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Groupe d'Intensification et d'Intrégration des Procédés Polymères (G2IP)
Institut de Chimie et Procédés pour l'Environnement, l'Énergie et la Santé
École de Chimie, Polymères et Matériaux
Université de Strasbourg

Engineering polymer micro- and nanoparticles with controlled size and morphology by microfluidics

Prof. Christophe A. Serra

collaborations with
Z. Chang, R. Zentel, M. Koehler, L. Prat, Y. Hoarau, I. Kraus, M. Schmutz, T. Vandamme & N. Anton

http://icpees.unistra.fr/caserra

Okayama U, July 16th, 2014

Outline

- 1. Introduction

- 2. Microparticles by capillary-based emulsification
  - Experimental setup
  - Applications

- 3. Nanoparticles
  - Micromixer-assisted nanoprecipitation
  - Elongational-flow emulsification

- 4. Conclusion

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- **1. Introduction**
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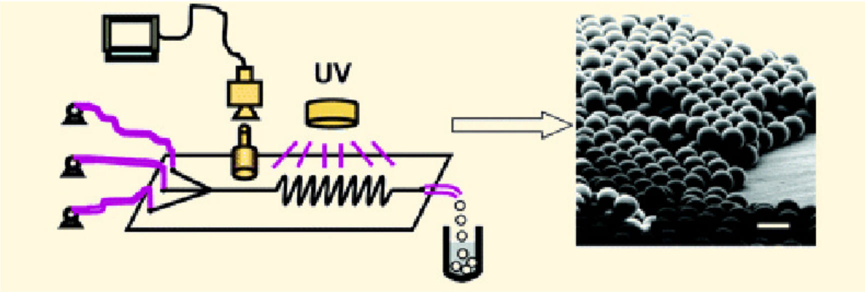
1. Introduction

- Microfluidic devices (MFDs) are
  - Efficient emulsification systems

- Advantages
  - Wide range of droplets sizes
    - Few microns to 100s μm / few tens to 100s nm
    - Simply controlled by operating parameters (e.g. Qc and Qd)
  - Monodispersed micro and nanodroplets (O/W or W/O)
    - CV < 2-5% / PDI < 0.4
  - Wide range of frequencies
    - Several Hz to few kHz
  - Various droplet morphologies
    - Multiple droplets, janus droplets, slug-like droplets

1. Introduction

- **Polymer particles are obtained by:**
  - **Thermically-induced polymerization**
  - **Photopolymerization under UV irradiation**



Polymer particles with controlled-size, -composition and -morphology

Kumacheva and coll., Langmuir, 2005, 21, 11614-11622

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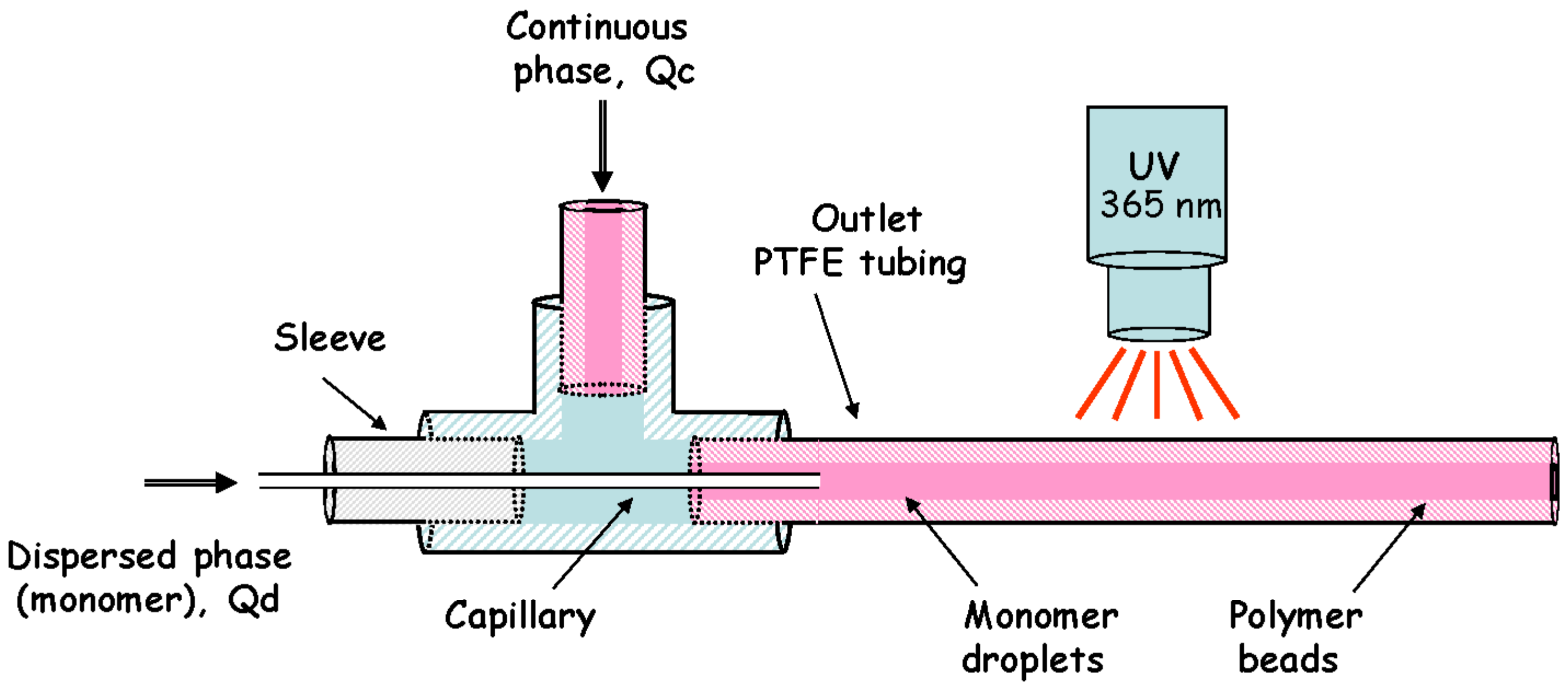
- **Axisymmetric single capillary co-flow device**



