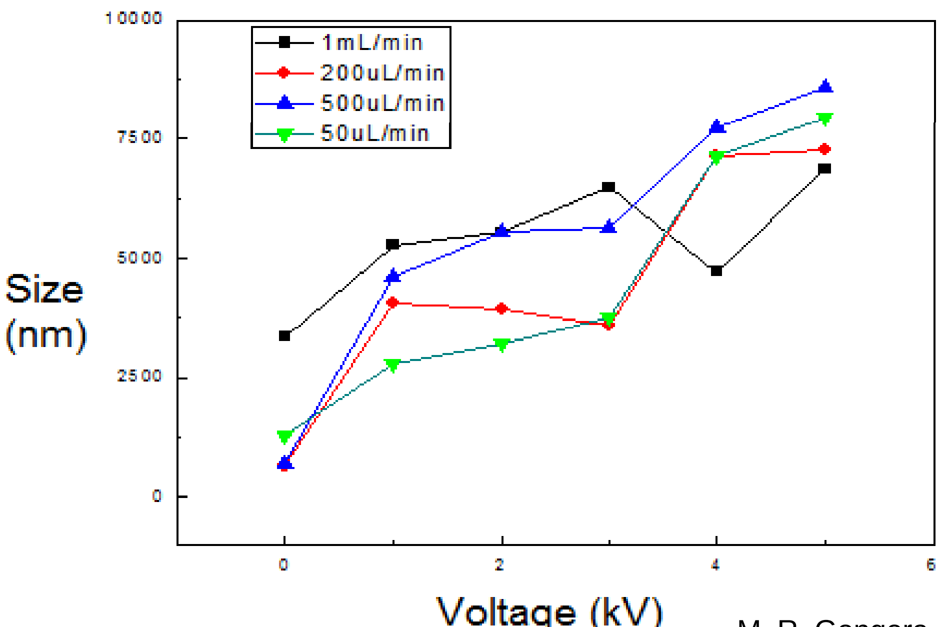
We use 3D geometry to get better control of flow focusing and HV to obtain fine control of particle size in different flow regimes



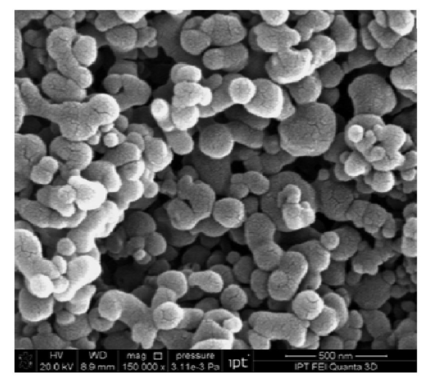
Raw Material



No HV Applied



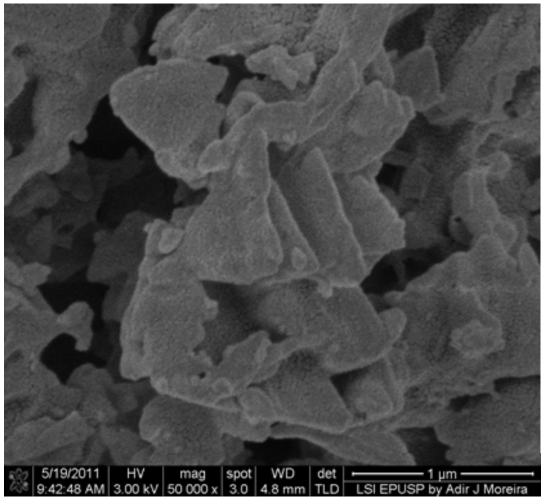
3KV applied



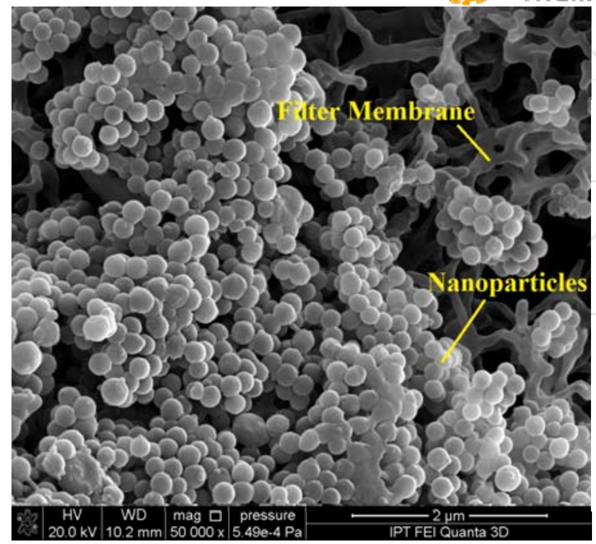
5KV applied

M. R. Gongora-Rubio, K. H., J. de Novais Schianti, A. Marim de Oliveira, N. Neto Pereira Cerize & M. H. Ambrosio Zanin, CICMT-2012

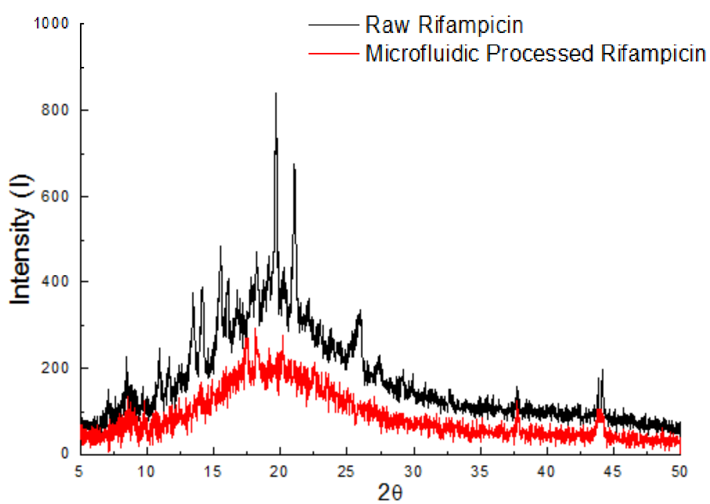
DEVICE FOR NANOPARTICLES



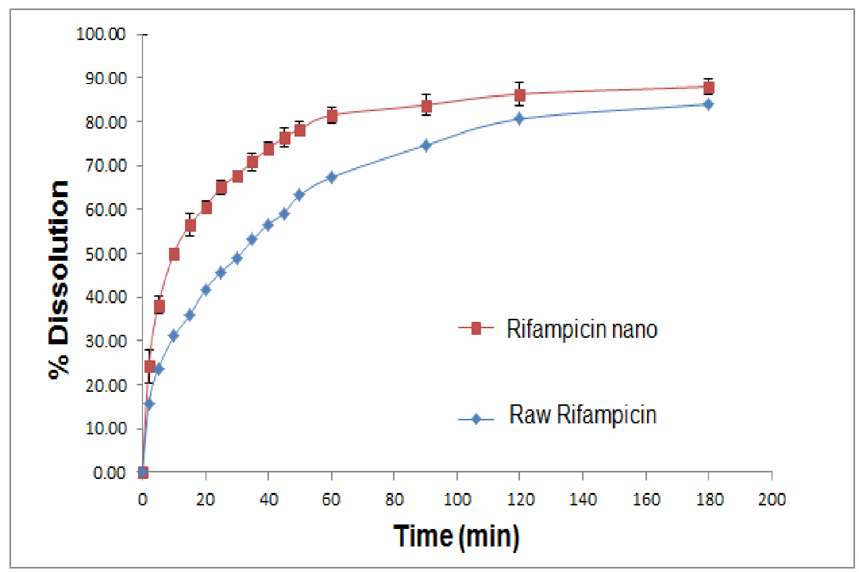
Raw Material



Rifampicin processed via Microfluidics



XRD profile of Raw Rifampicin and Processed Rifampicin.



Rifampicin Dissolution Profile

TECHNOLOGICAL PERSPECTIVES

- We showed several microfabricated devices for chemical process intensification, including synthesis of micro and nanoparticles for practical applications.
- Introduction of microfluidic techniques for micro and Nanoencapsulation applications.
- Feasibility of scaling microfluidic droplet/particle generation up to production rates of hundreds of milliliters per hour.
- This could lead to a Microfluidic route adapted to the encapsulation process in order to design capsule or emulsion with size and morphology controlled in continuous process.

Thank you!

Mário Ricardo Gongora-Rubio

gongoram@ipt.br

ipt INSTITUTO DE PESQUISAS TECNOLÓGICAS

MICROFLUIDIC DEVICES APPLICATIONS TO MICRO & NANOENCAPSULATION

Mário Ricardo Gongora-Rubio – gongoram@ipt.br

Center for Process and Product Technology
Chemical Processes and particle technology laboratory
CTPP-LPP

SUMMARY

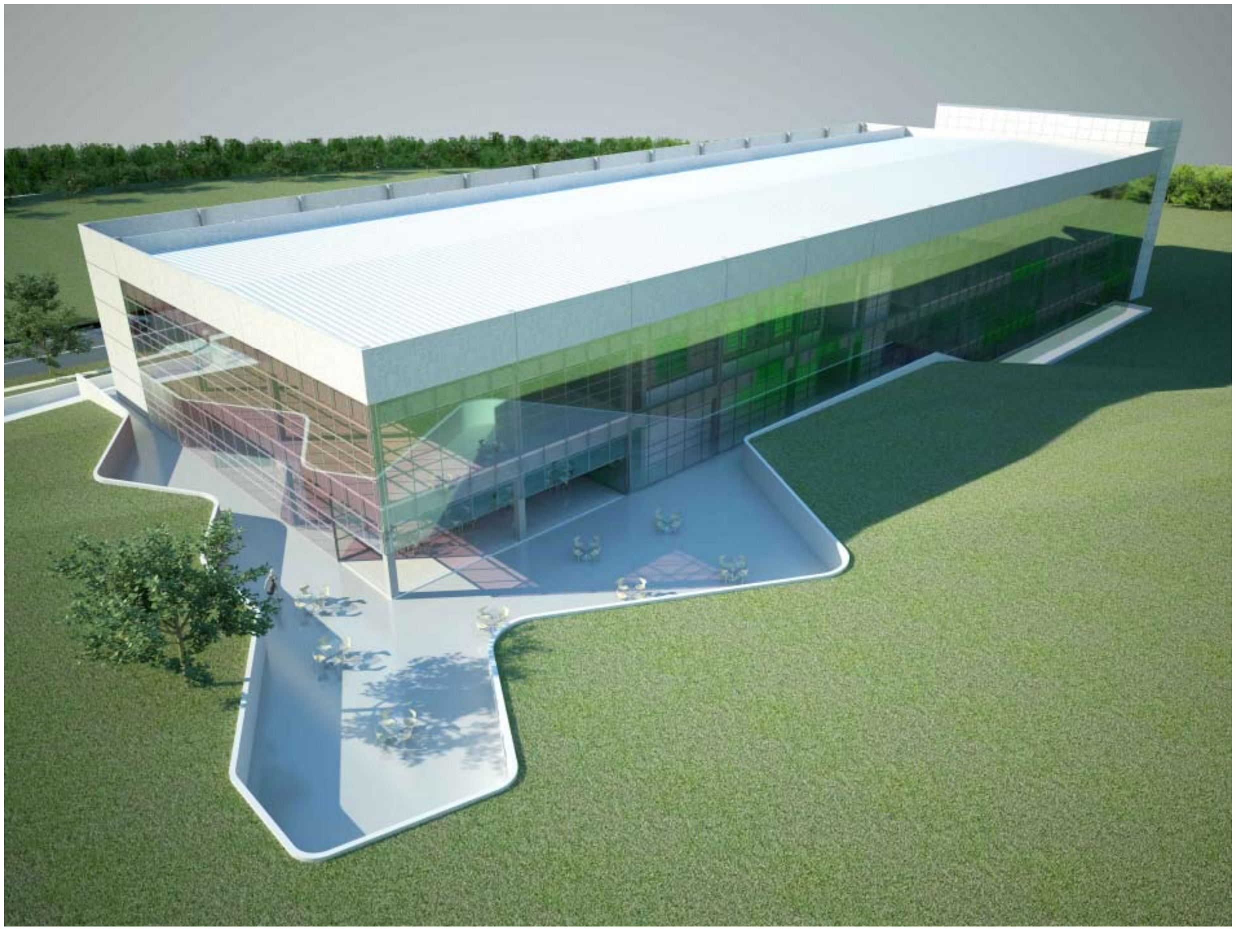
- Introduction
- Micro Technology
- Glass & LTCC MicroFluidic Technology
- Chemical Process Intensification
- Microfluidic Devices in Micro & Nanoencapsulation
- Conclusion

INTRODUCTION

IPT

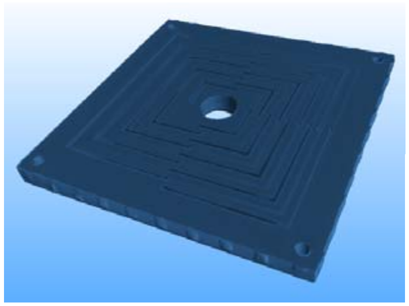
- Institute for Technological Research of the State of São Paulo S.A.
- One of the first applied R&D&I institutions in Brazil and one of the largest applied multipurpose R&D&I institutions in Latin America
- Linked to the Secretariat of Development of the State of São Paulo
- IPT provides technological solutions to public and private companies and institutions

BIO, NANO & MICROTECHNOLOGY AT IPT



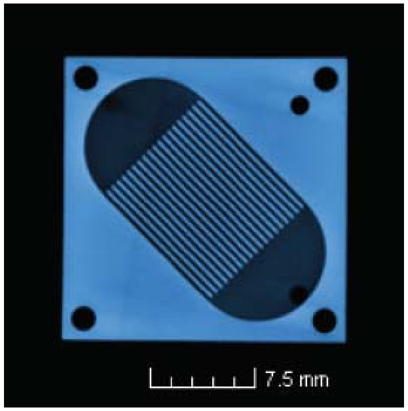
State Government invested R$ 50 Million in new facilities dedicated to Bio, Nano & Microtechnology research

MicroTechnology at IPT: Microfabrication Processes



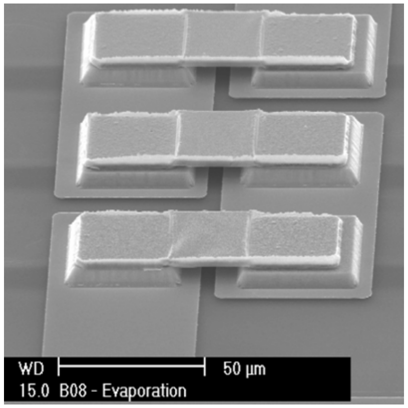
LTCC – *Low Temperature Cofired Ceramics process*

- Minimum feature: ~ 50 µm
- Processes: Micromachining, Screen printing, Lamination, Sintering & Packaging
- Materials: Green Tape Ceramics



Microusinagem NEW

- Minimum Feature: ~ 10 µm
- Processes: Laser Micromachining & Micro Drilling, Mechanical Micro Milling
- Materiais: Metals, Silicon, Glass, Polymers, Ceramics, Synthetic Diamond



Microfabrication in Clean Room NEW

- Minimum Feature : ~ 1 µm
- Processes: Photolithography, Thick & Thin Film Deposition, Wet and Dry Corrosion, Wet and Dry Cleaning, (CMP), Packaging
- Materials: Silicon, Glass, Polymers

MicroTechnology at IPT: Microfabrication Equipment

Deposition – PVD (*Sputtering and Evaporation*) e PECVD for silicon oxide & Nitrates, Thick film deposition & dispensing, Parylene biocompatible films, electrochemical deposition.

Photolitography –Mask direct write , mask Aligner, *spin coater, developer and baker* photoresist processing.

Corrosion & Cleaning - DRIE-ICP Plasma corrosion, Plasma Dry cleaning and surface activation, Wet corrosion and cleaning.

Micromachining - Laser UV (355 nm), 5 axes CNC with 0,1 µm resolution, LTCC laser Micromachining.

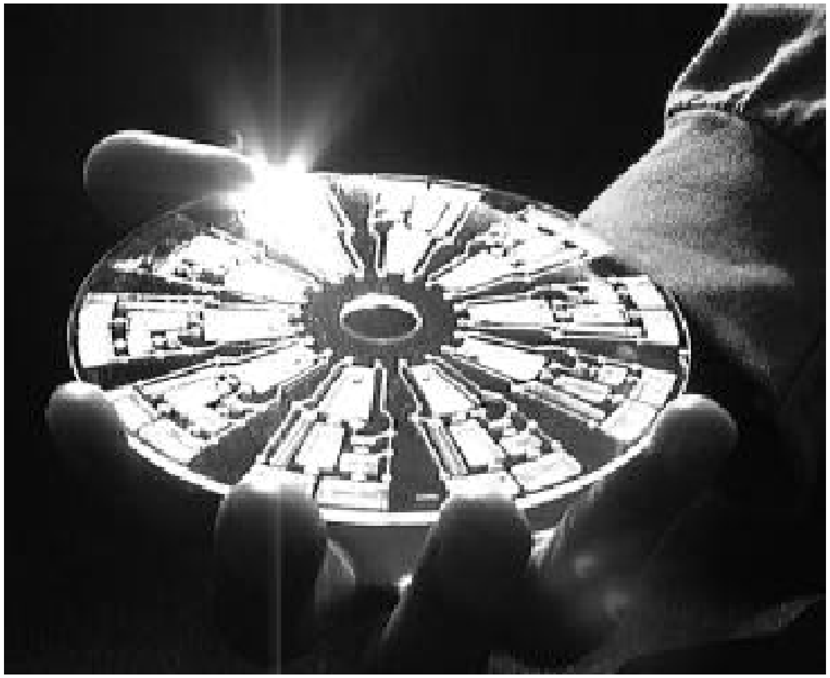
Packaging – Fluid dispensing, Re-work system, Wafer bonding system, Wire bonding, Chip to Chip bonding workstation.

Caracterization – SEM, Profilometers (1 for Thin Films + 1 for Thick Films), equipment for dimensional & geometrical measurements.

MICROTECHNOLOGY

MICROTECHNOLOGY

Is an outstanding strategy for miniaturization and integration where the same principles as in microelectronics, are applied to Mechanical, Acoustic, Optical, Magnetic, Thermal, Chemical or Biotechnical components and systems.



VALUE OF MICROTECHNOLOGY

MICROSYSTEM PLATFORMS

Parameter	ICs	MEMS	µTAS	MECS
Function	Signal processing	Signal acquisition & Control	'Lab on chip'	Process intensification
Primary Materials	Semiconductors	Silicon, Ceramics, glass & polymers	Silicon, Ceramics, glass & polymers	Metals, Silicon, LTCC Ceramics, Glass & polymers
Key Element	Transistors	Transducers & actuators	Microfluidic pumps and valves	Microchannel arrays
Characteristic Feature Size	100 nm	µm	tens of µm	1 to 500 µm
System Size	mm to cm	mm to cm	mm to cm	mm to meters

GLASS MICROFLUIDIC DEVICES

Glass Microfluidic Devices

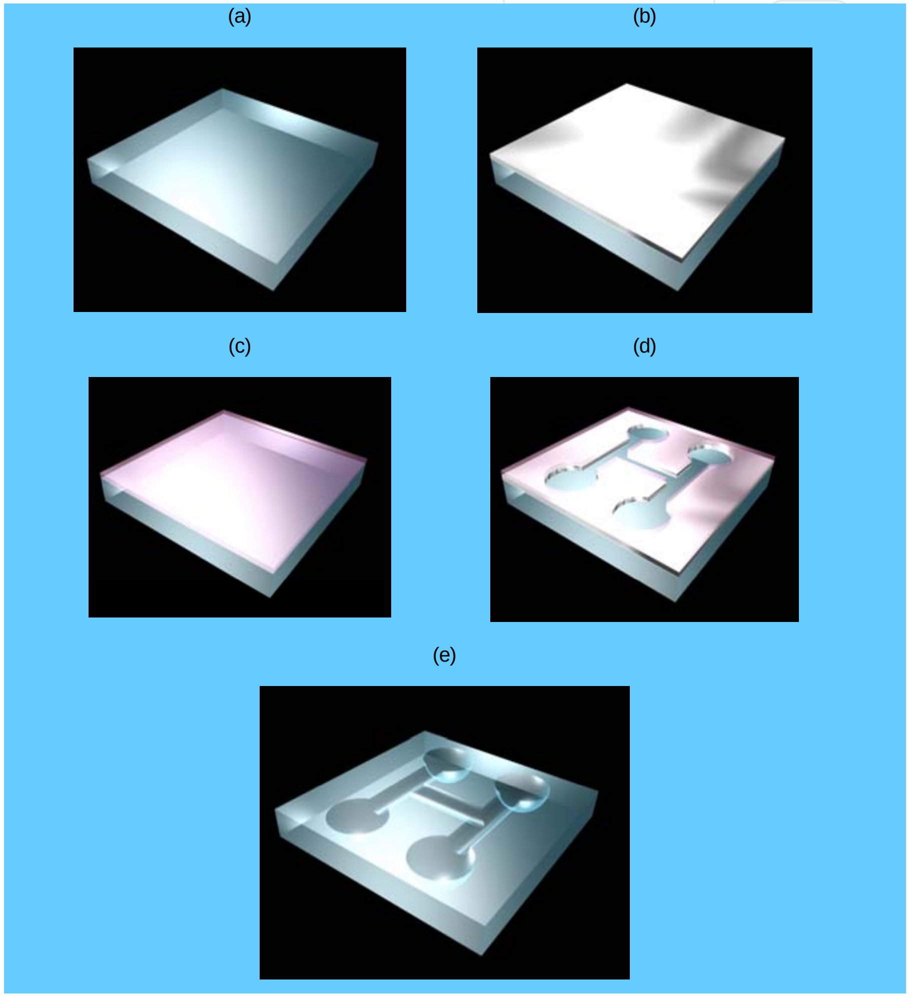
a) Glass substrate cleaning

b) Chrome film deposition and oxidation

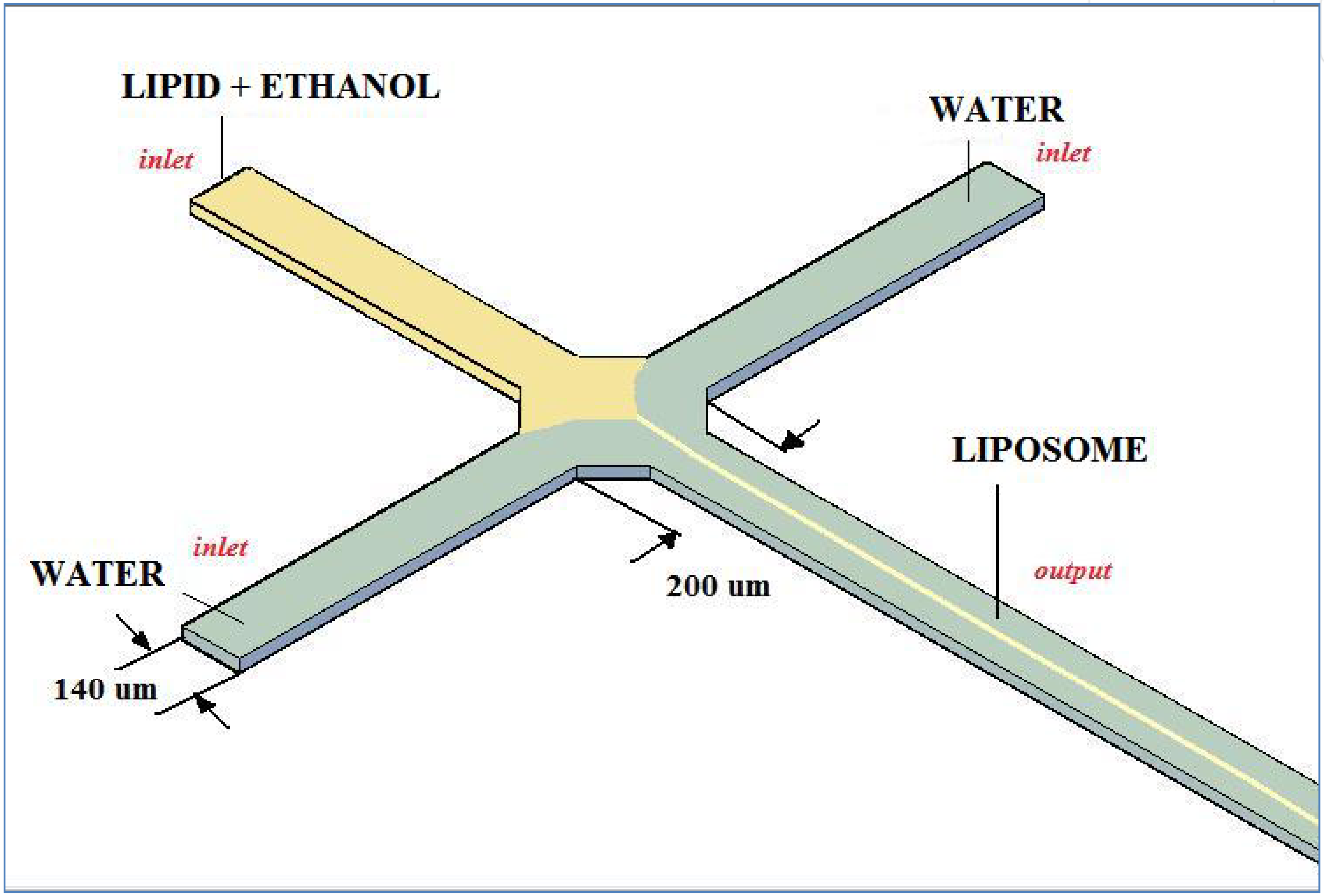
c) Photoresist deposition and Photolithography

d) Glass etching to obtain microchannels

e) Bonding of upper glass substrate

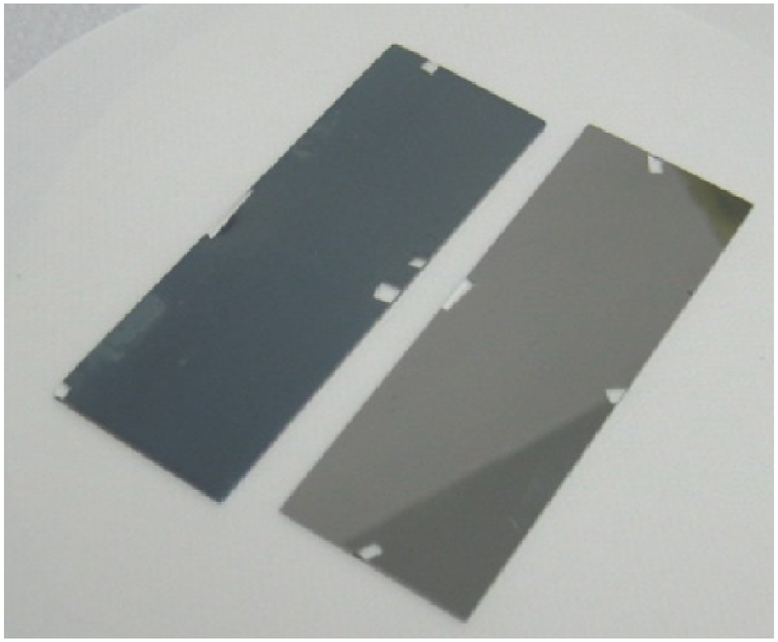


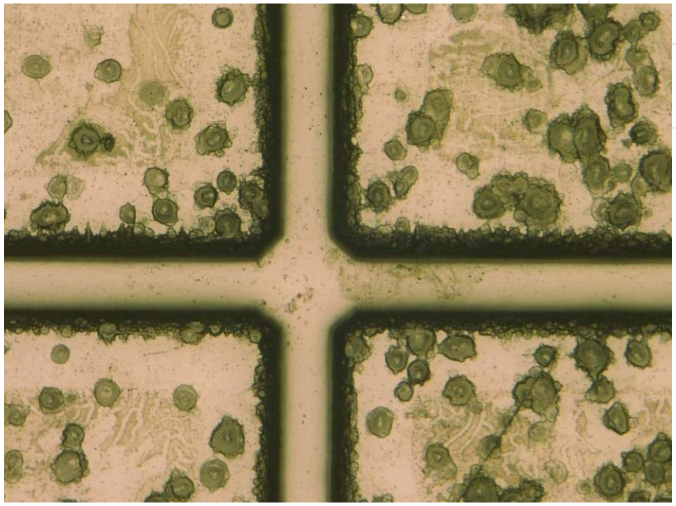
GEOMETRY

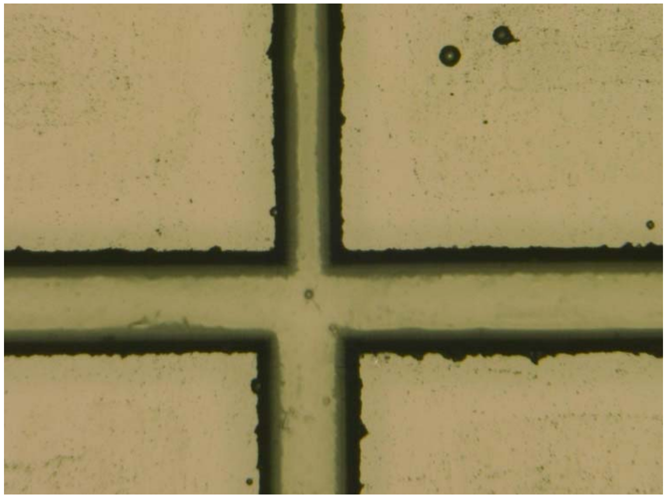


LIPID + ETHANOL
inlet
WATER
inlet
LIPOSOME
output
inlet
WATER
200 um
140 um

CHROMIUM FILM



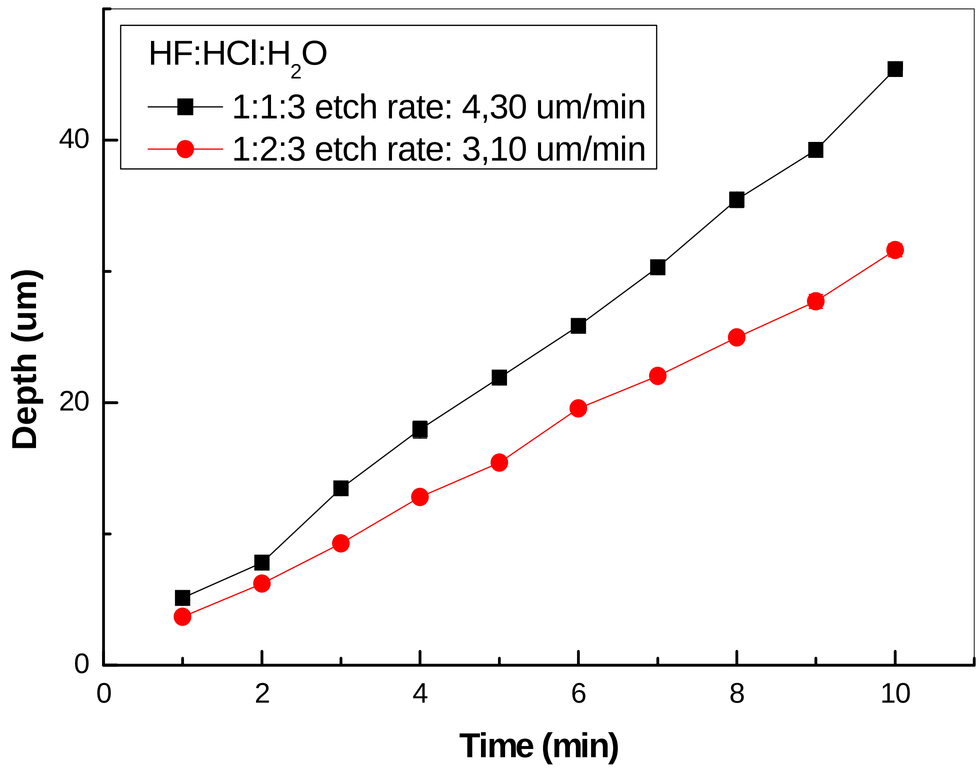


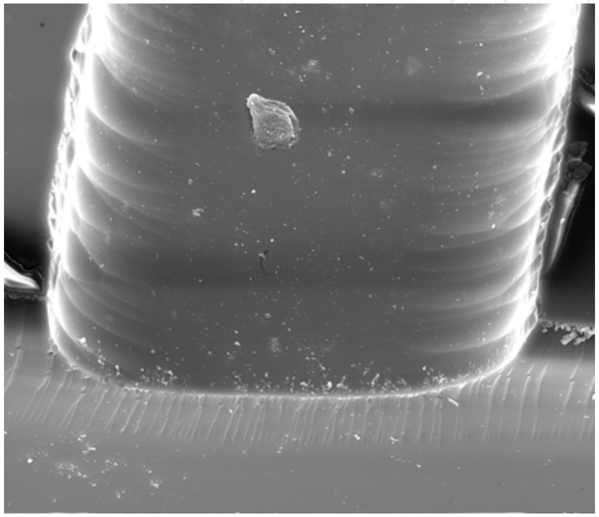


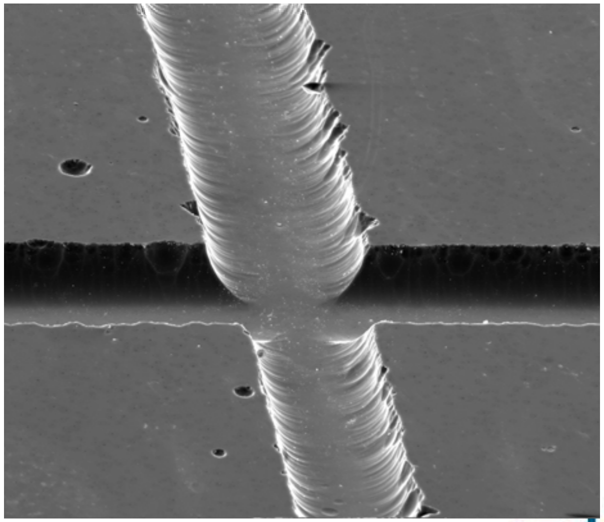
HEAT TREATMENT

MICROCHANNELS – WET ETCHING

- Wet Isotropic etching with HF







II WORKSHOP EM MICROFLUÍDICA

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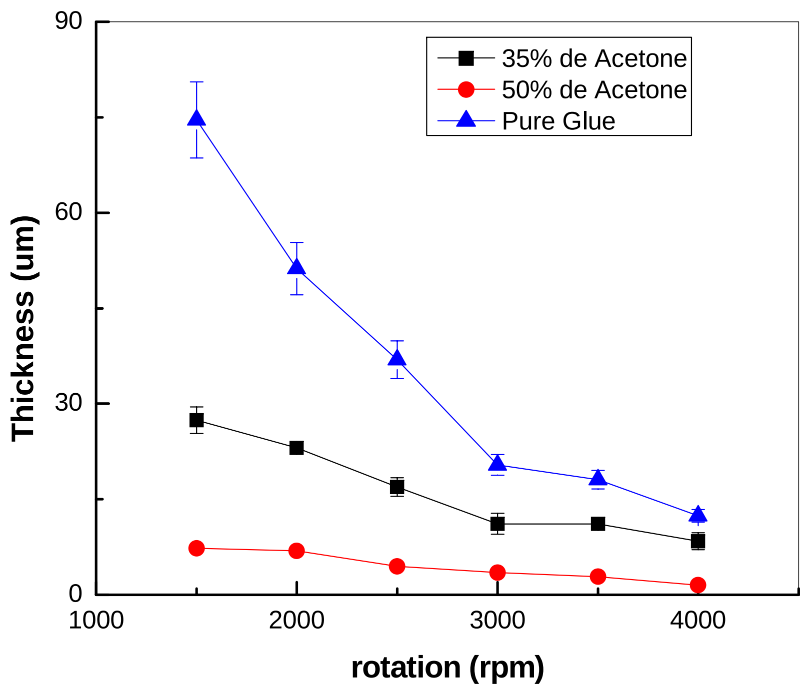
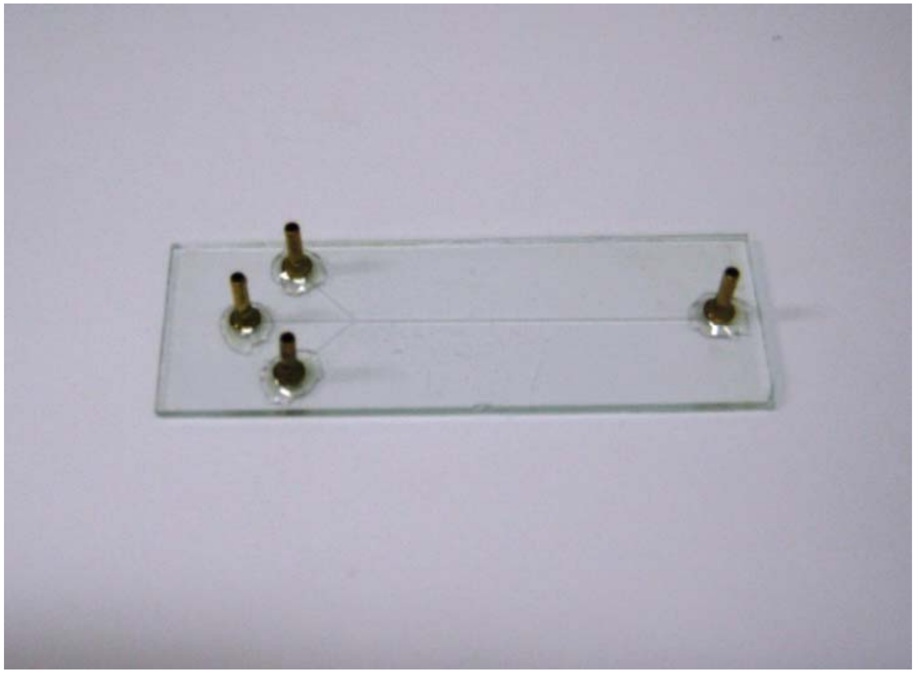
SEALING PROCESS

- Utilization of UV Glue, diluted with acetone to render thinner films



II WORKSHOP EM MICROFLUÍDICA

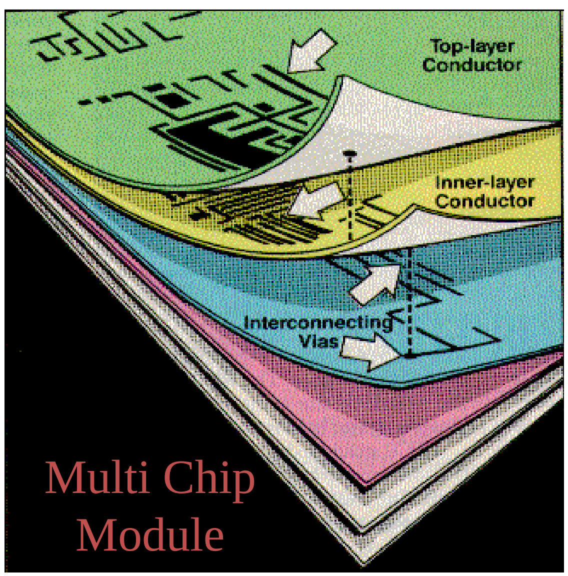
FABRICATED MICROFLUIDIC DEVICE



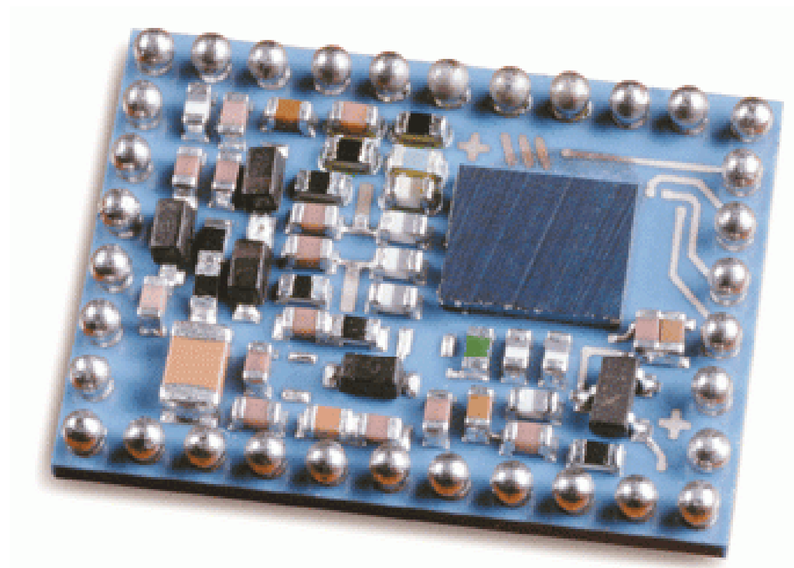
LTCC AS A MICROSYSTEM PLATFORM

What is LTCC ?