1/16 "
T-junction

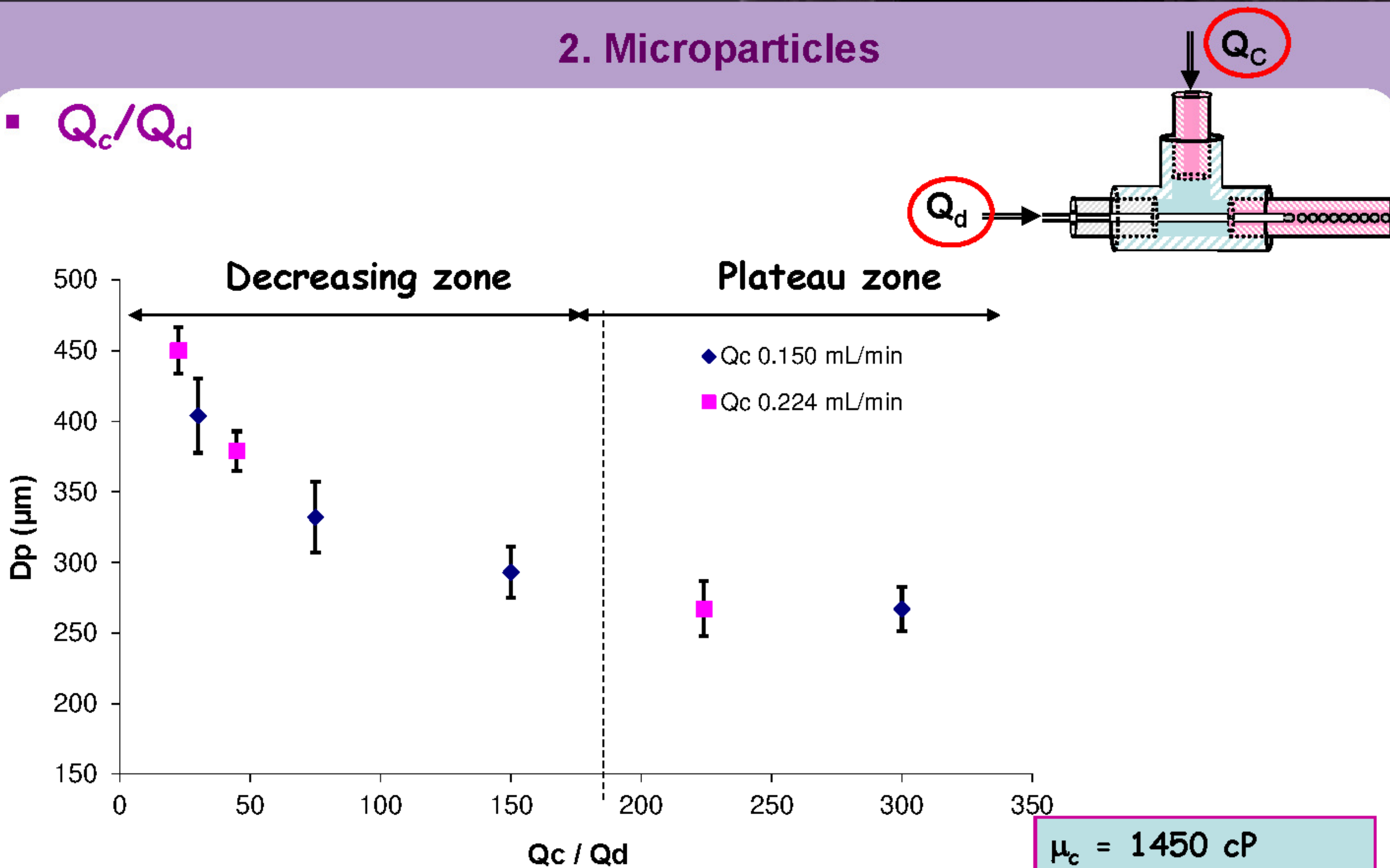
Procedure

Microdrops generation

- **Influence on particle diameter (D_p) of:**
  - Flow rate ratio (Q_c/Q_d)
    - *From 10 to 300*
  - Carrier fluid viscosity (μ_c)
    - *From 350 to 1450 cp*
  - Capillary I.D. (D_{cap})
    - *Gauge-25 = 260 µm*
    - *Gauge-32 = 110 µm*
  - Outlet tubing I.D. (D_{tube})
    - *1.6 mm*
    - *1.06 mm*
  - Monomer (M)
    - *Methyl methacrylate (MMA)*
    - *Ethoxy ethyl methacrylate (EEMA)*
  - Amount of a functional comonomer (w_f)
    - *From 0 to 8 wt%*

2. Microparticles

- Q_c/Q_d



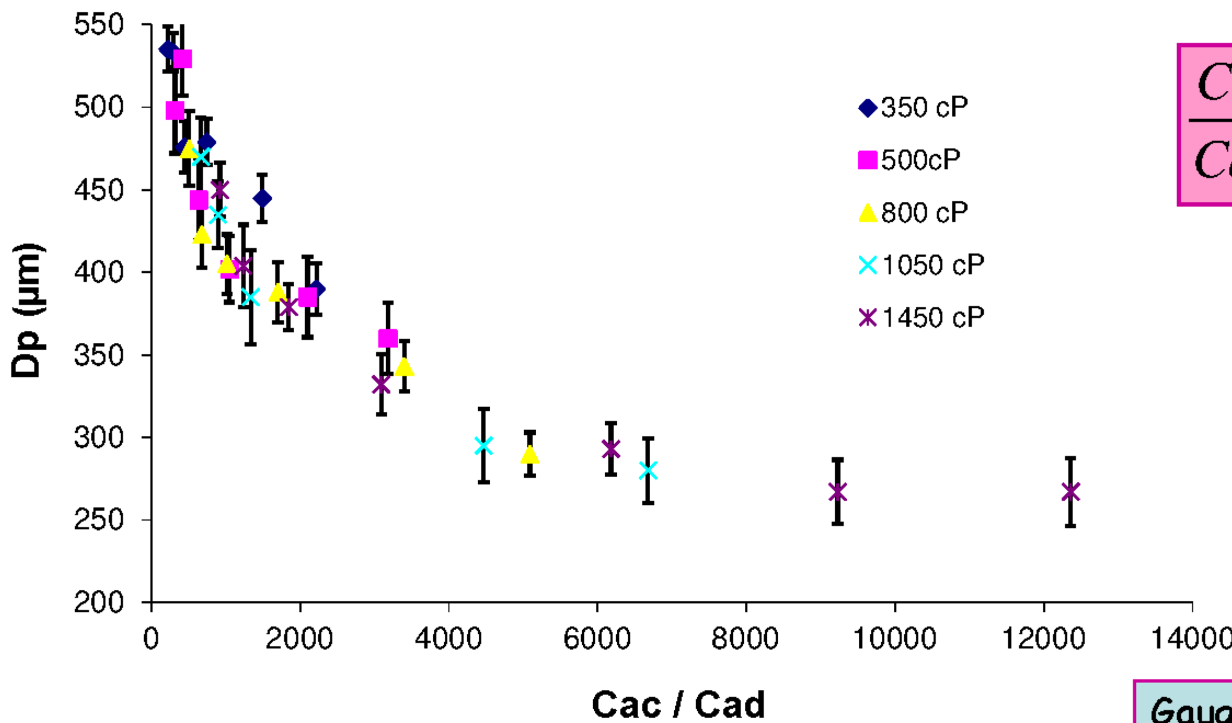
μ_c = 1450 cP
Gauge-25: 260 µm
Tubing 1.6 mm i.d.