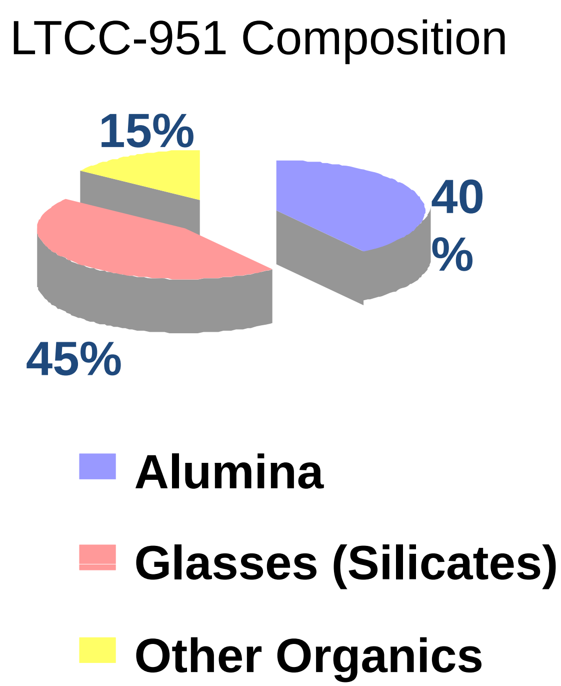
- LTCC was originally developed by Hughes and DuPont for Military Systems, using Glass-Ceramic Composite Materials.
- The (LTCC) technology can be defined as a way to produce multilayer circuits with the help of single tapes, which are to be used to apply conductive, dielectric and / or resistive pastes on.
- These single sheets have to be laminated together and fired in one step all.

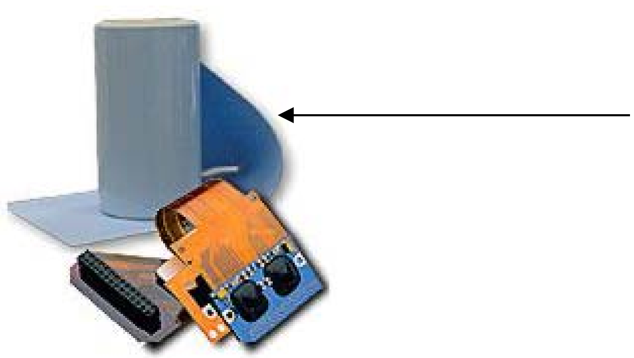


Multi Chip Module


Bluetooth Interface (National)

LOW TEMPERATURE CO-FIRED CERAMICS (LTCC) GREEN TAPE MATERIAL





- Glass-ceramic composite materials
- The ceramic filler is usually alumina, Al2O3
- The regular composition also includes a glass frit and an organic binder (plasticizer and anti-flocculant)
- Called green tape before firing and sintering

FABRICATION PROCESS OF MICROFLUIDIC LTCC DEVICES

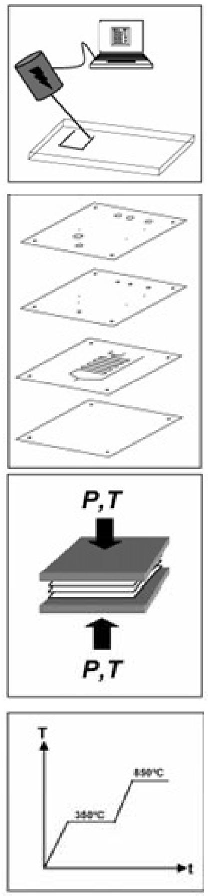
Microusinagem
(Laser)

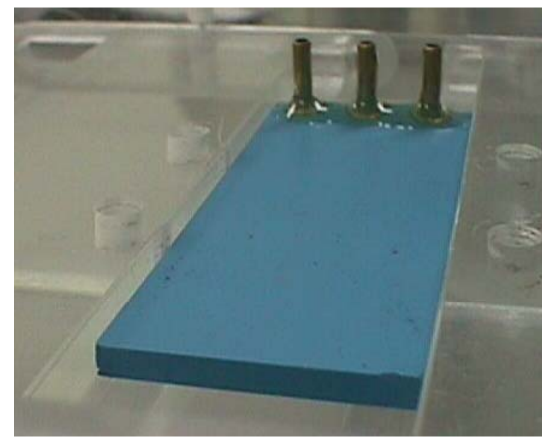
Serigrafia
(Deposição filmes espessos)

Laminação
(Prensa Uniaxial)

Sinterização
(Forno)

Corte





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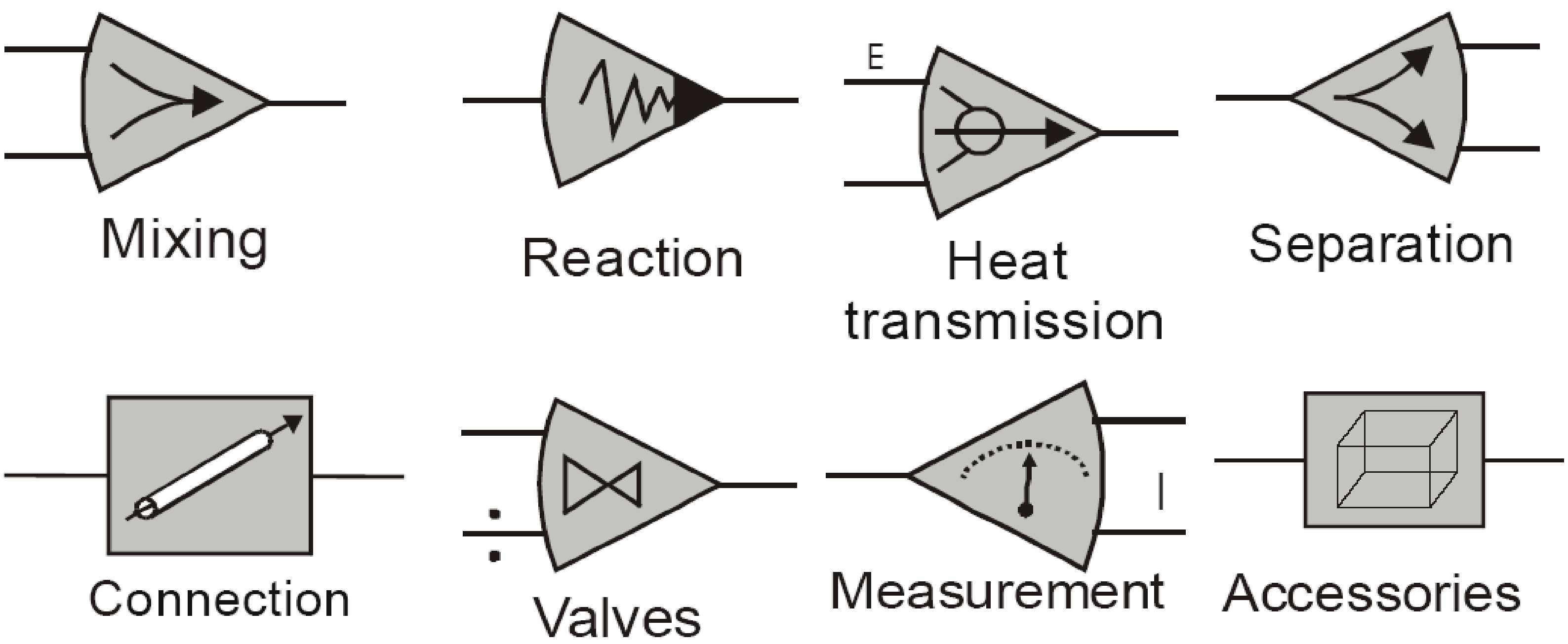
LTCC Advantages for MicroSystems

- Simplicity of tape machining in the green state with feature size of 50 μm to several mm;
- Ability of 3D multilayering and high layer count;
- Integration of a wide range of materials with different properties & technologies;
- Adaptability of embedded structures;
- Microfluidics are readily implemented;
- Tapes of different compositions can be formulated to obtain desired layer properties;
- Integrated Electronic circuits because of its hybrid nature;
- Possibility of auto-packed devices fabrication;
- Mass production methods can be readily applied;
- Fabrication techniques are relatively simple, inexpensive and environmentally benign.

LTCC MICROFLUIDIC APPLICATIONS

- Fluid Management Systems
- Micro Analytical Systems
- Micro Reaction Systems
- Micro Heat Exchange Systems

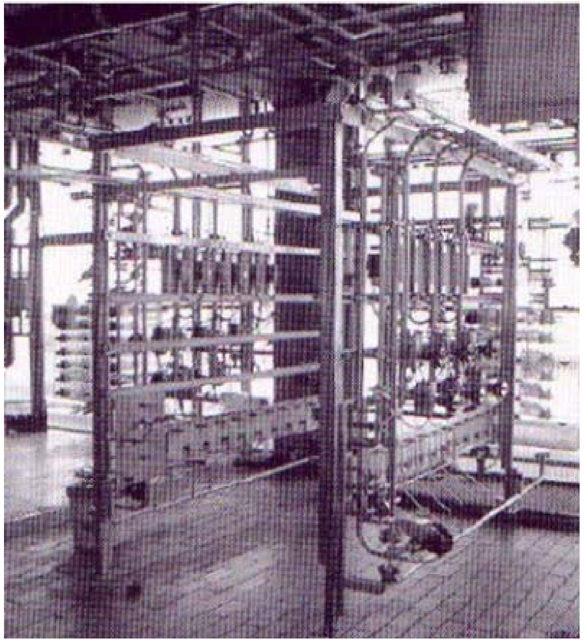


CHEMICAL PROCESS INTENSIFICATION

PROCESS INTENSIFICATION : MINIATURIZED CHEMICAL PROCESSES

Yesterday

Today



Tomorrow (Today in Merck)

Miniature reaction and other unit operations,
Have advantages over conventional chemical systems

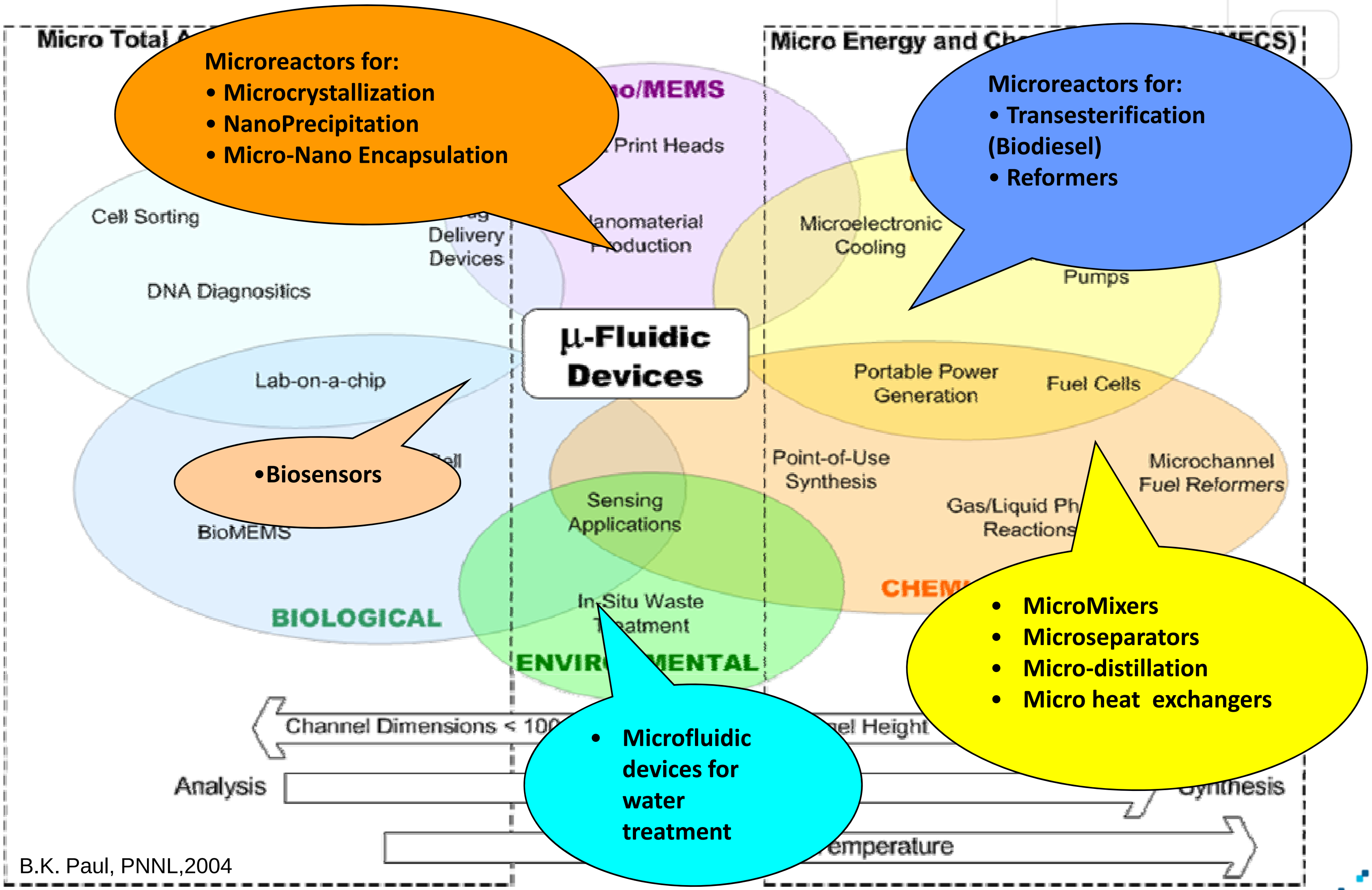
PROCESS INTENSIFICATION ADVANTAGES

1. Novel or Enhanced Products
2. Improved Chemistry
3. Enhanced Safety
4. Improved Processing
5. Energy and Environmental Benefits
6. Sustainable Technologies
7. Capital Cost Reduction
8. Low Inventory Advantage
9. Enhanced Corporate Image

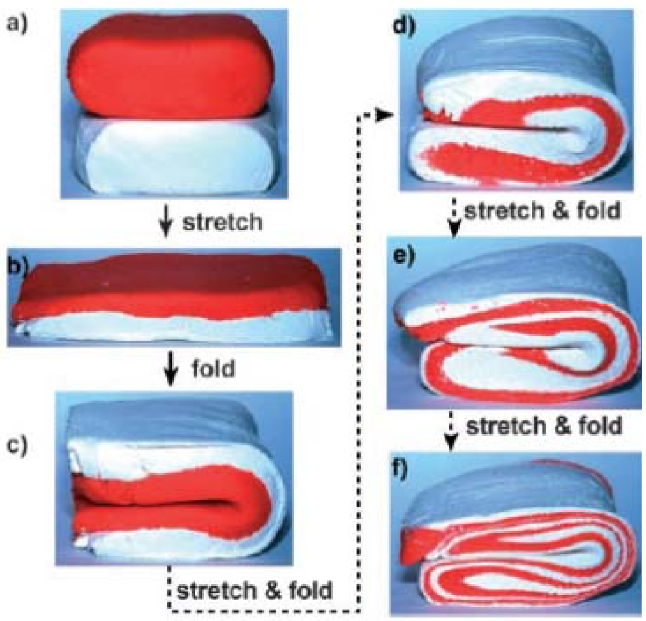
MICROFLUIDIC DEVICES IN
MICRO & NANOENCAPSULATION

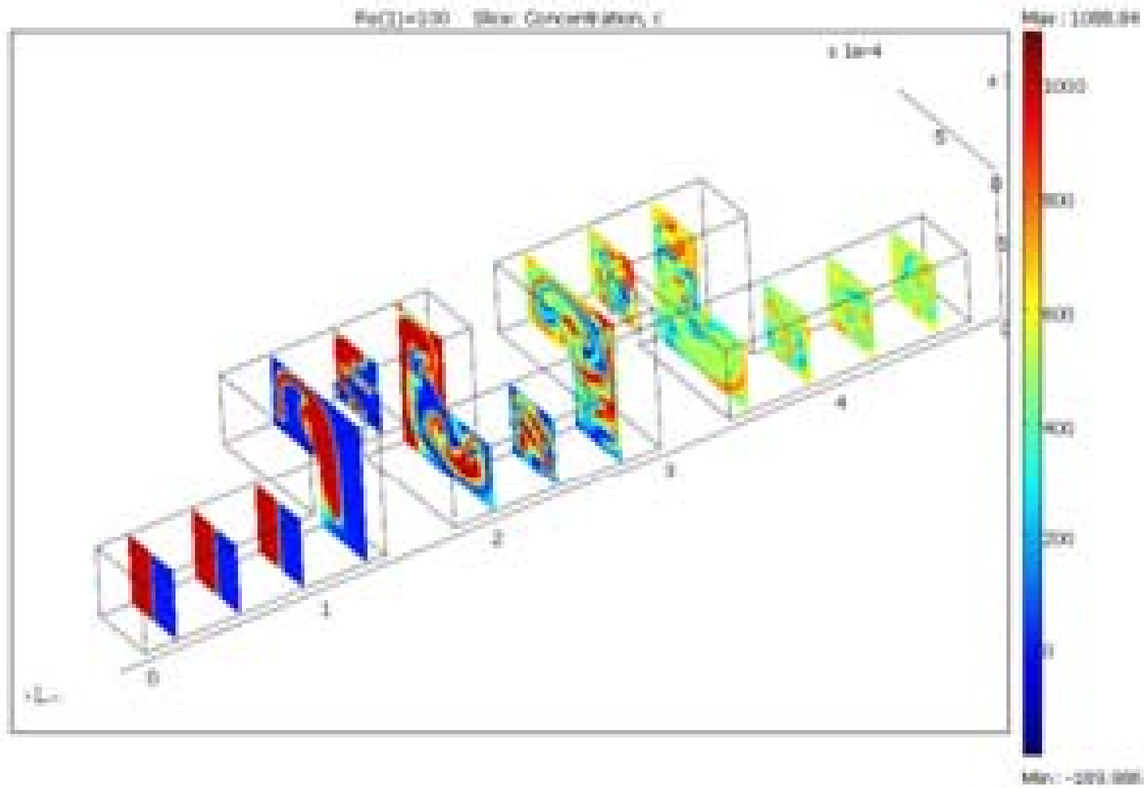
II WORKSHOP EM MICROFLUÍDICA

MICROFLUIDICS & MICROREACTORS



CHAOTIC ADVECTION MIXING





Chaotic advection mixing simulation in a 3D serpentine micromixer

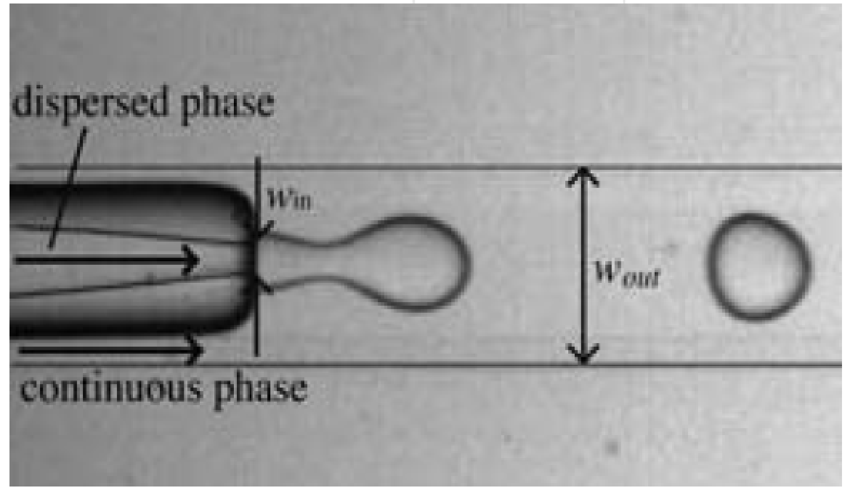
DROP GENERATION

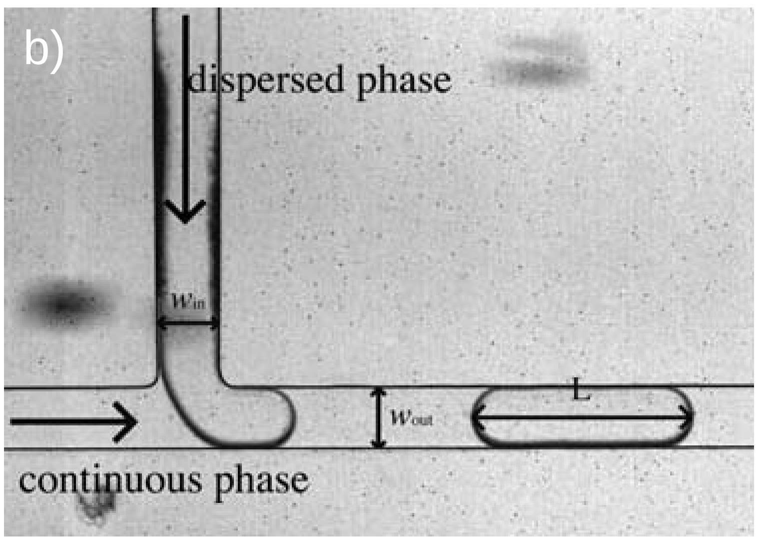
Three main approaches for drop generation based on different physical mechanisms are:

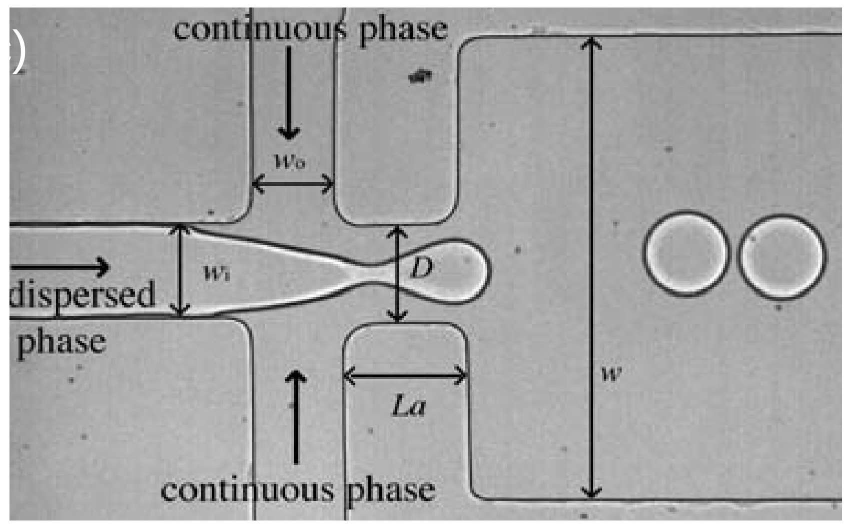
a) breakup in co-flowing streams

b) breakup in cross-flowing streams

c) breakup in elongational strained flows





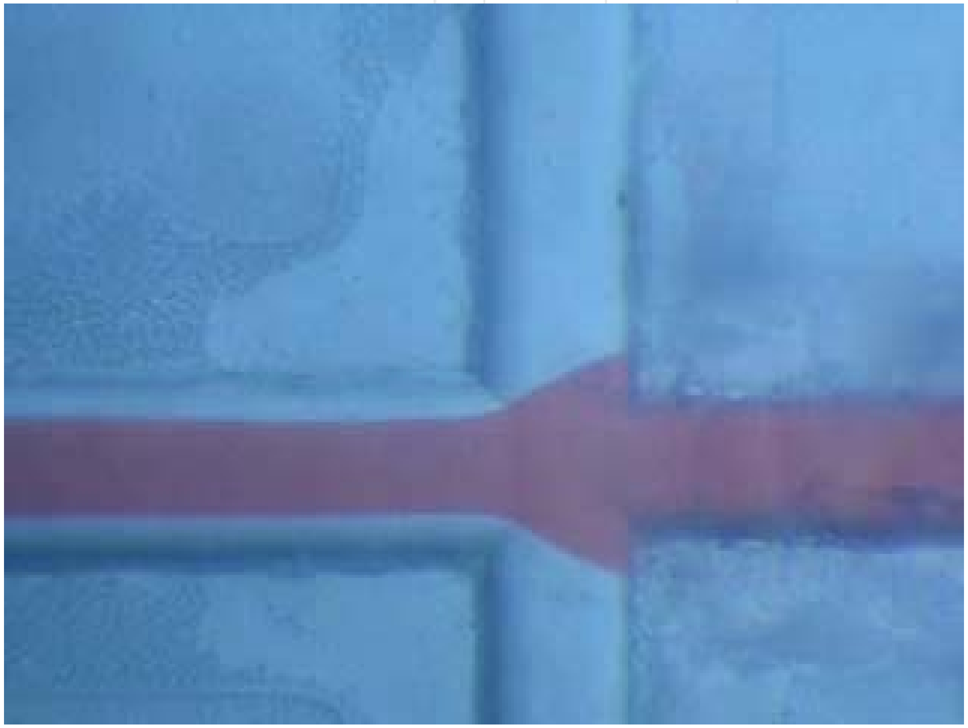


C. N. Baroud, F. Gallaire and R. Dangla
Lab Chip, 2010, 10, 2032–2045

HYDRODYNAMIC FLOW FOCUSING

Hydrodynamic flow focusing can be used as drop generator allowing drop control of frequency and size.

Can be used as well in diffusion based processes or reactions

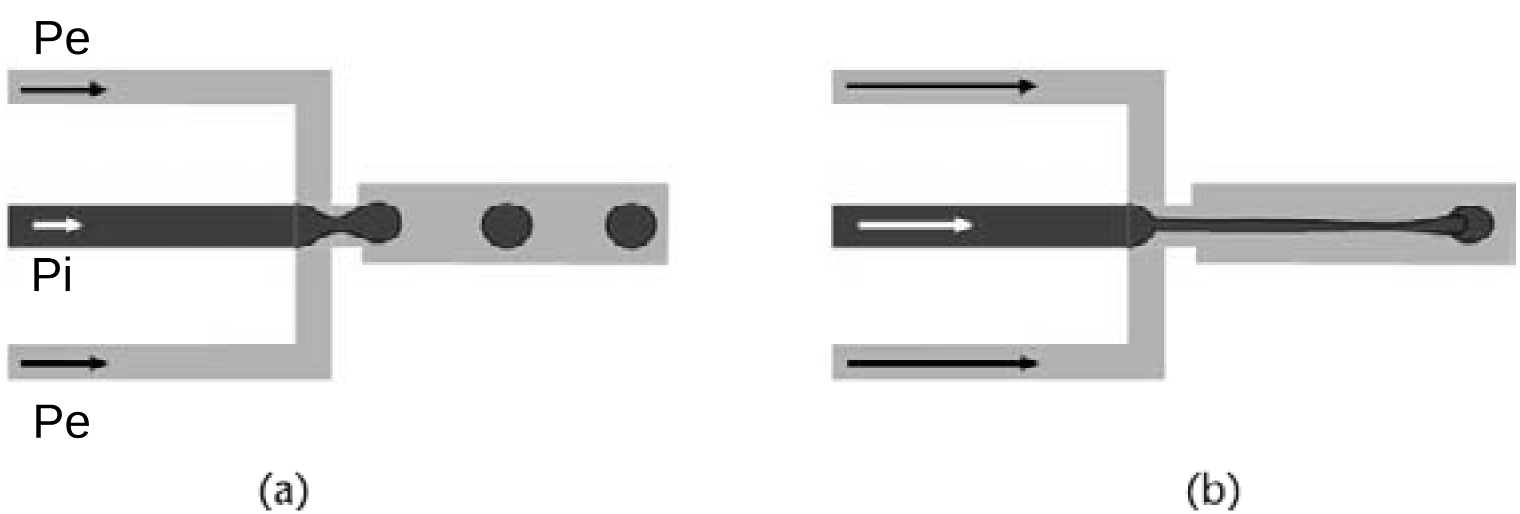


FLOW REGIMES IN FLOW FOCUSING DEVICES

The two principal flow regimes in flow focusing devices are:

DRIPPING AND JETTING.

In the **dripping** regime, the flow rates are small enough so that the droplet forms immediately after the nozzle. In the **jetting** regime, a thread or filament stretches far into the outlet channel

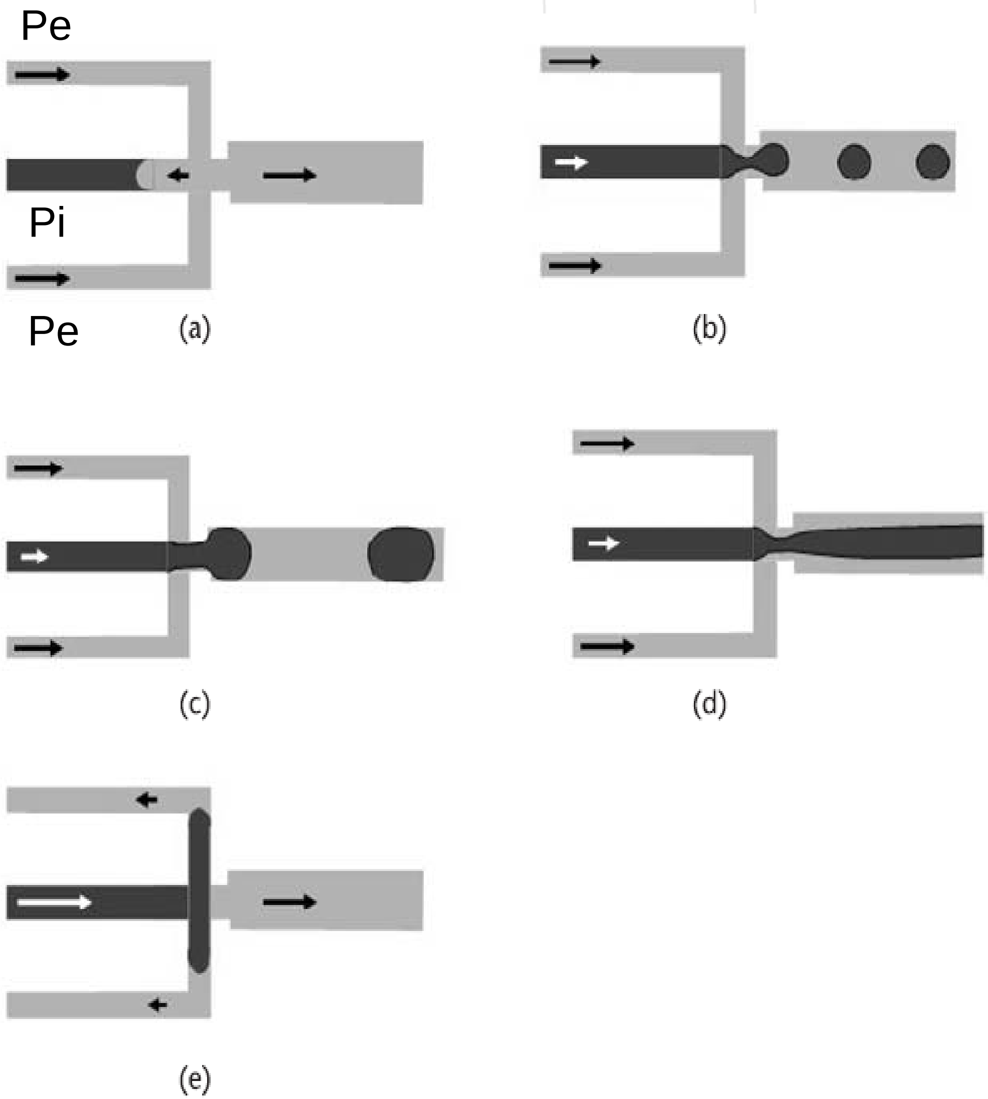


J. Berthier & P. Silberzan, Microfluidics for Biotechnology, 2ED, Artech House, 2010.

DRIPPING MODES IN MICROFLUIDIC FFD

Depending on the relatives values of the driving pressures Pi and Pe, different operating modes appear:

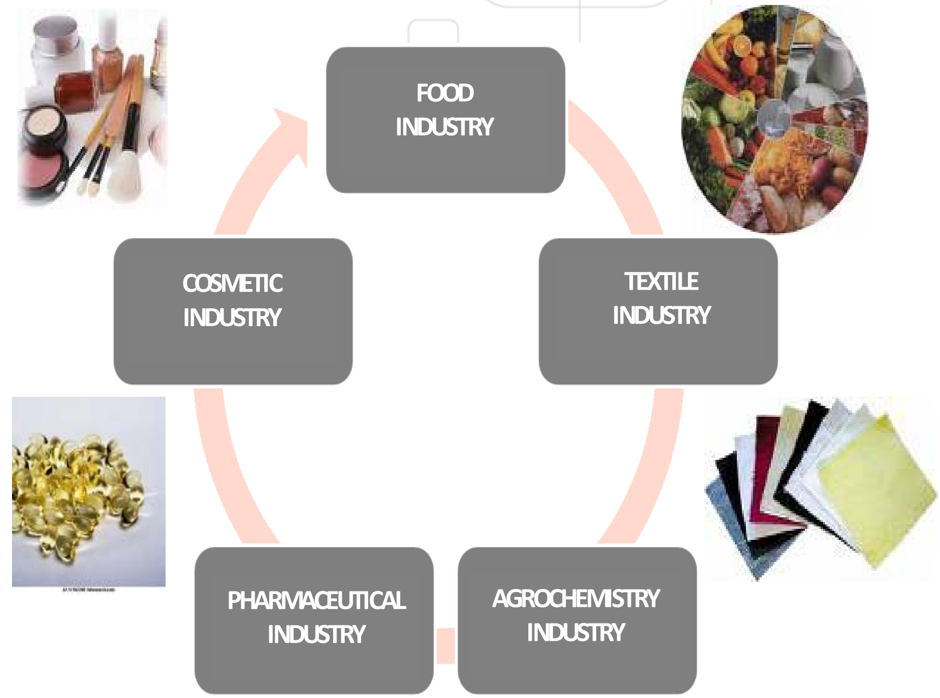
- (a) a flow reversal in the central channel if Pe >> Pi;
- (b) a droplet mode;
- (c) a plug mode — large droplets touching the walls;
- (d) annular flow mode — dispersed phase flowing inside the continuous phase;
- (e) reversal of the flow in the external channels if Pi >> Pe



J. Berthier & P. Silberzan, Microfluidics for Biotechnology, 2ED, Artech House, 2010.

MICRO-NANO ENCAPSULATION

Encapsulation is the technology of packaging solid, liquid, or gaseous materials in small (Micro or Nano) capsules that release their contents at controlled rates

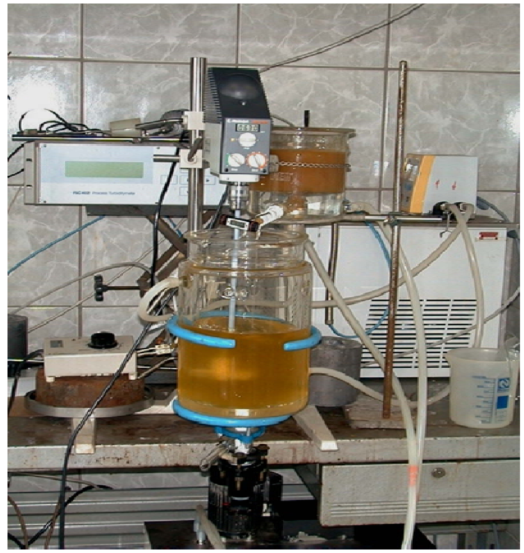


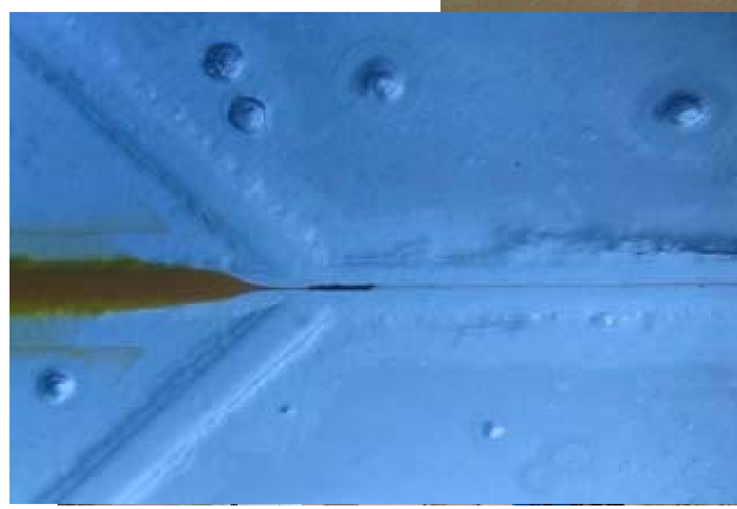
MICRO-NANOENCAPSULATION AT IPT

Technologies

- ❑ Spray drying
- ❑ Coacervation
- ❑ Emulsion/solvent extraction
- ❑ Gelification
- ❑ Polymerisation
- ❑ Electrospinning

Microfluidics





CONTINUOUS MICROFLUIDIC REACTORS

- Functional characteristics of microfluidic continuous reactors relative to conventional batch reactors comprise:
  - A high surface area to volume ratio;
  - Diffusion dominated mass transfer in laminar flow;
  - Intensified surface effects involving rapid heat and mass transfer;
  - Spatial and temporal control of reagents and products;
  - Scaling readiness (numbering-up)
  - The possibility to integrate processes and instrumentation systems on a single technology platform leading to the concept of the FAB ON A CHIP.

MICROFLUIDICS

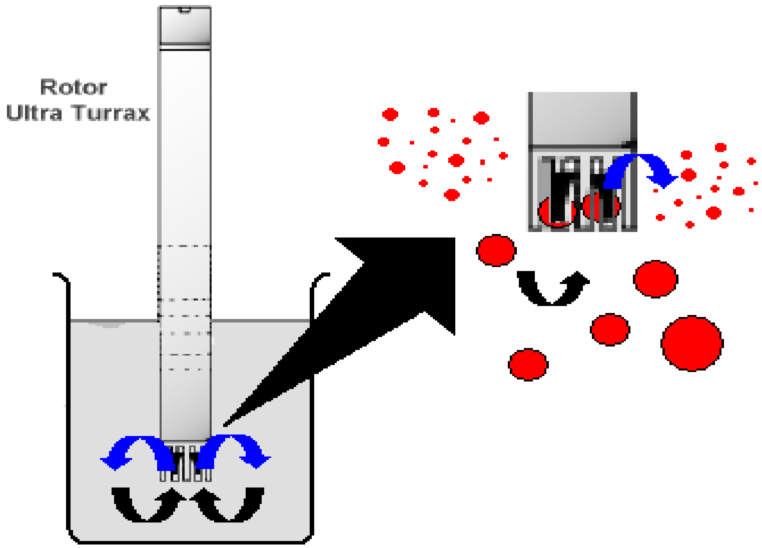
Microprocesses → Micro & Nanoparticles

By combining geometry design of microchannels and fluid flow rate is possible to obtain particles with high size control, reproducibility and low polidispersivity.

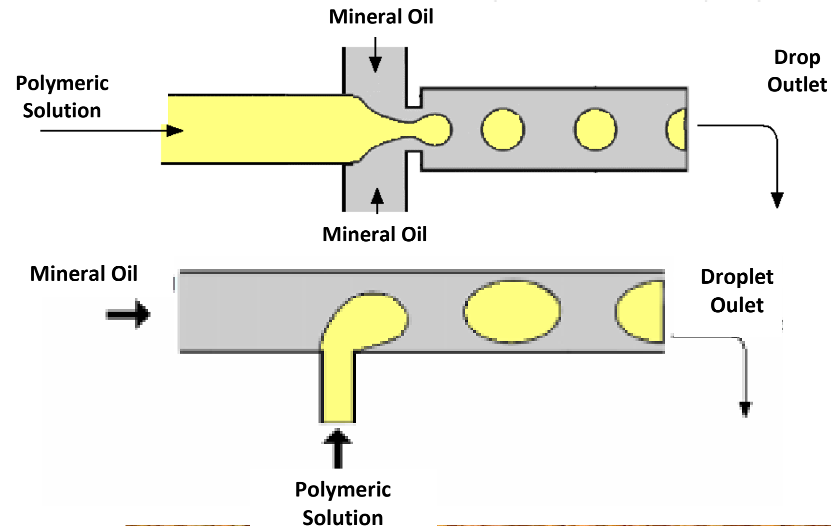
Microfluidics is a powerful tool to obtain particles in micro and nanoscale and for encapsulate drugs based on:

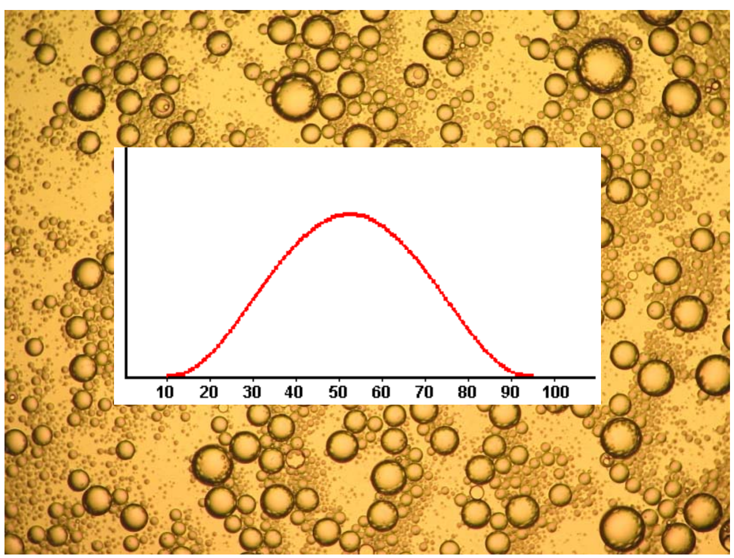
- Emulsions (simple & double)
- Liposomes
- Nanocrystals

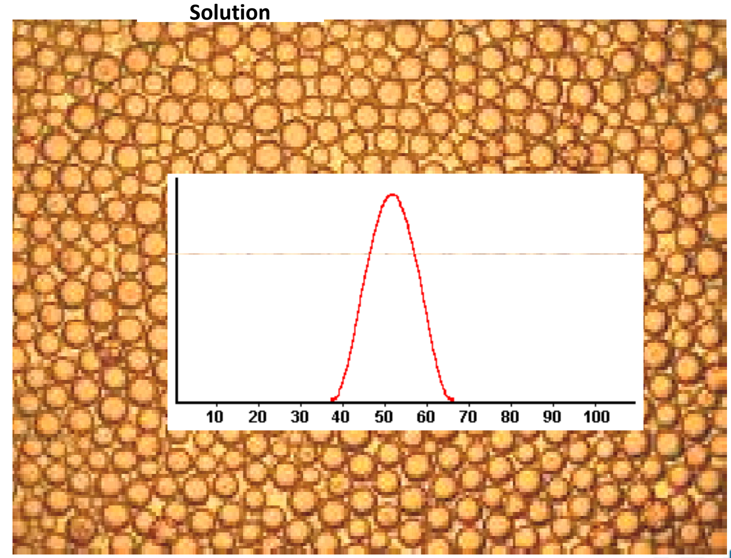
EMULSIONS: BATCH VS CONTINUOUS



Microfluidic Devices

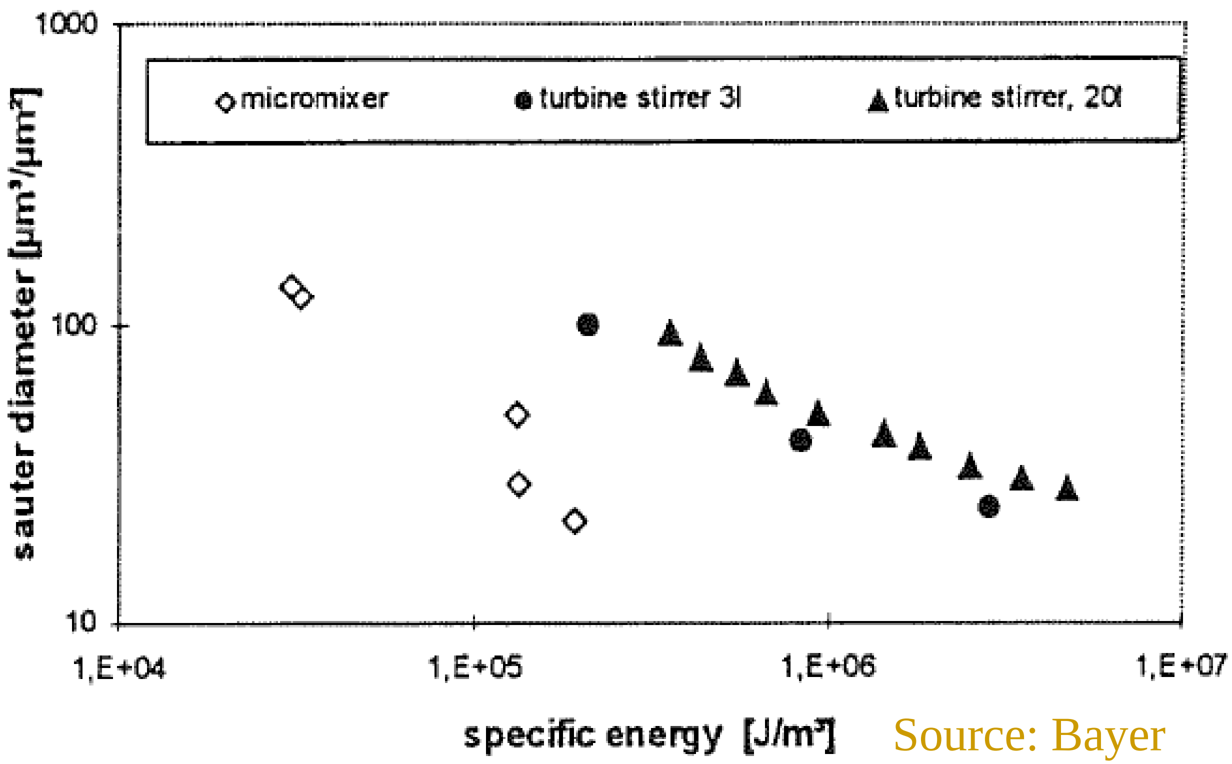






LESS ENERGY CONSUMPTION

- Micromixers consume less energy for stable emulsion production compared to conventional stirrers



Source: Bayer

ADVANTAGES OF PRODUCING EMULSION VIA MICROFLUIDICS

In Products

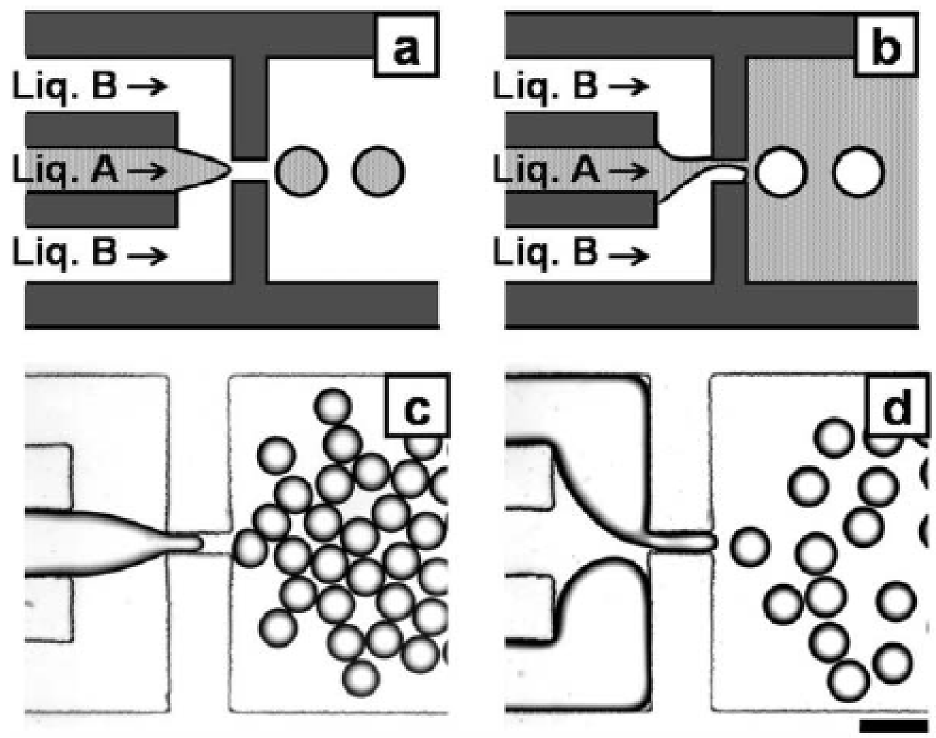
- Formulation flexibility (single & double emulsions)
- Drop distribution control
- Less raw material consumption (less surfactant for emulsion stabilization)
- Emulsion can stand thermal processes
- System free of contamination

In Processes

- Elimination of mixing mechanical forces, emulsions based on microfluidic principles
- More portable equipment with less size and volume
- Less energy consumption
- Scaling possibility (numbering-up)
- Maintenance easiness

MICROFLUIDIC SINGLE EMULSIFICATION

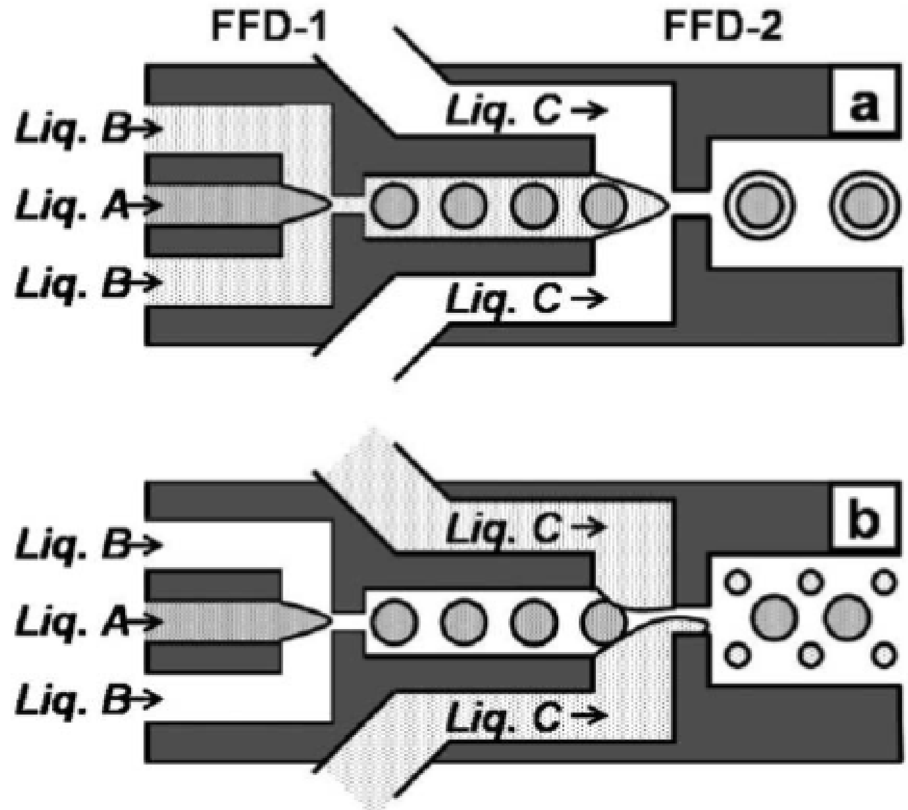
Using one flow focusing device enable us to obtain single emulsions water/oil with controlled characteristics



Soft Matter, 2007, 3, 986–992

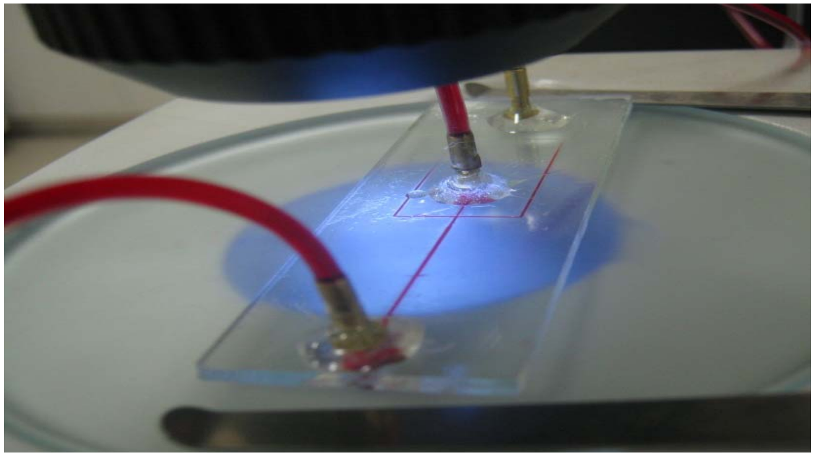
DOUBLE EMULSIFICATION

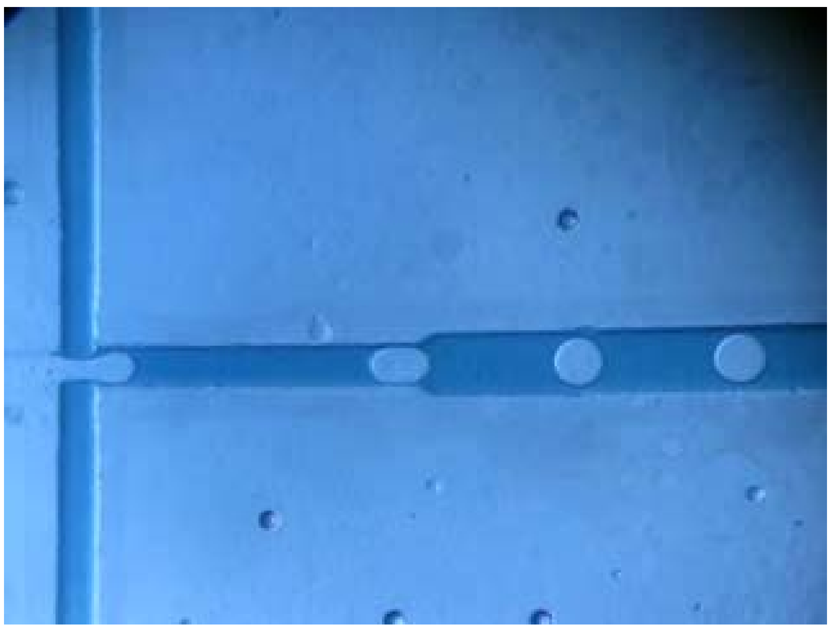
Using two consecutive flow focusing devices enable us to obtain double emulsions oil/ water/oil/ with controlled characteristics



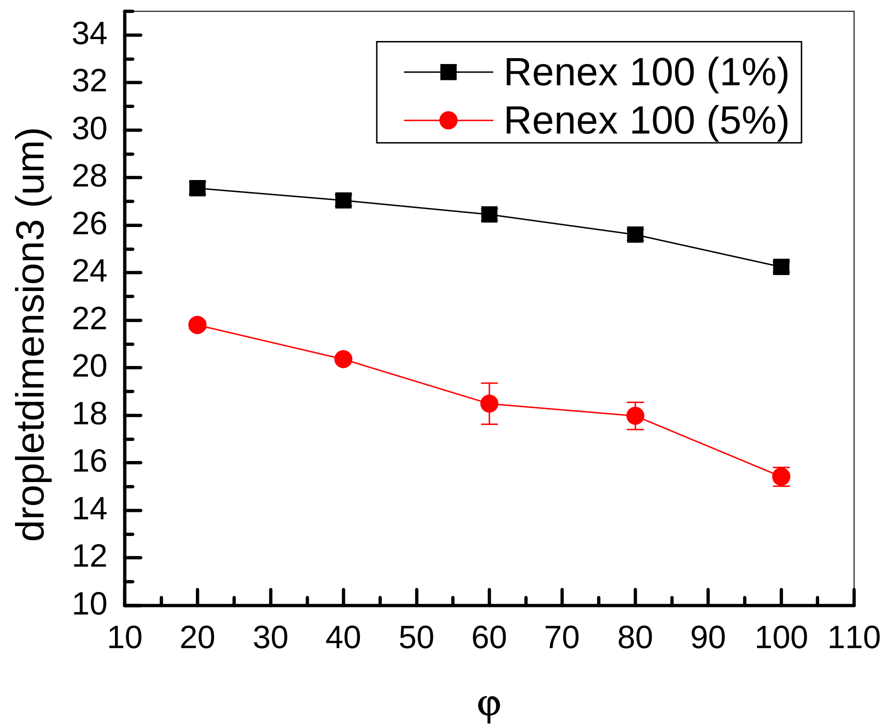
Soft Matter, 2007, 3, 986–992

EMULSIONS USING GLASS DEVICES





Single emulsion production (Water-oil)
Drop size Vs. input fluid ratio

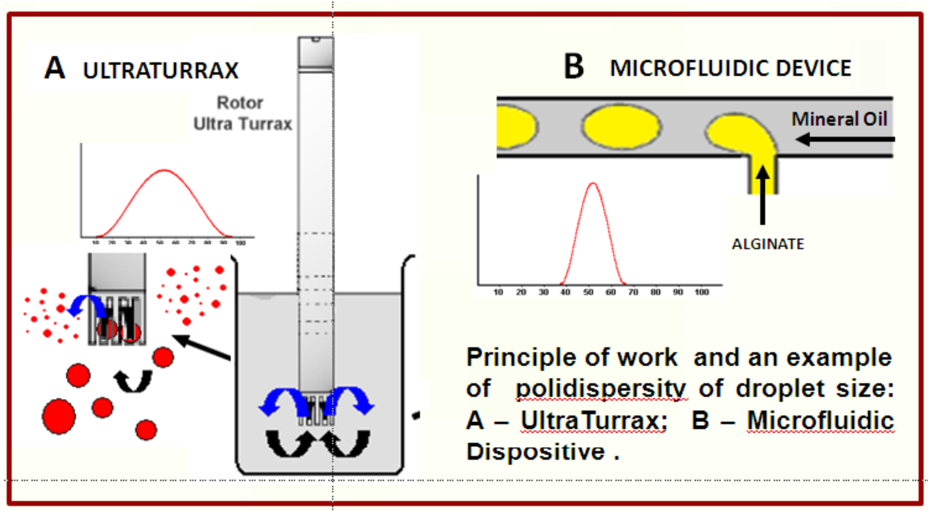


J. N. Schianti, et al. Emulsion production using glass microfluidic devices, Proc: IBERSENSOR 2010

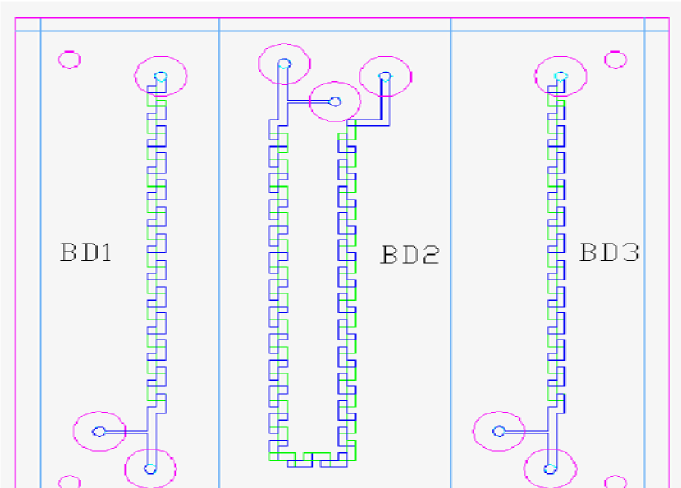
II WORKSHOP EM MICROFLUÍDICA

IONIC GELATION MICROPARTICLES

- Techniques such as solvent evaporation microencapsulation, complex coacervation and **ionic gelation** can be carried out in microfluidic devices, producing particles.
- An experimental arrangement with two syringe pumps was used to apply the solutions of polymer and calcium in the proper inlets of microfluidic LTCC devices under test . An oil flow cut the polymeric solution in droplets. These droplets were conducted to the calcium solution, to promove the ionic gelation (30 minutes). Finally after this period, the microspheres were filtered and washed with distillate water, this particles were compared with standard method.



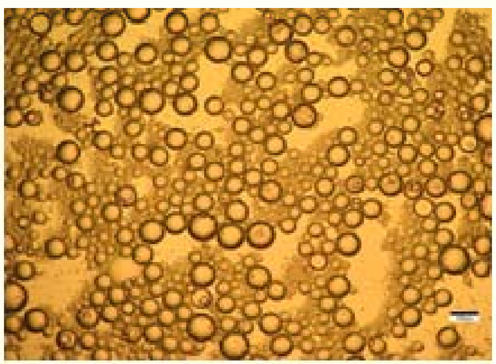
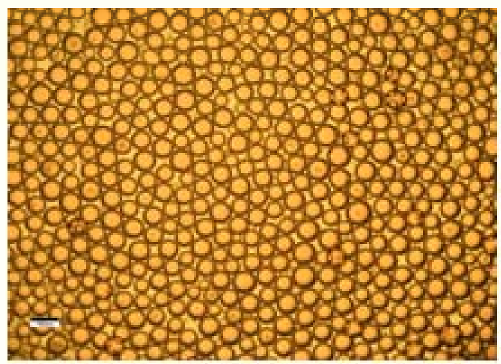
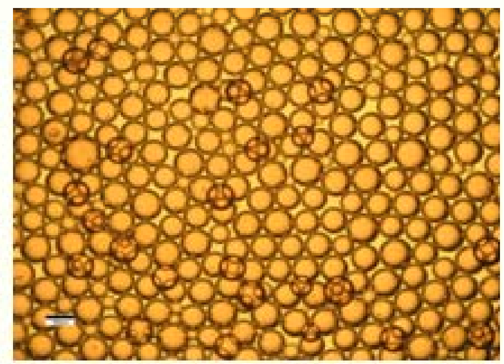
Principle of work and an example of polidispersity of droplet size: A – UltraTurrax; B – Microfluidic Dispositive .