2. Microparticles

- **Viscosity (μ_c): a master curve**

$$Ca = \frac{\mu V}{\gamma_{12}}$$

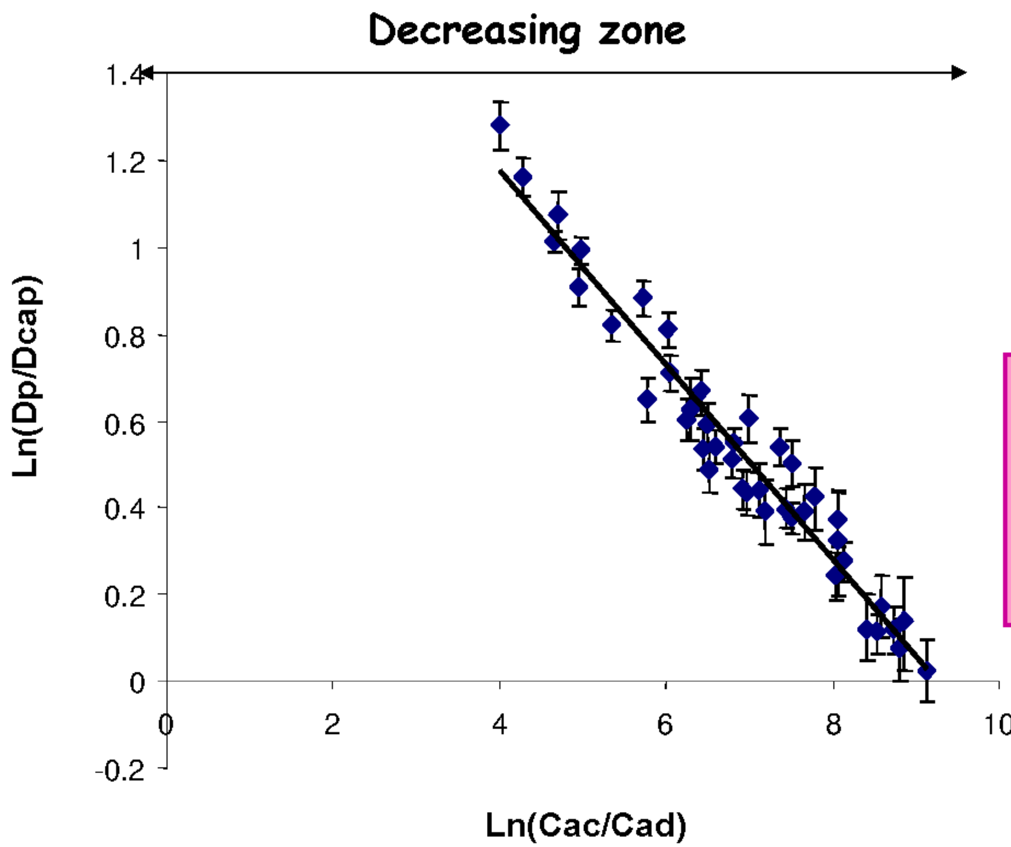
$$\frac{Ca_c}{Ca_d} = \frac{\mu_c . V_c}{\mu_d . V_d}$$



Gauge-25: 260 µm
Tubing 1.6 mm i.d.

2. Microparticles

- An overall master curve



Empirical relationship between two dimensionless numbers ☺

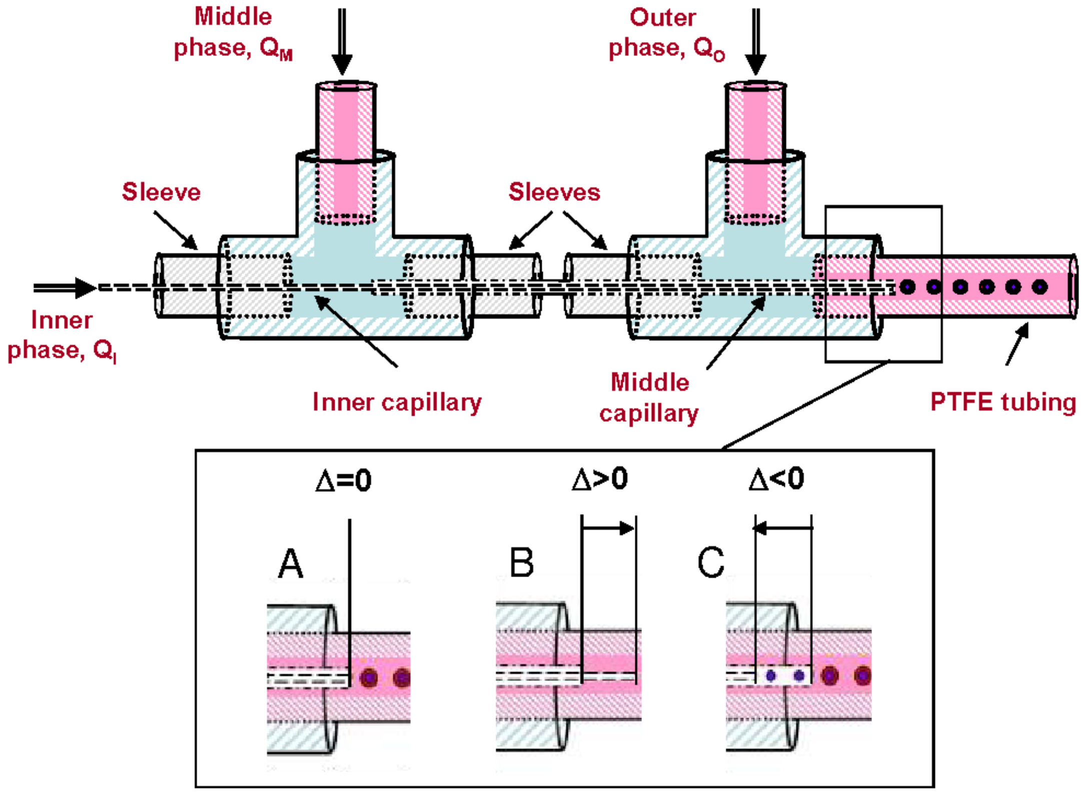
$$\frac{Dp}{Dcap} = K\left(\frac{Ca_c}{Ca_d}\right)^{-0.22}$$