LTCC Devices Tested

EMULSIONS OBTAINED

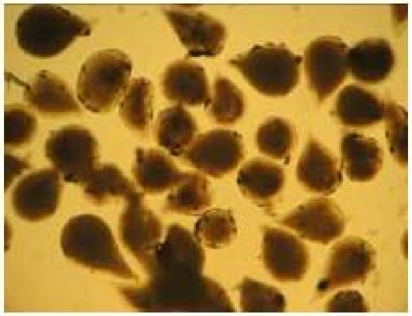
Comparison between mean diameters, spans e morphologies of emulsions obtained in microfluidic device for two different conditions (proportions of polymer solution - disperse phase – DP and mineral oil - continuous phase – CP) and UltraTurrax.

UltraTurrax 11000 rpm/1 min	**Microfluidic device** DP: CP = 1:20	**Microfluidic device** DP: CP = 1:10
D = 37,3 ± 24,1 μm Span = 2,2	D = 49 ± 10,5 μm Span = 0,37	D = 127 ± 26,2 μm Span = 0,48
		

Microphotographs acquired with magnification of 40x in the microscope.

PARTICLES OBTAINED

Mean diameters, spans e morphologies of microparticles obtained in microfluidic device for two different conditions (proportions of disperse phase – DP and continuous phase – CP).

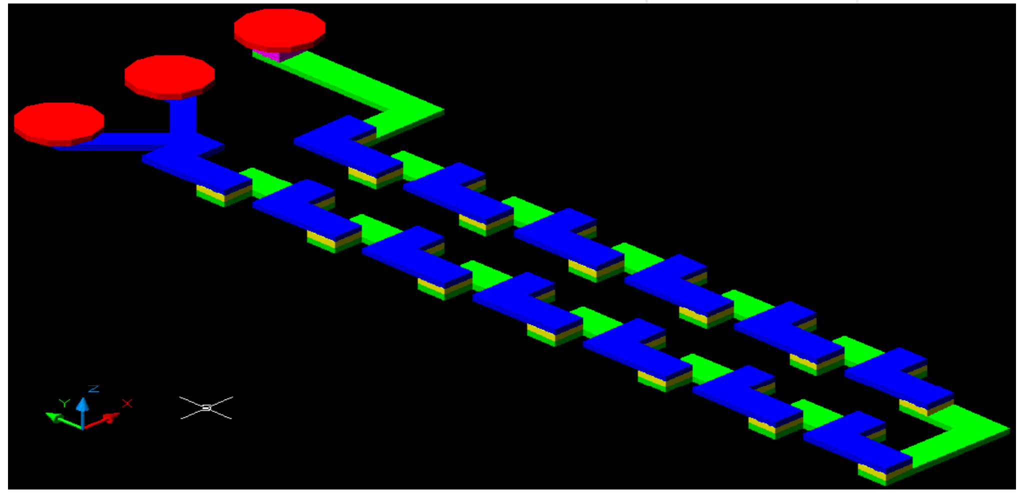
Proportions DP : CP	Mean Diameter (µm) and Span	Morphology
microfluidic devices DP: CP = 1:20	33.6 ± 11.7 (0.7)	
microfluidic devices DP : CP = 1:10	111.2 ± 35.8 (0.6)	

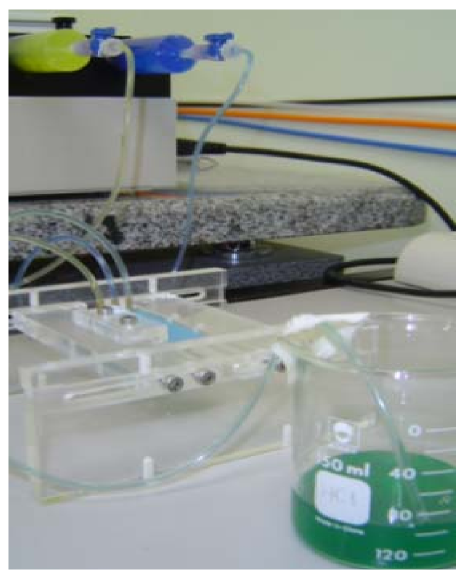
Microphotographs acquired with magnification of 10x in the microscope.

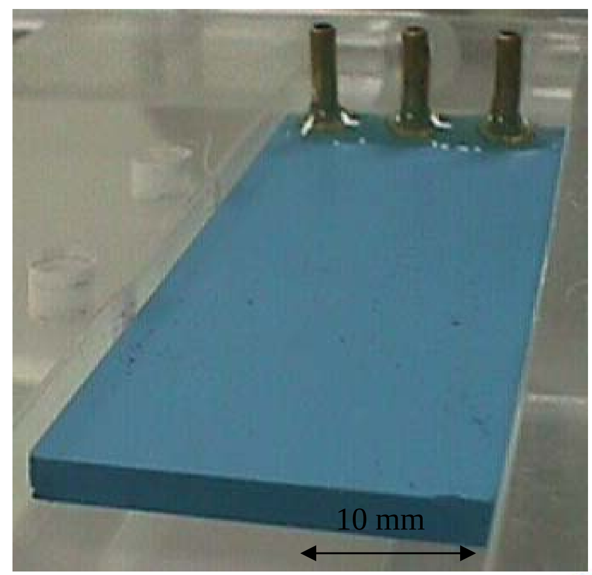
Alvim D I, Cunha M. R, Ré MI, Gongora-Rubio M R, Microfluidic Chip Technology applied on production of Microparticles by ionic gelation for Food application, IFT (Institute of Food Technologists) Annual meeting 2011.

3D MICRO MIXERS IN LTCC

- 3D Serpentine Micromixers can be used for chemical Microreactors in order to fabricate emulsions, particle packaging and nanomaterial fabrication

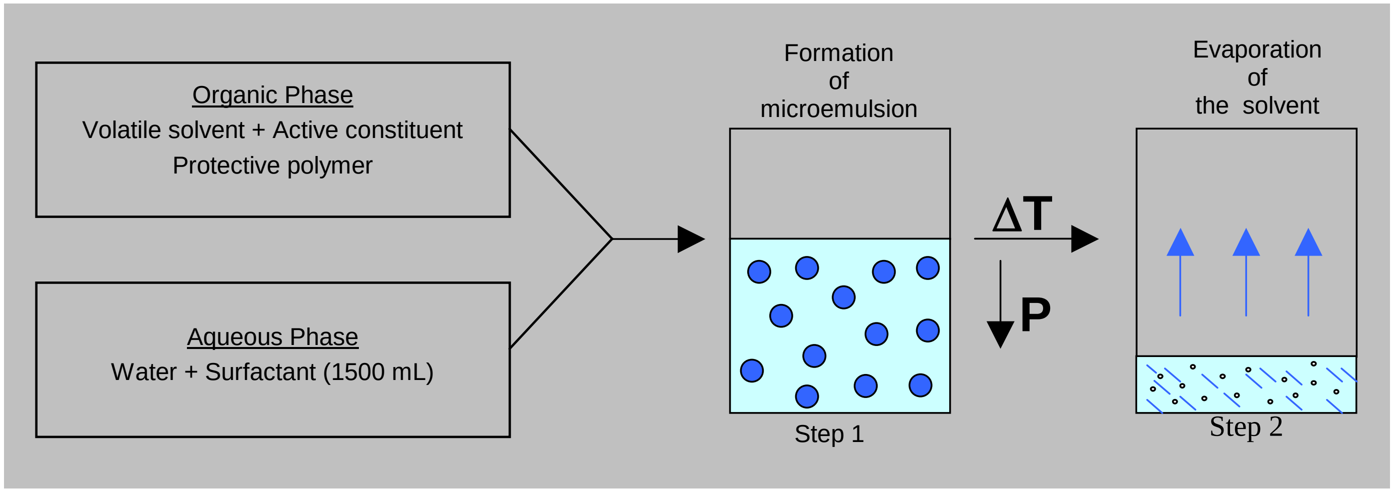




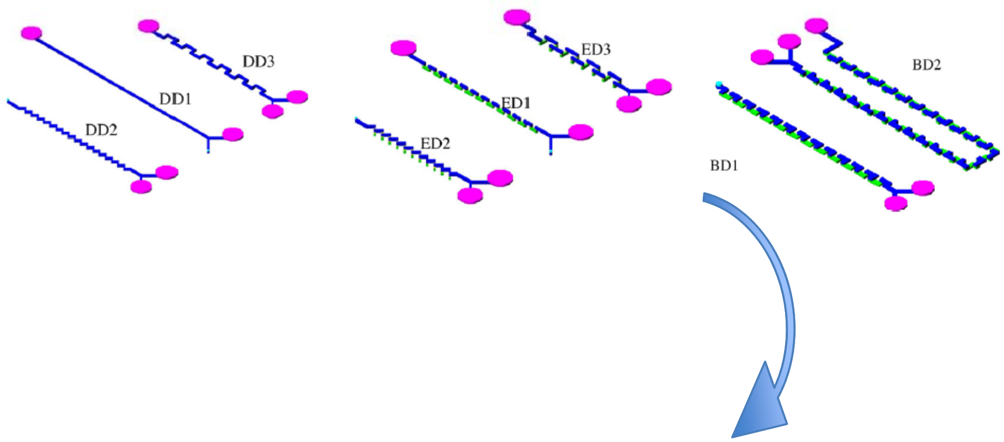


PLGA MICROPARTICLES

- A microfluidic approach to prepare poly(lactic-co-glycolic acid) PLGA microspheres by means of LTCC passive micromixers integrated to an emulsion/solvent evaporation process .
- Passive LTCC micromixers are integrated to the encapsulation process in two steps.
- The first step is the mixing of two immiscible liquids to generate an emulsion.
- Secondly, sequential phenomena such as solvent diffusion and crystallisation generate solid particles such as polymeric microspheres for drug delivery.



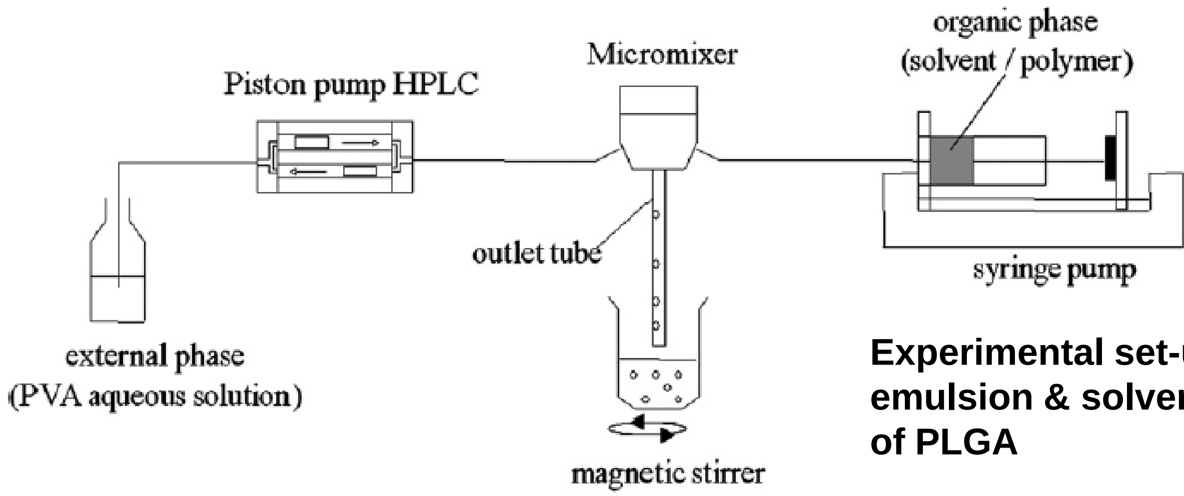
TESTED DEVICES & EXPERIMENTAL SET-UP



Particles size range for PLGA microspheres (without BSA) produced by the emulsion/solvent evaporation method, employing different LTCC microfluidic structures

PLGA microspheres	$d_{(4,3)}$ µm	$d_{(v,\ 0.1)}$ µm	$d_{(v,\ 0.5)}$ µm	$d_{(v,\ 0.9)}$ µm	Span
BD1[a]	14.7	2.0	22.0	39.7	1.7
BD1[b]	9.9	1.5	13.6	26.1	1.7
BD2[a]	6.0	1.3	7.3	20.6	2.7
BD2[b]	4.6	1.1	5.8	13.3	2.1
DD1[a]	36.7	16.6	45.5	86.2	1.5
DD1[b]	33.5	14.7	41.0	80.3	1.5
DD2[a]	26.0	9.9	35.2	63.0	1.5
DD2[b]	20.4	5.6	24.5	56.8	2.0
DD3[a]	33.6	15.8	42.1	74.0	1.3
DD3[b]	19.6	4.2	26.4	54.2	1.8
ED1[a]	26.7	8.5	36.0	70.0	1.7
ED1[b]	9.0	1.4	11.1	39.2	3.3
ED2[a]	23.7	8.7	31.1	57.4	1.5
ED2[b]	9.0	1.6	11.4	32.8	2.7
ED3[a]	30.8	15.5	38.6	61.9	1.1
ED3[b]	9.7	1.7	11.6	38.1	3.1

[a] Flow rate of 1.1 l/h.
[b] Flow rate of 2.2 l/h.

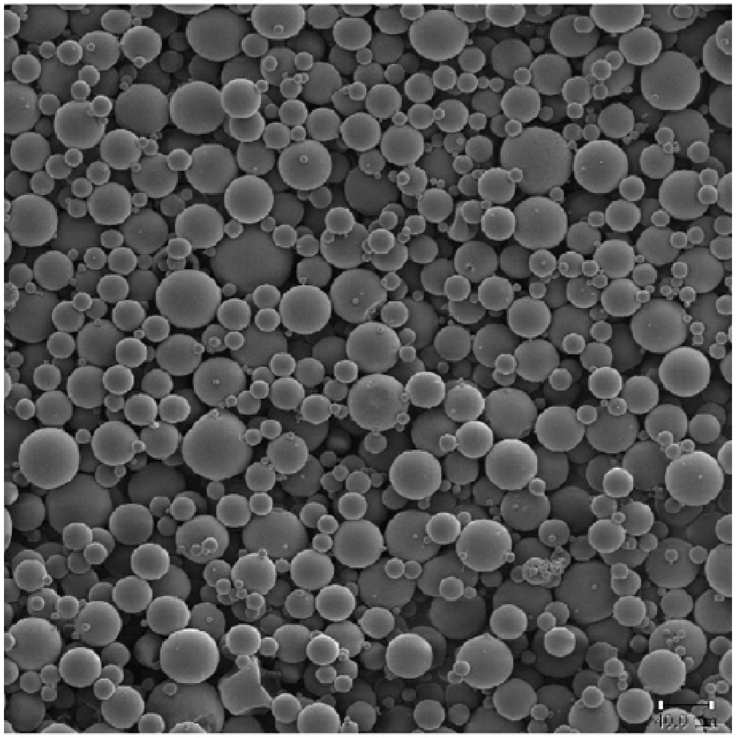


Experimental set-up for emulsion & solvent evaporation of PLGA

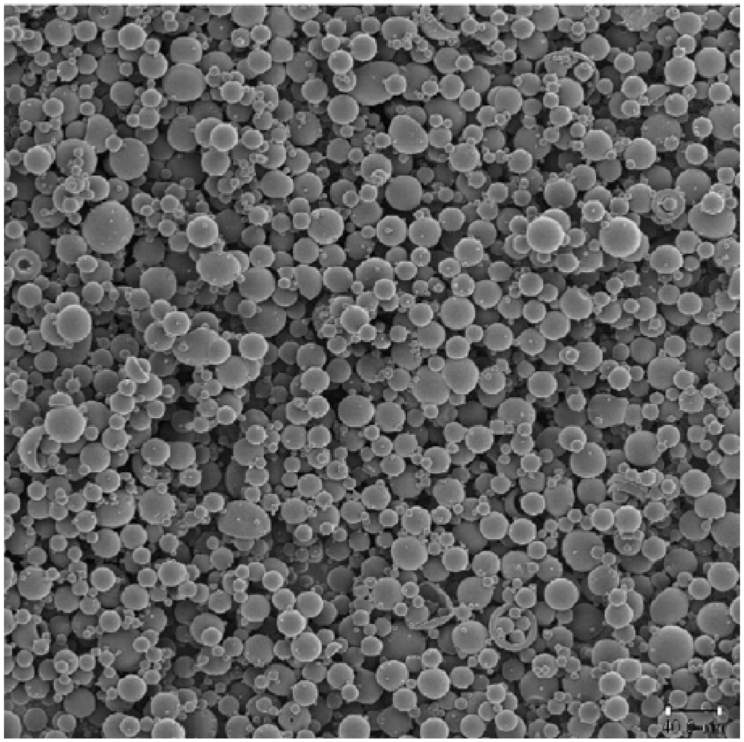
PLGA MICROPARTICLES

- SEM micrographs (750 ×) of PLGA microspheres generated by emulsion/solvent evaporation process, with a LTCC micromixer (BD1) at different flow rates: A) 1.1 l/h; B) 2.2 l/h. The results show that the LTCC micromixers could generate PLGA microspheres with mean diameter $d_{(4,3)}$ from 4.7 to 36.7 µm and span variation from 1.1 to 3.3.

A



B



II WORKSHOP EM MICROFLUÍDICA

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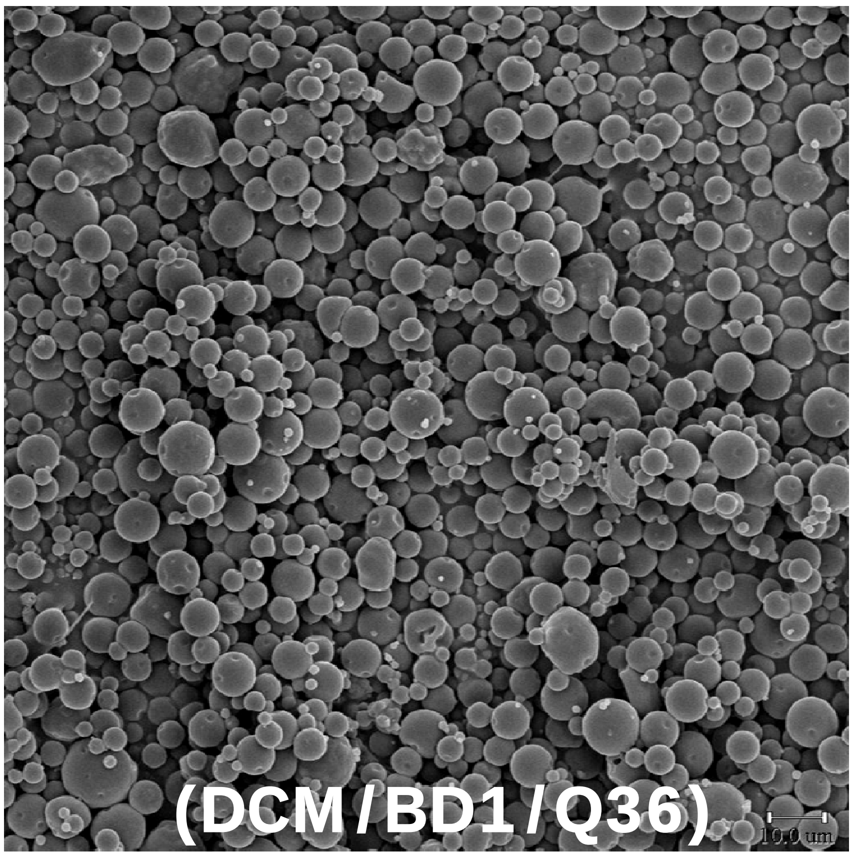
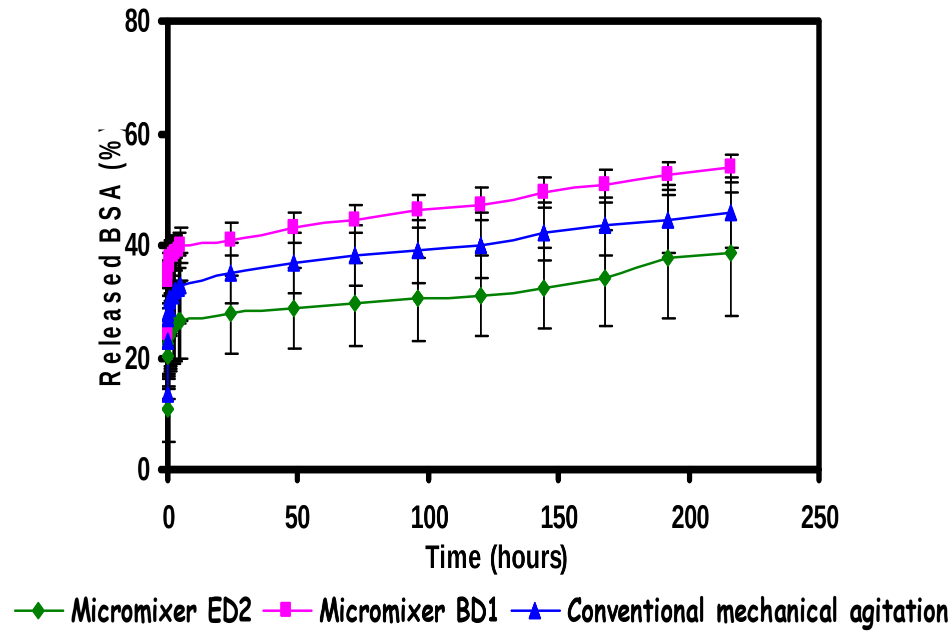
PLGA for Microencapsulation

PLGA (Poly (DL-lactide co-glycolide) microspheres loaded with BSA (Bovine serum albumin) (750x)



Comparison of particle release obtained with micromixers and standard methods (Turrax agitation)



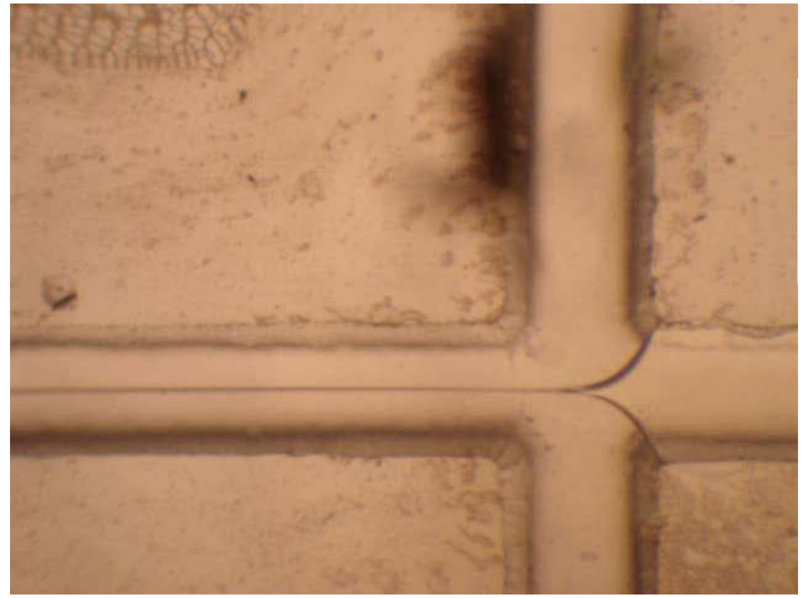
M. Ribeiro-Costa, et al. Preparation of protein-loaded-PLGA microspheres by an emulsion/solvent evaporation process employing LTCC micromixers, Powder Technology Vol-190, p.107–111, (2009)

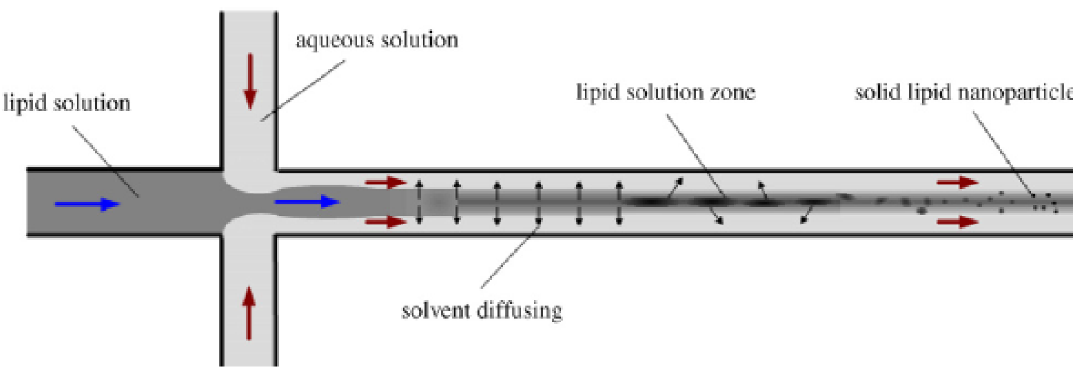
NANOLIPOSOME PRODUCTION VIA MICROFLUIDICS

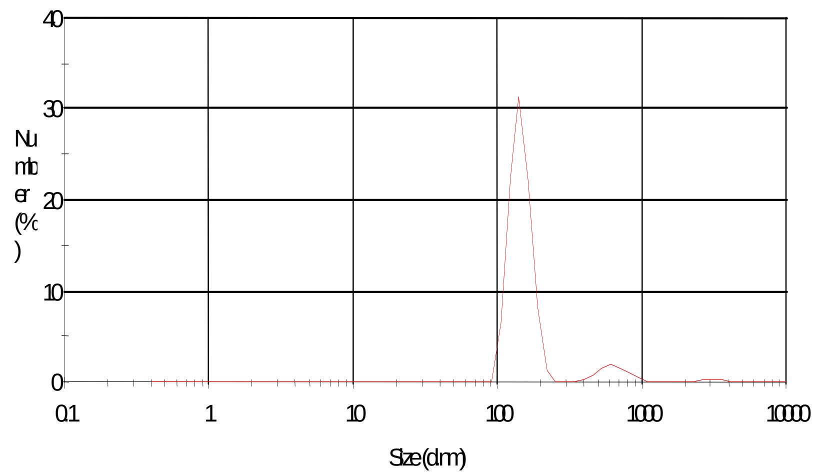
- BOTTOM - UP

Liposome Microfluidic Hydrodynamic Focusing

Glass Microfluidic device in flow focalization regime were used to obtain nanoliposomes







J. N. Schianti, et al. Glass flow focusing microfluidic device for nanoliposome production, Proc: IBERSENSOR 2010

UNICAMP

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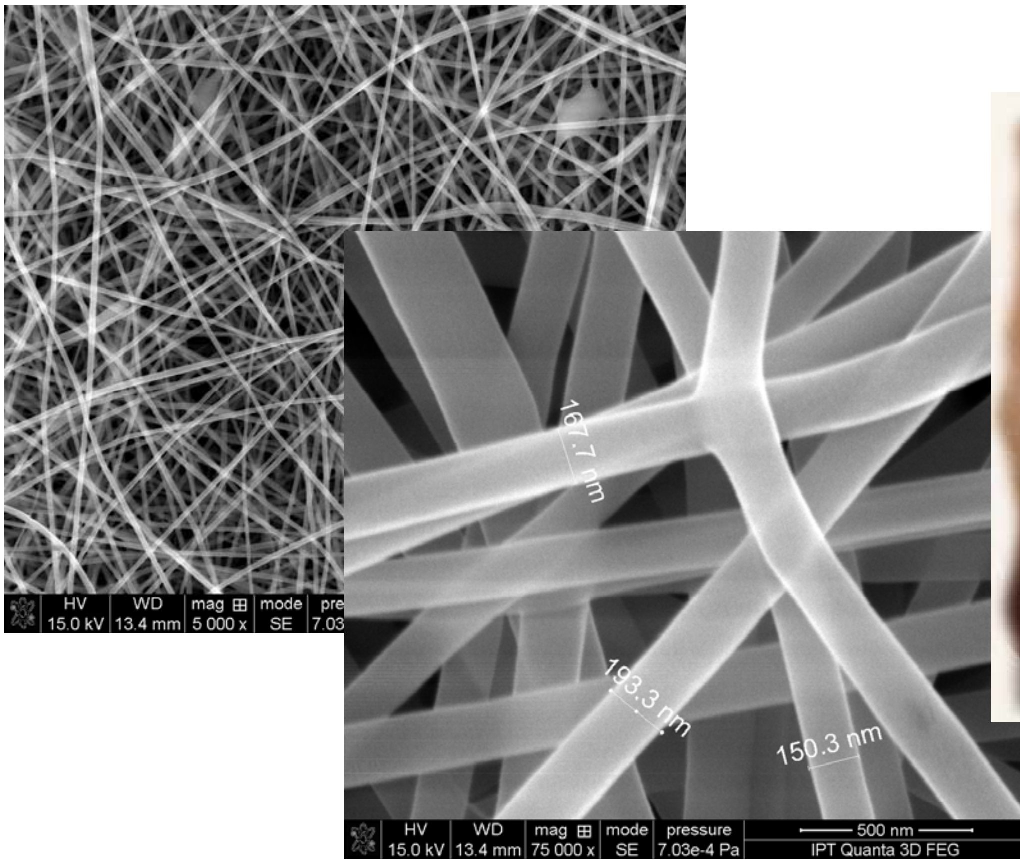
ELECTROSPINNING

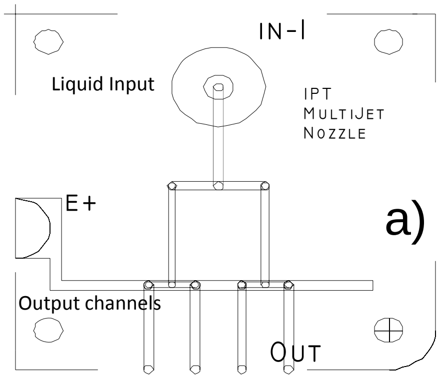
Development of nanofibers by electrospinning process using biocompatible polymer to incorporate pharmaceutical actives.

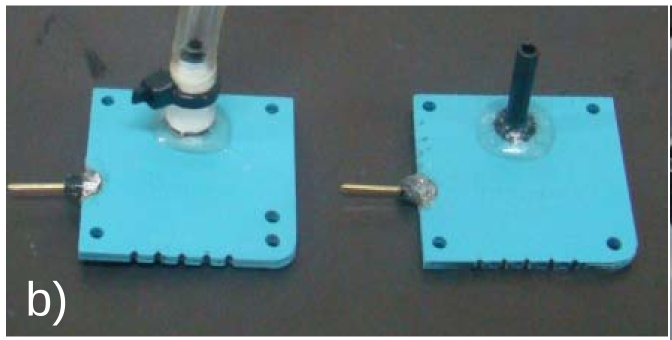


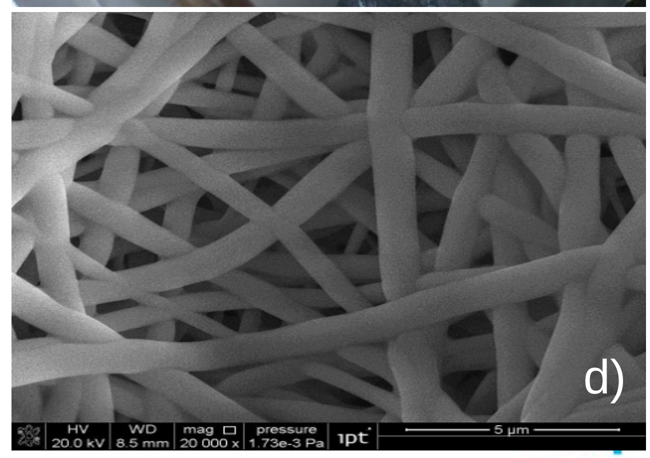
II WORKSHOP EM MICROFLUÍDICA

MULTI-JET ELECTROSPINNING USING LTCC DEVICE

A multi-jet electrospinning LTCC device was used to produce nanofiber mats from different polymer solutions in order to overcome the trade-off between applied voltage and flow rate.

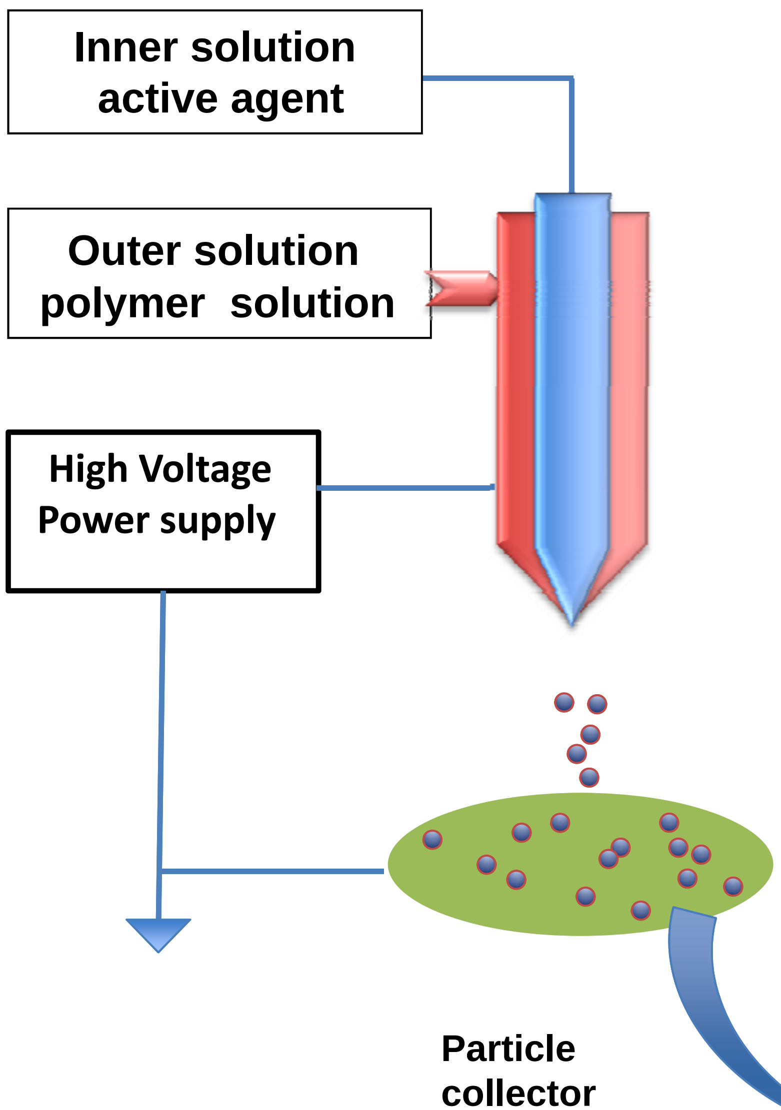


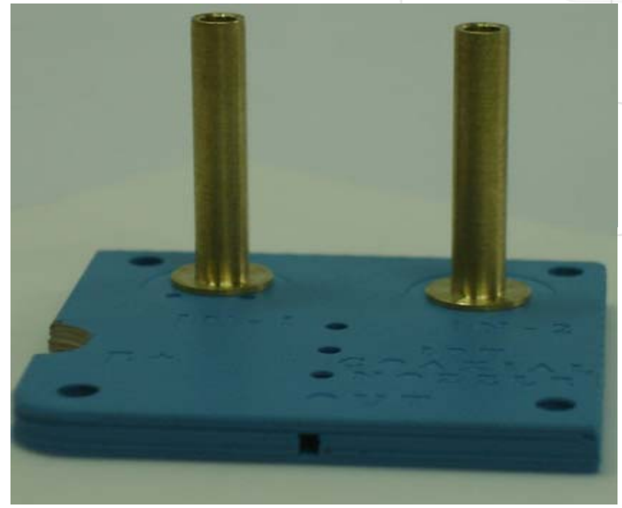


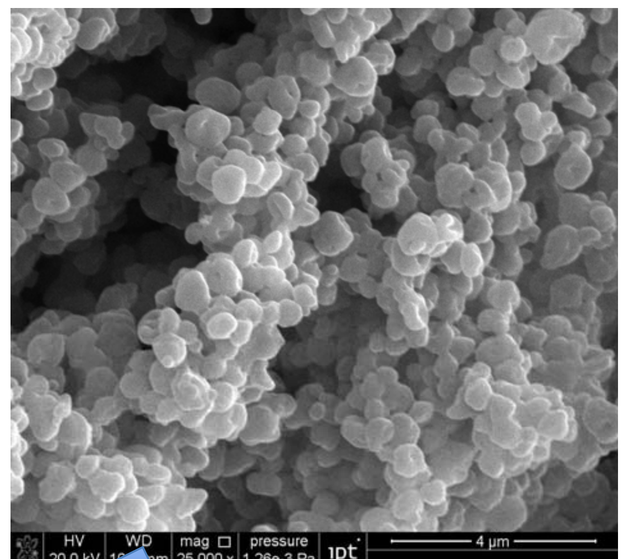


a) Device Lay-out
b) Fabricated devices
c) Experimental disposition
d) Fabricated mat.

ELECTROSPRAY MICRODEVICES







DEVICE FOR SILVER NANOPARTICLE PRODUCTION

Contamination of catheters inserted in the blood stream causes infection and subsequent sepsis.

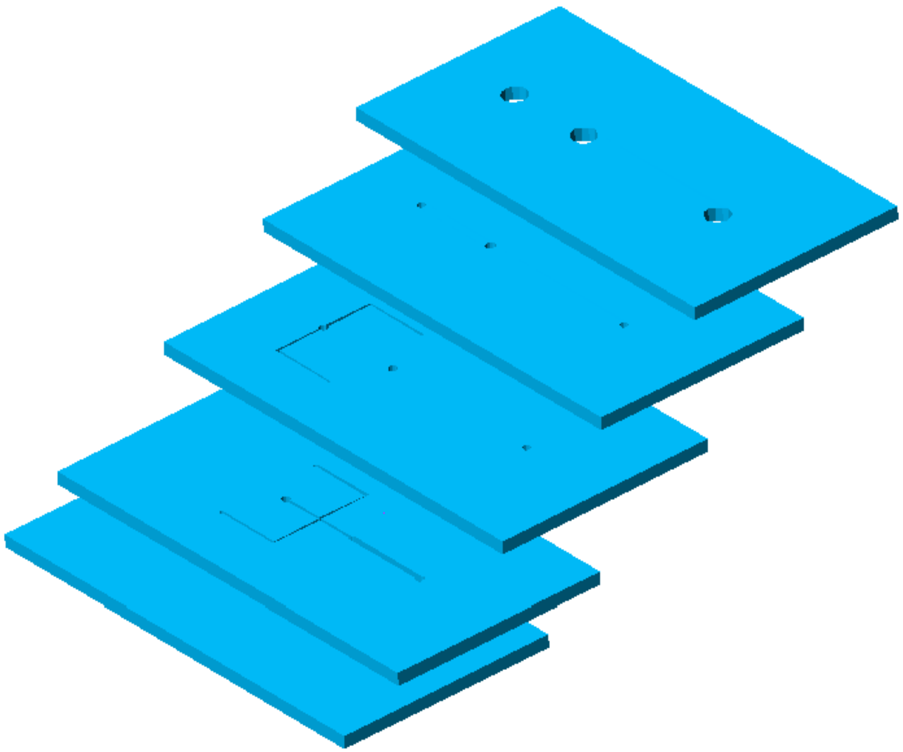
The foresee application is consists of associating silver nanoparticles with a polymeric material that coats a catheter surface.