$$with \quad K = 7.92$$

C. Serra et al., Langmuir, 23 (14) (2007) 7745-7750

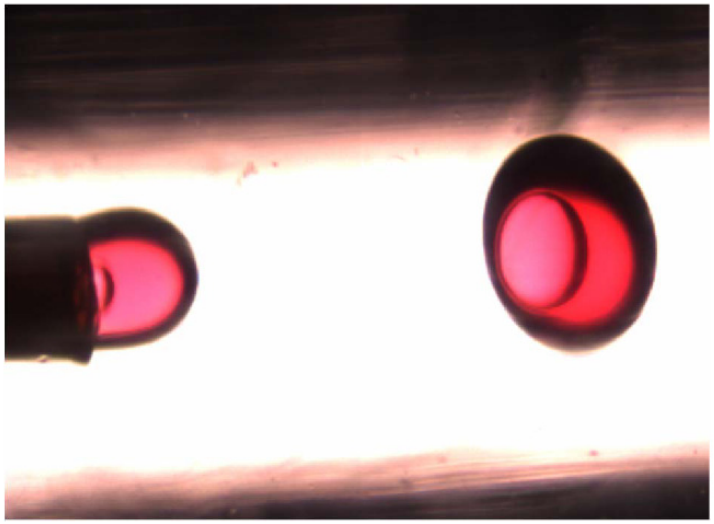
2. Microparticles

- **Axisymmetric co-axial capillaries co-flow device**

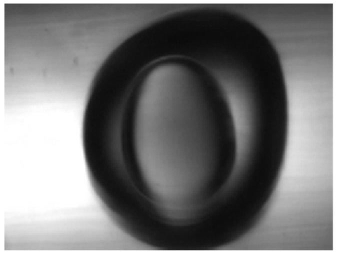


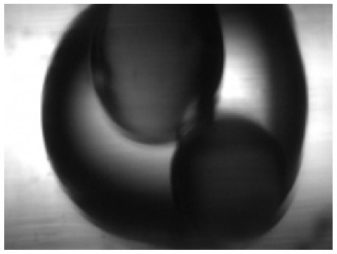
2. Microparticles

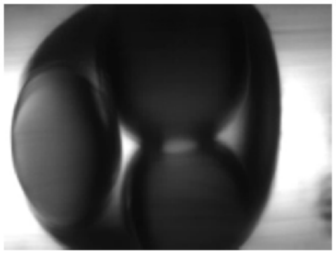
- **Axisymmetric co-axial capillaries co-flow device**
  - **Same relative position (Δ = 0)**