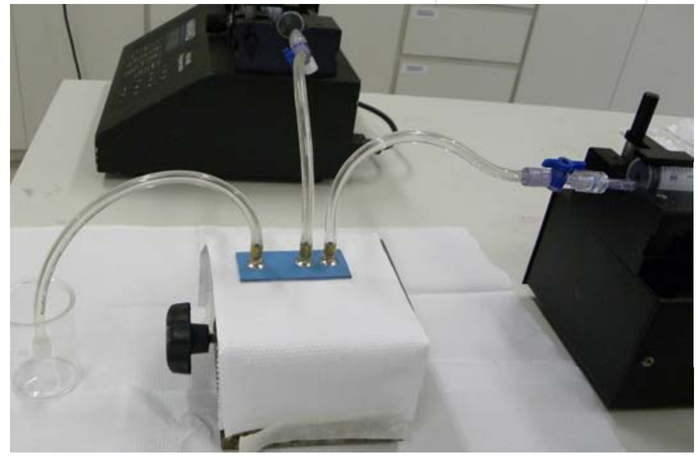
LTCC Microreactors can be used to obtain silver nanoparticles in continuous fashion using the following reaction:

$$2AgNO_{3(aq)} + 2NaBH_{4(aq)} \longrightarrow 2Ag_{(s)} \downarrow + 2NaNO_{3(aq)} + \uparrow H_{2(g)} + \uparrow B_2H_{6(g)}$$

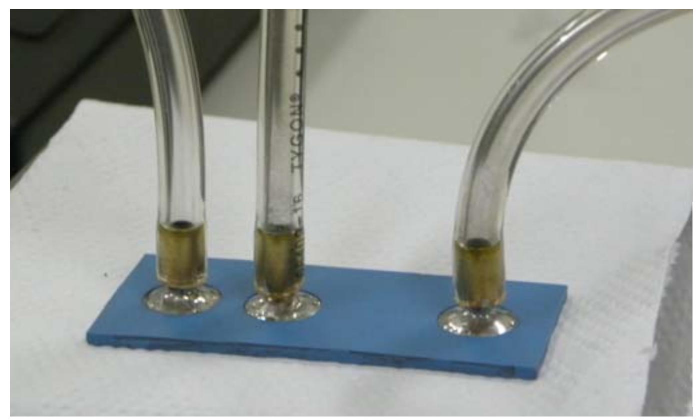
LTCC DEVICE FOR SILVER NANOPARTICLES

Device layers





Experimental line-up



Fabricated device

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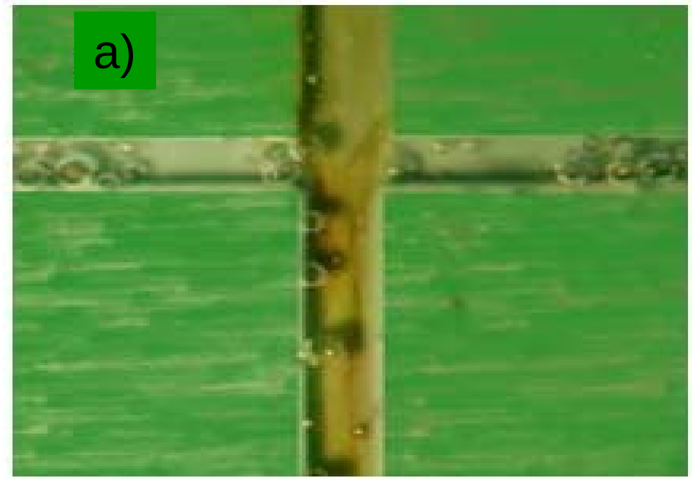
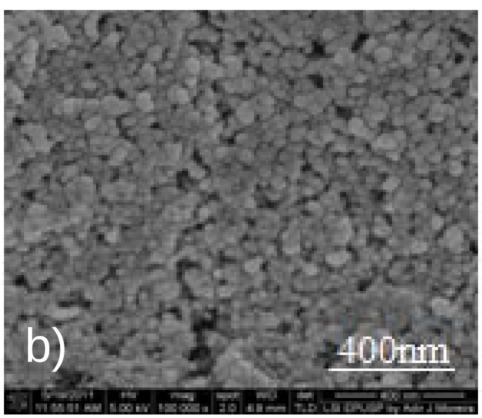
FABRICATED NANOPARTICLES

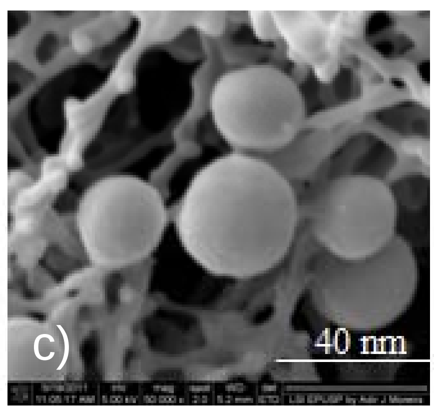
a) Ag NP's reaction obtained in LTCC device with a glass window.

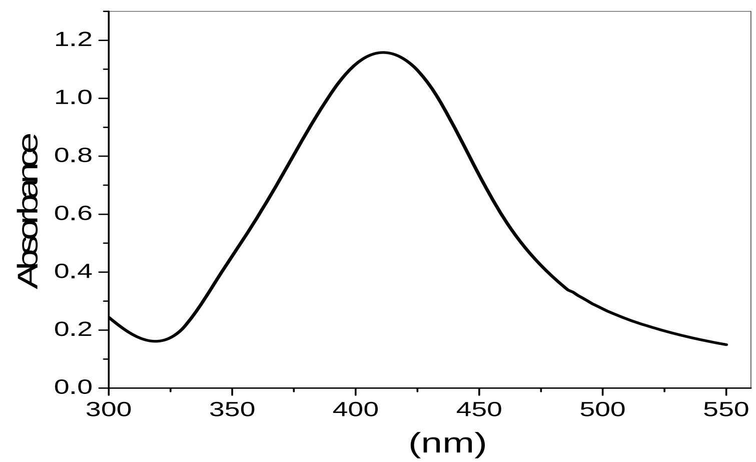
b) and c) fabricated nanoparticles

d) UV-Visible spectra of silver nanoparticles solution.







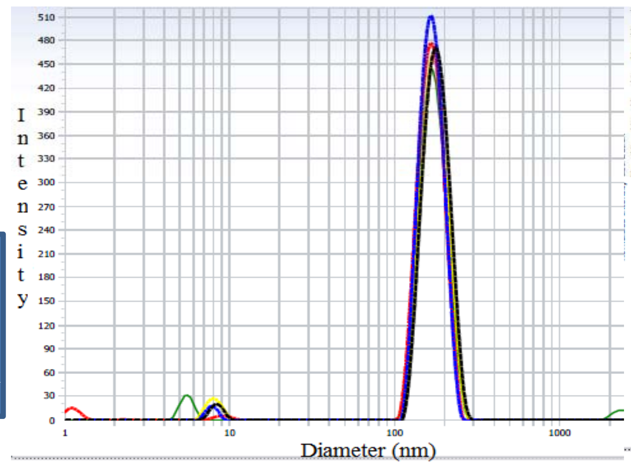


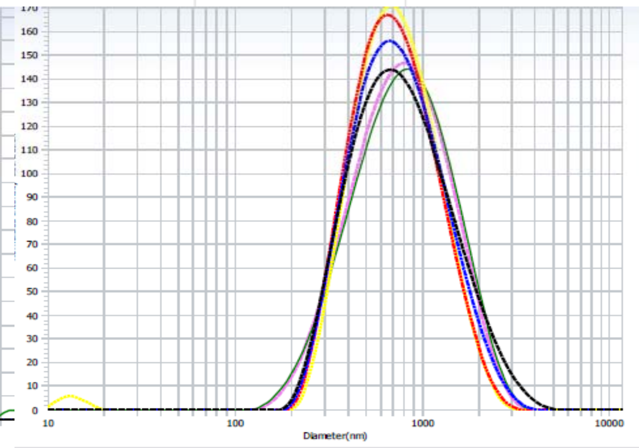
MICROFLUIDIC PROCESS FOR MICRO AND NANO CRYSTALS

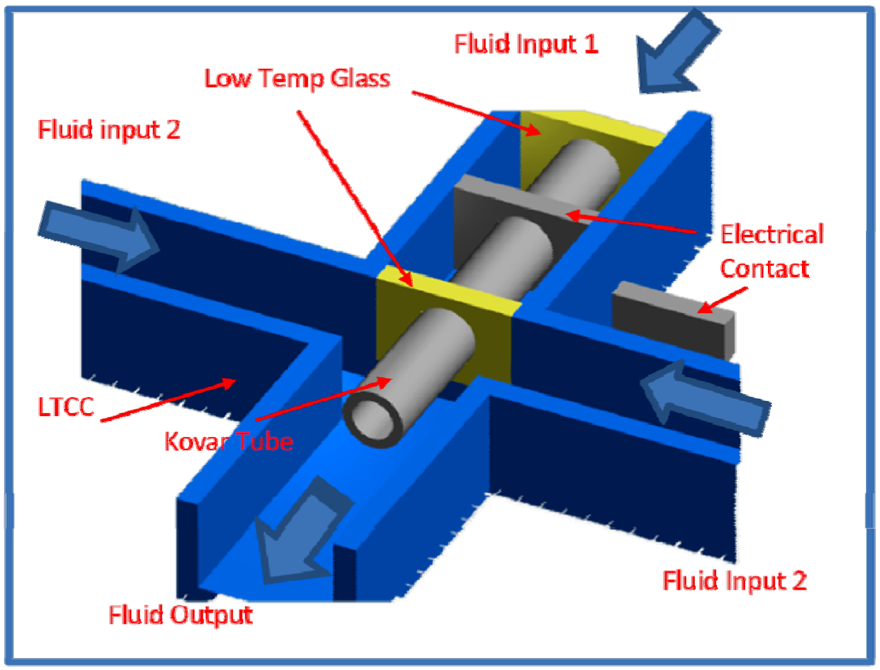
CRYSTALLIZATION PROCESS TO OBTAIN RIFAMPICIN AMORPHOUS NP's

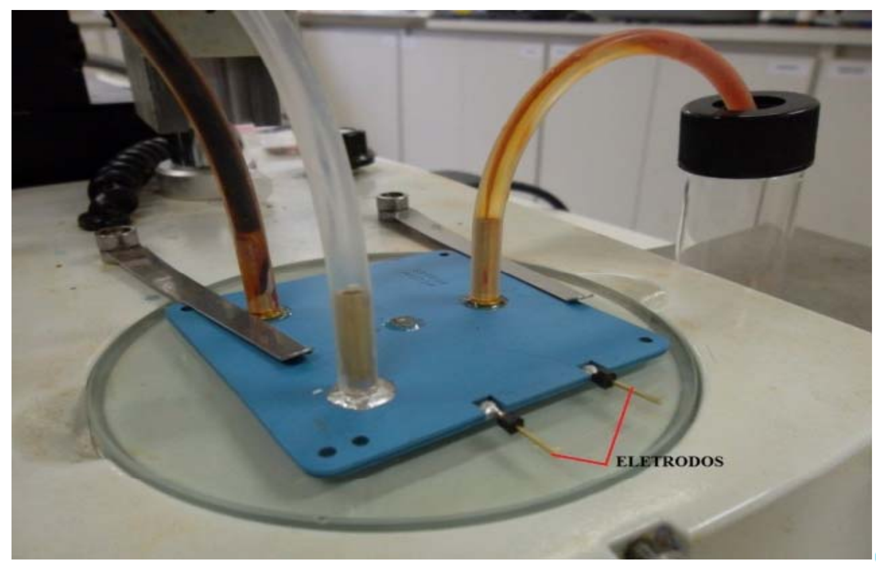
BOTTOM - UP

Nanocrystals
Microfluidic 3D Flow Focusing
+ HV size tuning



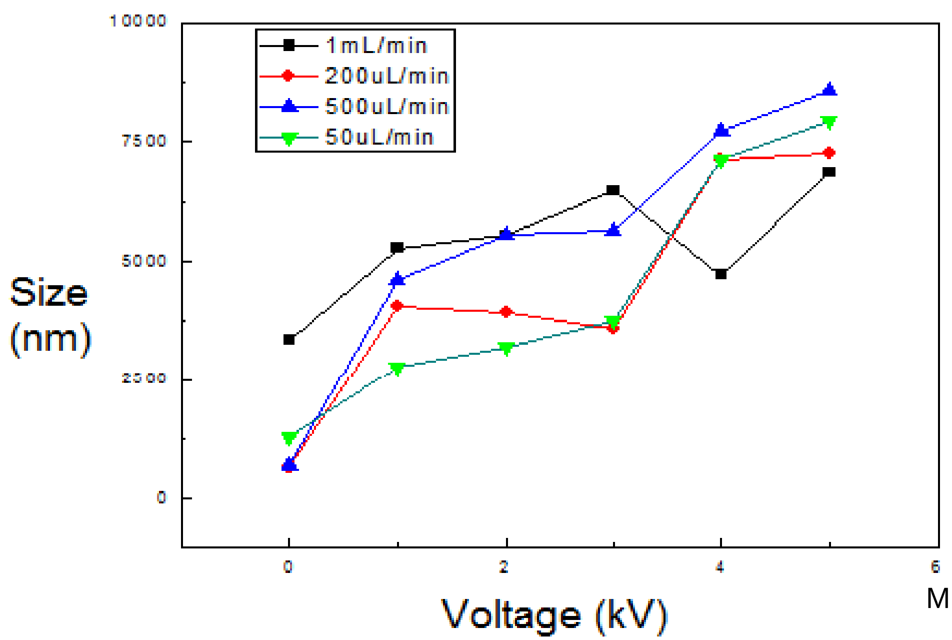


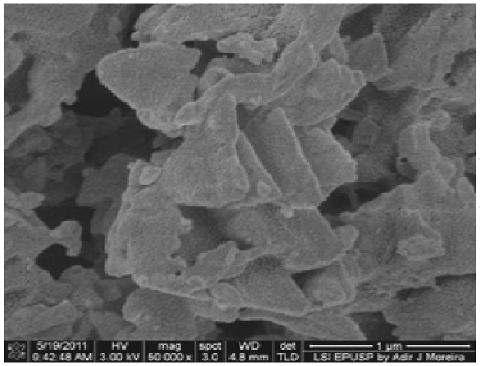




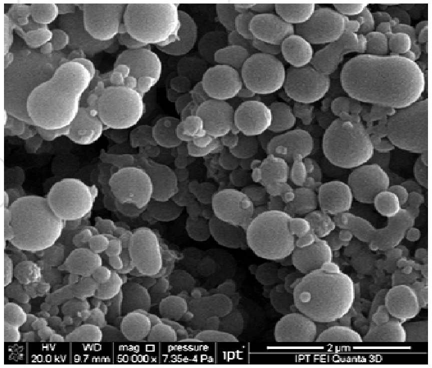
DEVICE FOR MICROPARTICLES

We use 3D geometry to get better control of flow focusing and HV to obtain fine control of particle size in different flow regimes

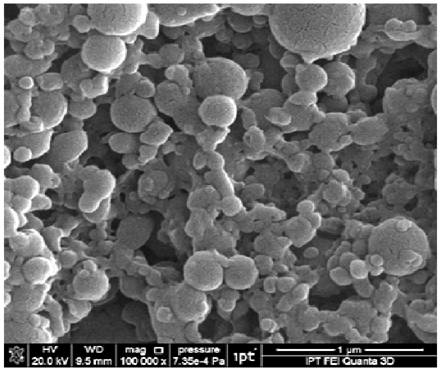




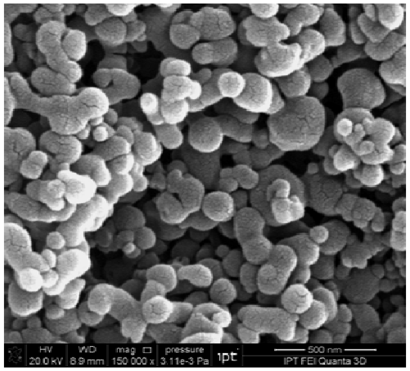
Raw Material



No HV Applied



3KV applied



5KV applied

M. R. Gongora-Rubio, K. H., J. de Novais Schianti, A. Marim de Oliveira, N. Neto Pereira Cerize & M. H. Ambrosio Zanin, CICMT-2012

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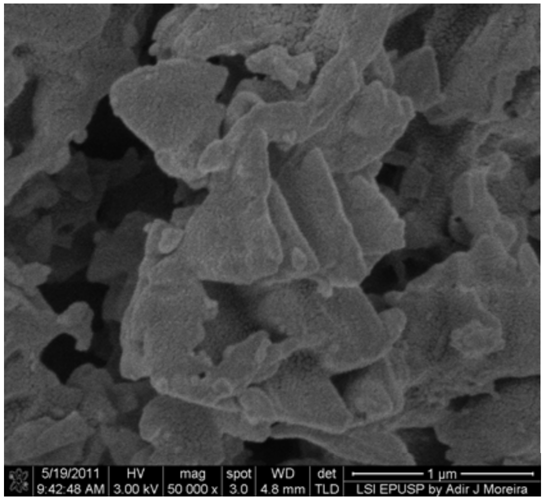
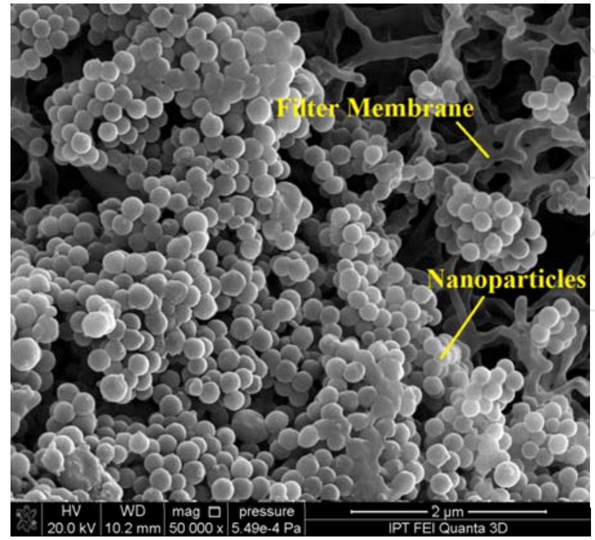
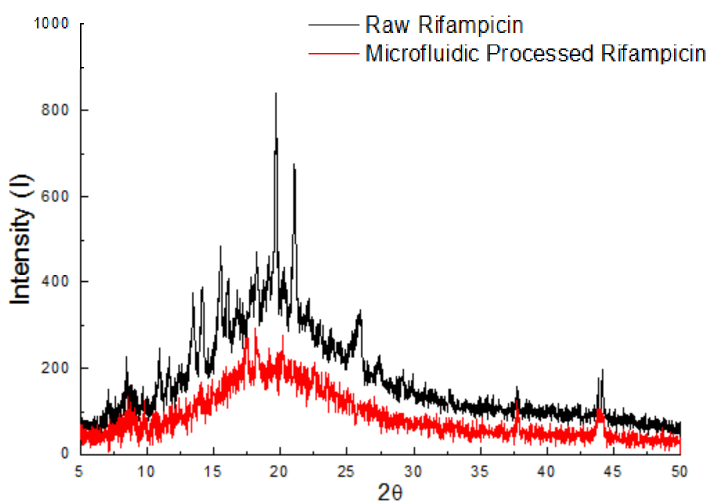
DEVICE FOR NANOPARTICLES



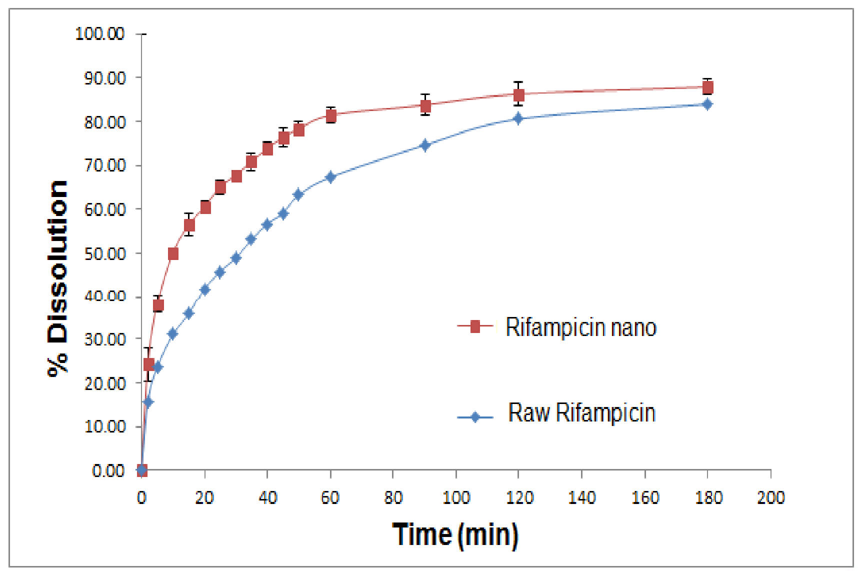
Raw Material



Rifampicin processed via Microfluidics



XRD profile of Raw Rifampicin and Processed Rifampicin.



Rifampicin Dissolution Profile

CONCLUSIONS

- We showed several microfabricated devices for chemical process intensification, including synthesis of micro and nanoparticles for practical applications.
- Feasibility of scaling microfluidic droplet/particle generation up to production rates of hundreds of milliliters per hour.
- This could lead to a Microfluidic route adapted to the encapsulation process in order to design capsule or emulsion with size and morphology controlled in continuous process.

Thank you!

Mário Ricardo Gongora-Rubio

gongoram@ipt.br