Double droplet



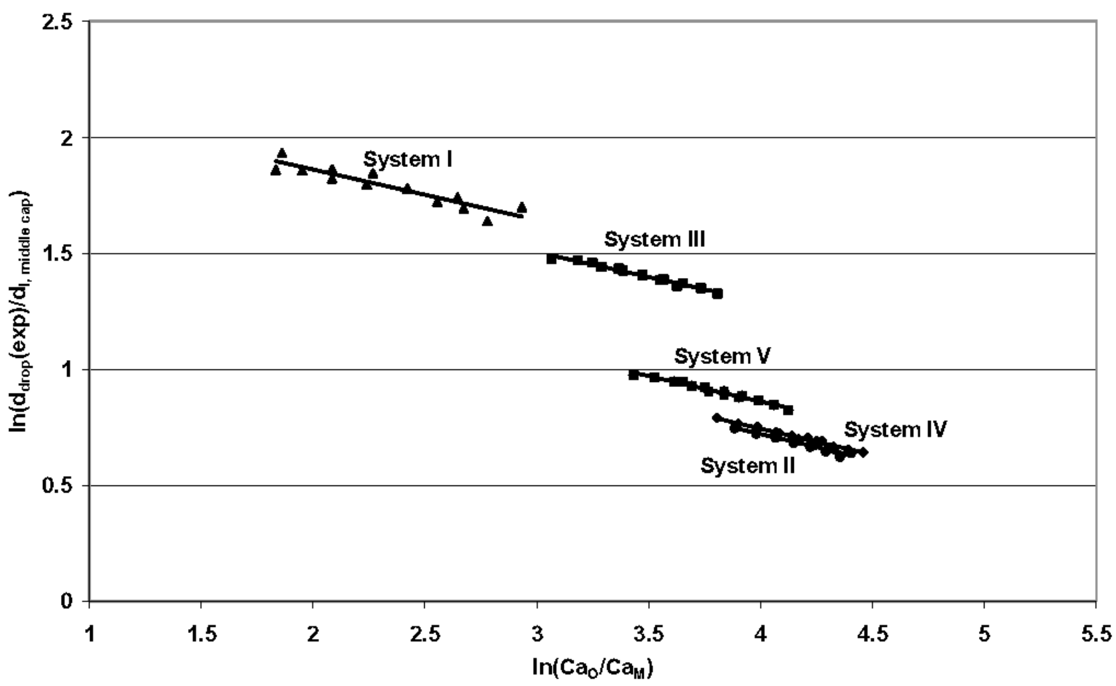




Z. Chang et al., Lab. Chip., 9 (2009) 3007-3011

2. Microparticles

- **Overall droplet diameter prediction**

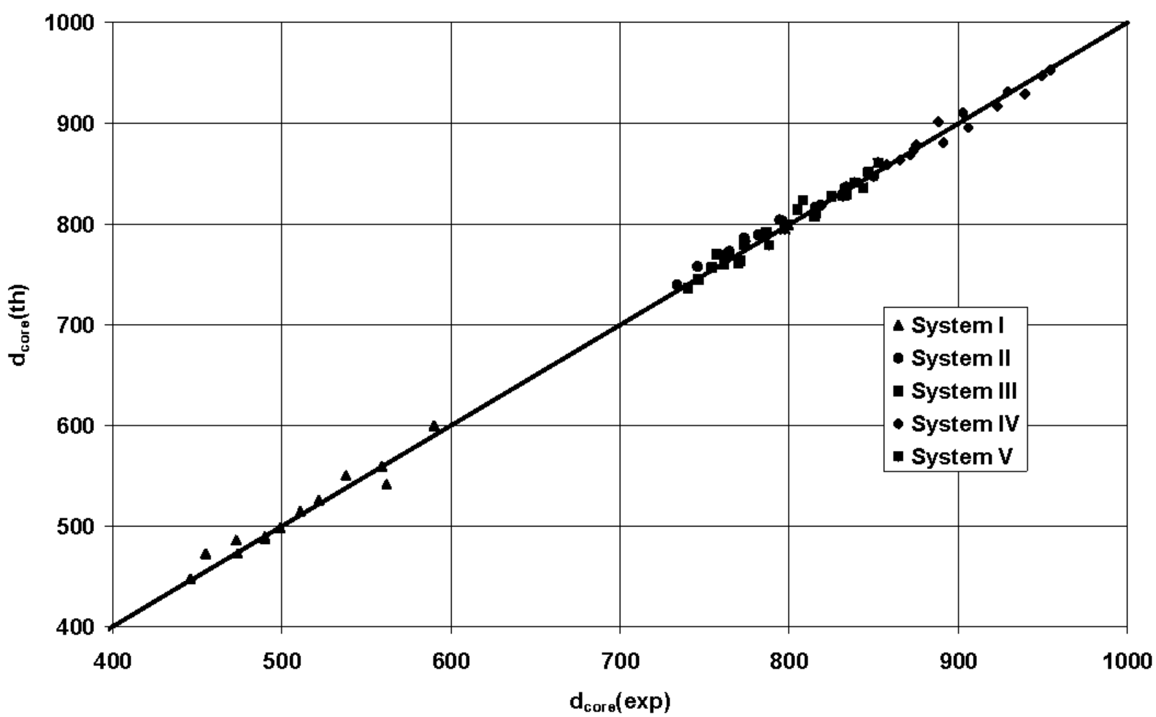


$$\frac{d_{drop}}{d_{I,middle\ cap}} = K\left(\frac{Ca_O}{Ca_M}\right)^{-0.22}$$

Z. Chang et al., Lab. Chip., 9 (2009) 3007-3011

2. Microparticles

- Core droplet diameter prediction

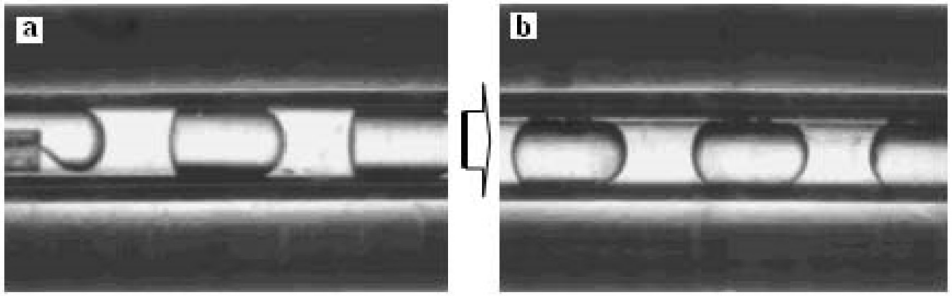


$$d_{core} = \sqrt[3]{\frac{Q_I}{Q_I + Q_M}}\, d_{drop}$$

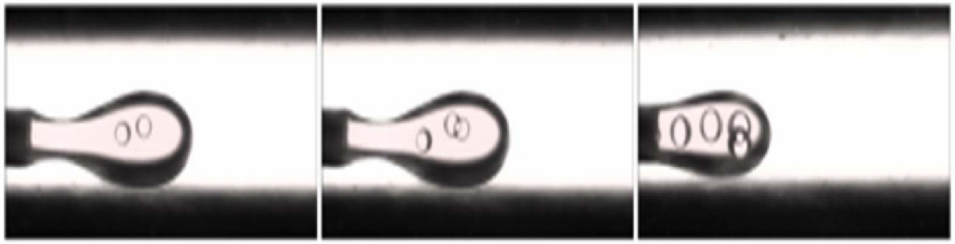
Z. Chang et al., Lab. Chip., 9 (2009) 3007-3011

- *Axisymmetric co-axial capillaries co-flow device*
  - Negative relative position (Δ < 0)

Hydrophylic
Hydrophylic

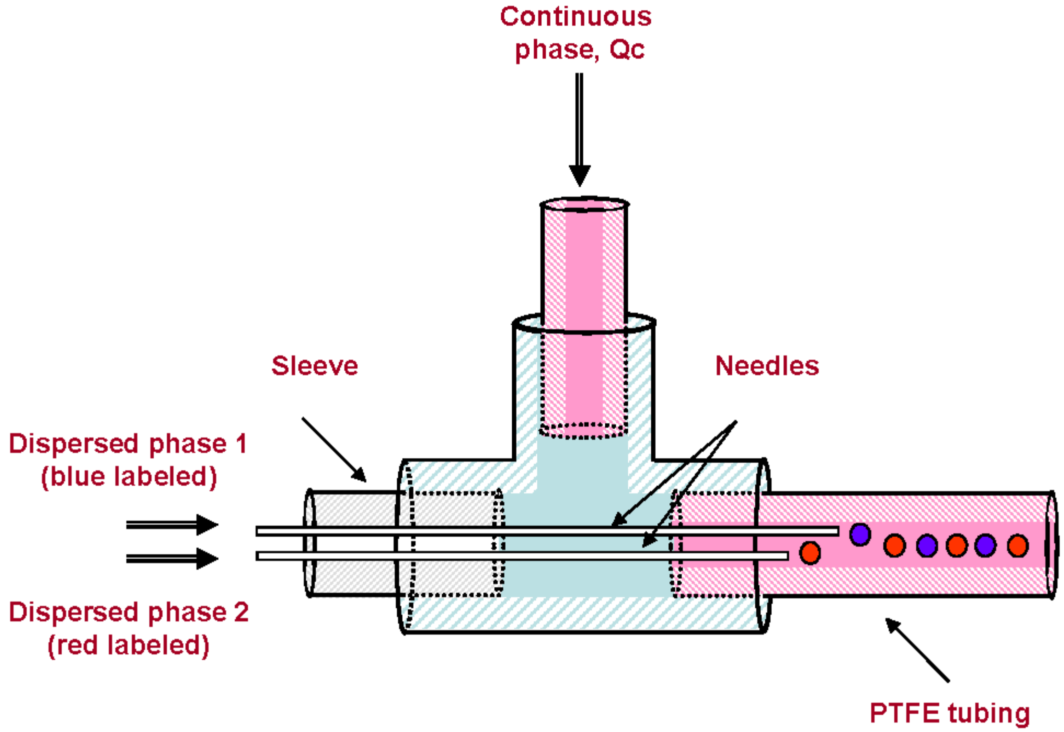


Hydrophobic
Hydrophylic



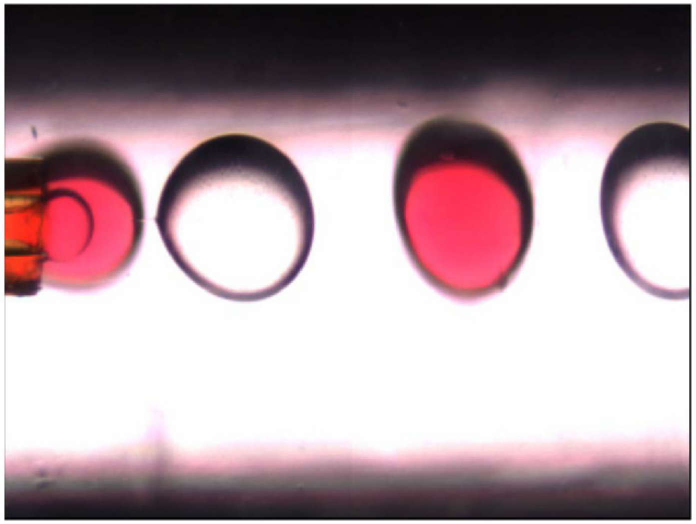
Z. Chang et al., Lab. Chip., 9 (2009) 3007-3011

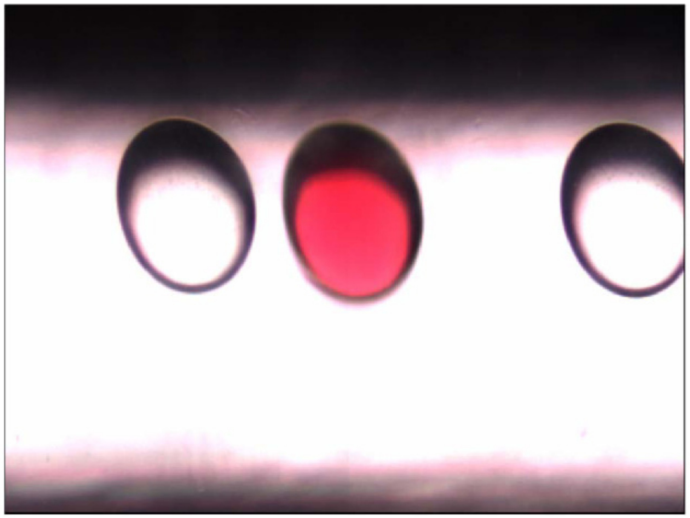
- **Axisymmetric side by side capillaries co-flow device**



2. Microparticles

- Side by side capillaries
  - Alternated droplets

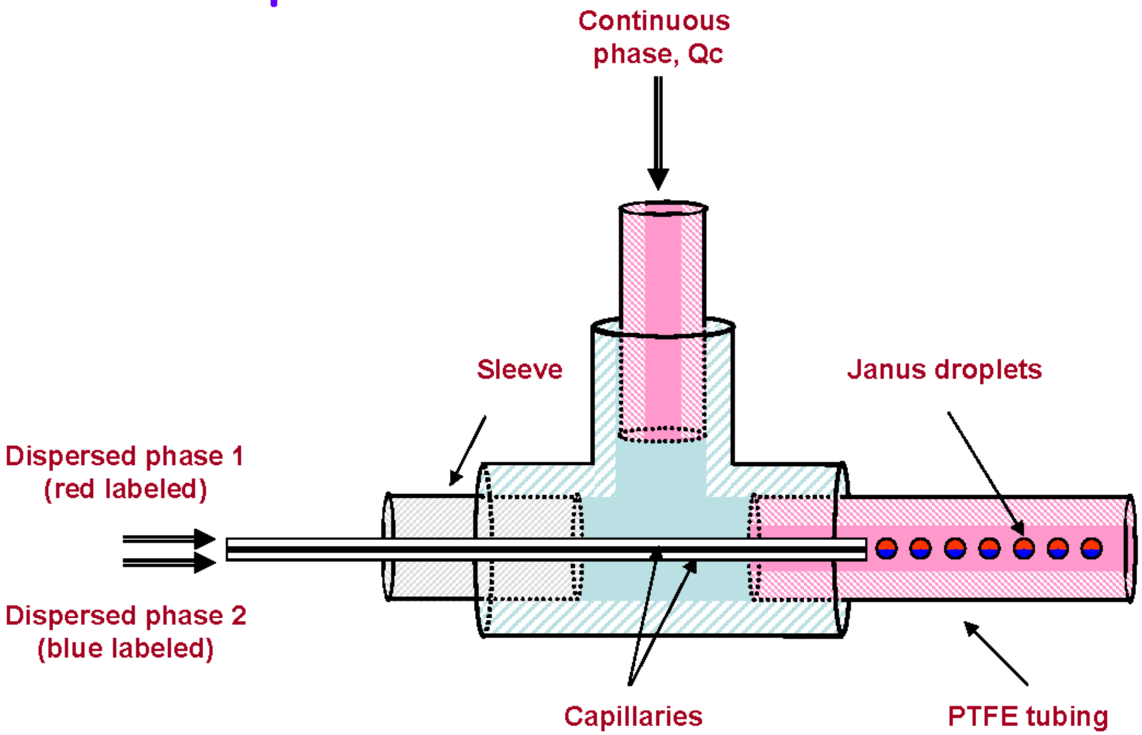


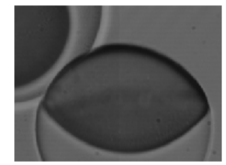


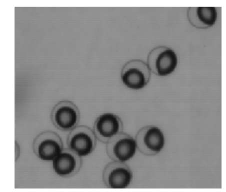
Unpublished/Under submission results

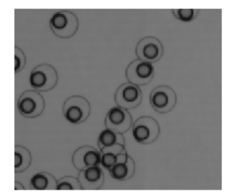
2. Microparticles

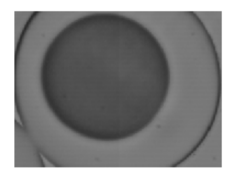
- **Side by side capillaries**
  - **Janus droplets**







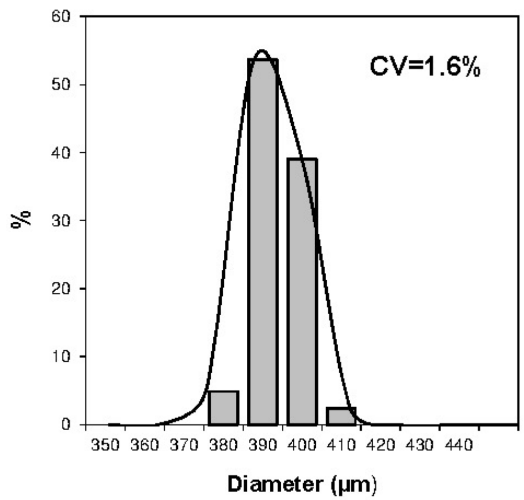


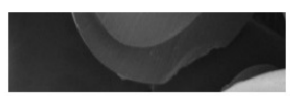


- **Particles with different shapes & morphologies**

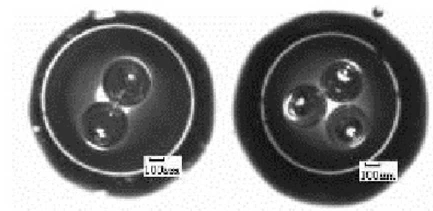
Spherical

Rods

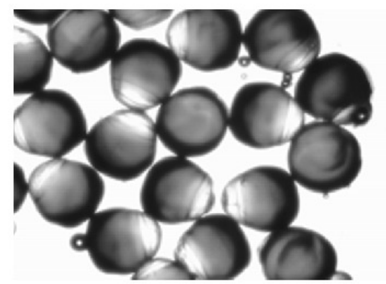




Core-shell



2 cores 3 cores



Janus

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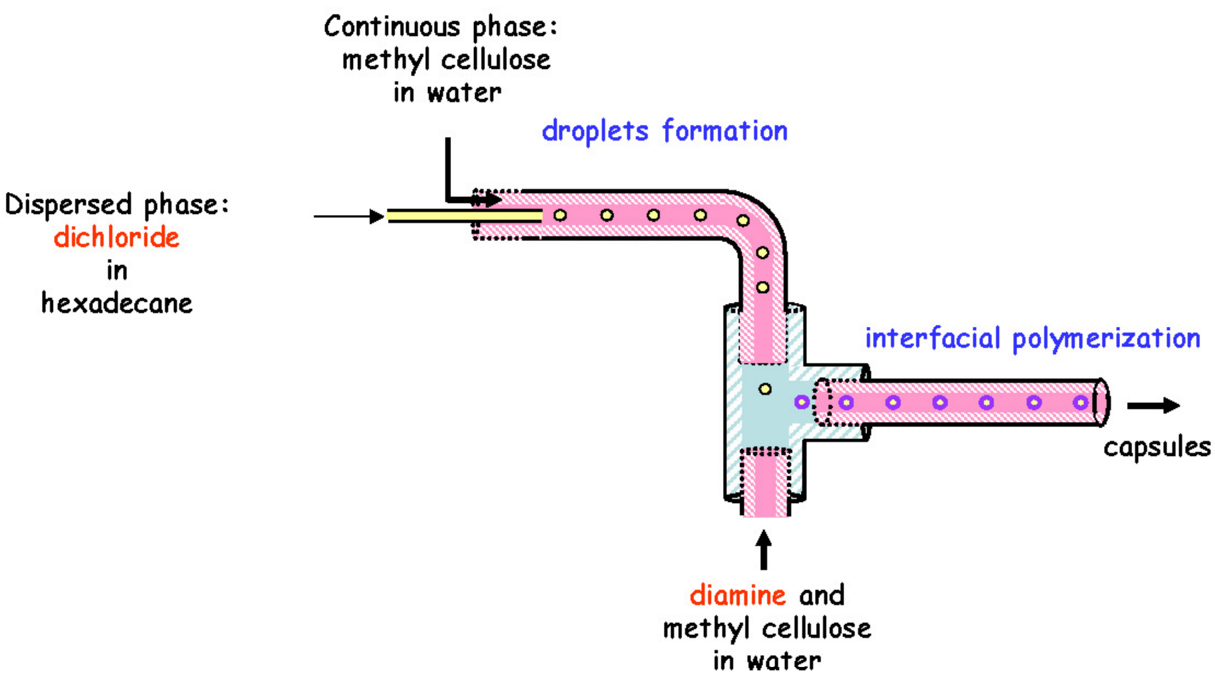
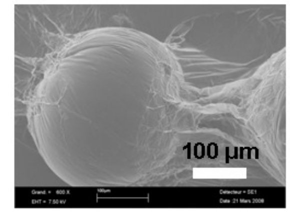
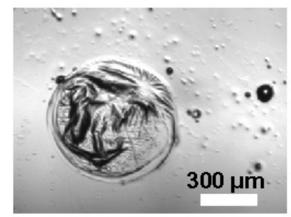
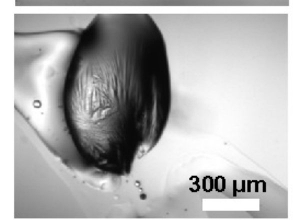
2. Microparticles

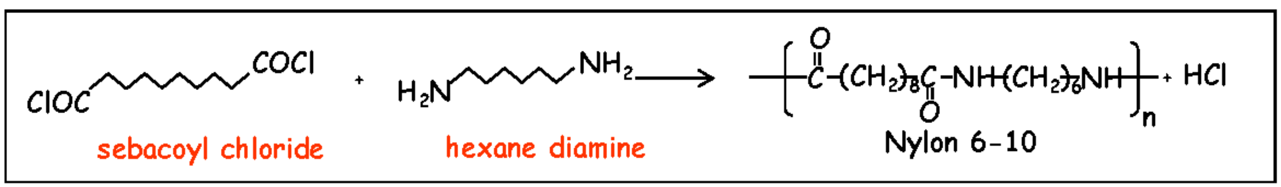
- # Capsules







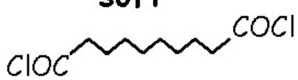


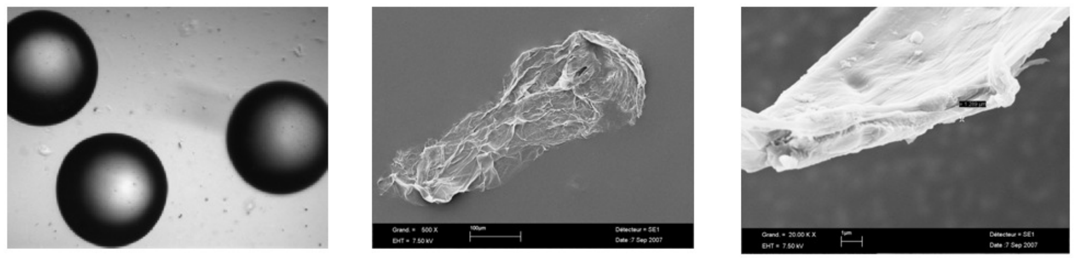


C.A. Serra et al., J. Flow Chem., 3 (3) (2013) 66-75

- **Capsules (cont'd)**
  - **Rapid screening**

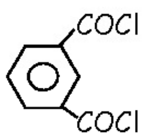
Sebacoyl chloride:
transparent capsules
soft

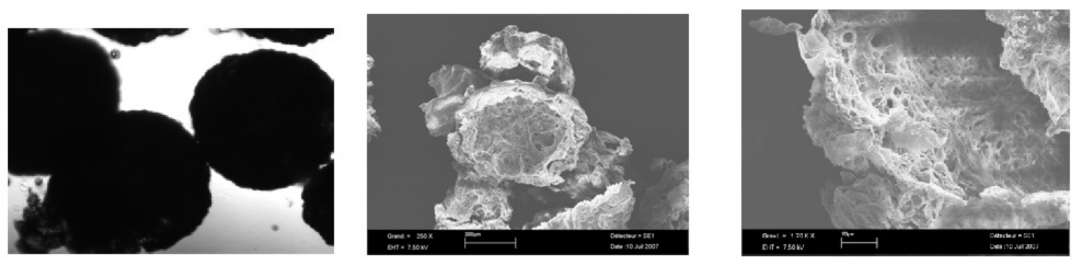




e ~ 1 µm

Isophtaloyl chloride:
opaque capsules
hard

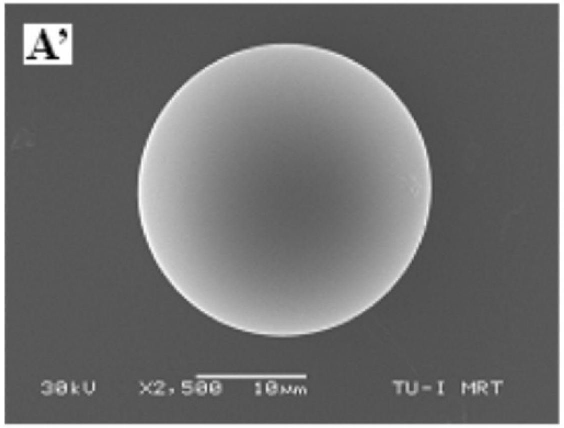


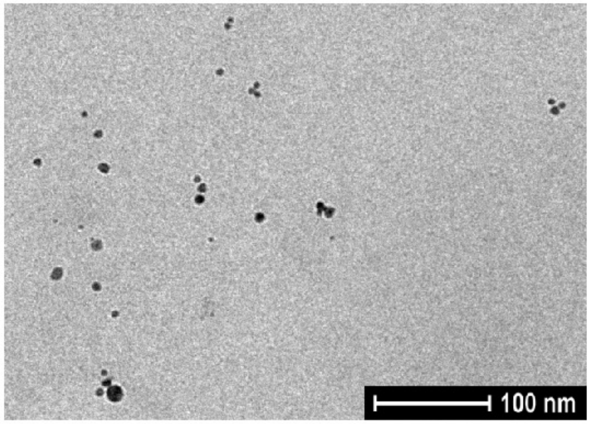


e ~ 20 µm

$F_{Dichloride}$ = 2.1 mM/min

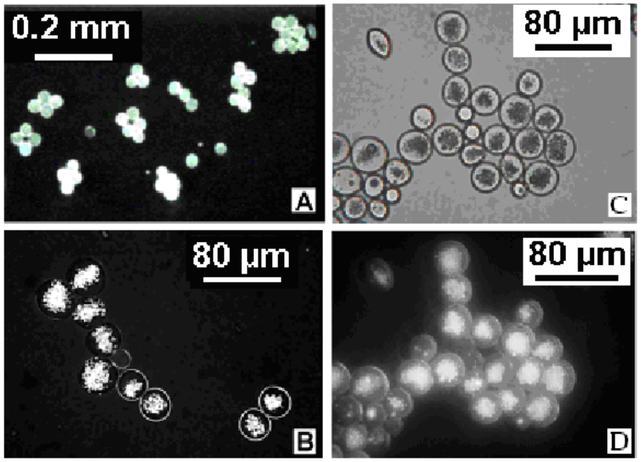
- **Composite materials**
  - **Au NP doped particles**
    - Dispersed phase
      - Tri(propylene glycol) diacrylate
      - Au NP (Ø=13 nm)
    - Continuous phase
      - Aqueous solution





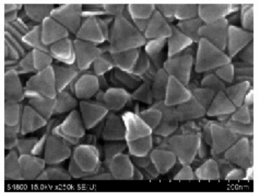
Z. Chang et al., Nanotechnology, 21 (1) (2010) 015605.

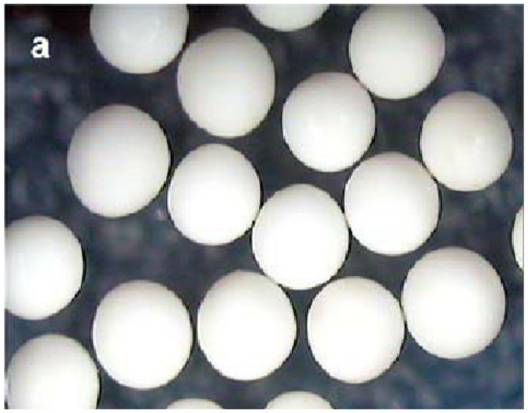
- **Composite materials (cont'd)**
  - **ZnO NP doped particles**
    - **Dispersed phase**
      - Tri(propylene glycol) diacrylate
      - ZnO NP (Ø=200 nm – 2 μm)
    - **Continuous phase**
      - Aqueous solution



Z. Chang et al., Nanotechnology, 21 (1) (2010) 015605.

- **Composite materials (cont'd)**
  - **Ag NP doped particles**
    - **Dispersed phase**
      - Acrylamide + Photoinitiator + crosslinker
      - In situ Ag nanoprisms reinforcement
    - **Continuous phase**
      - Silicon oil

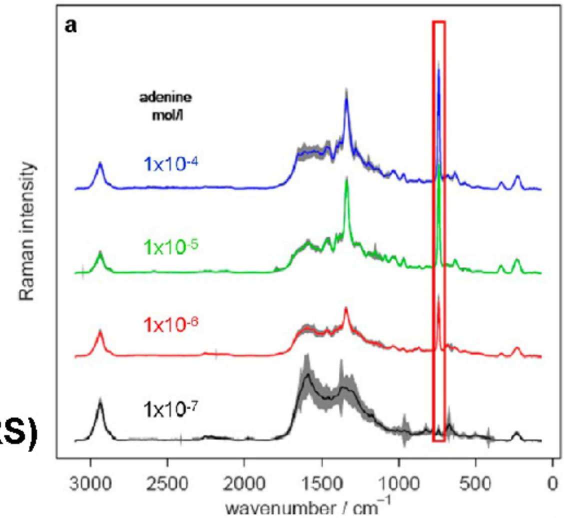




Ademine

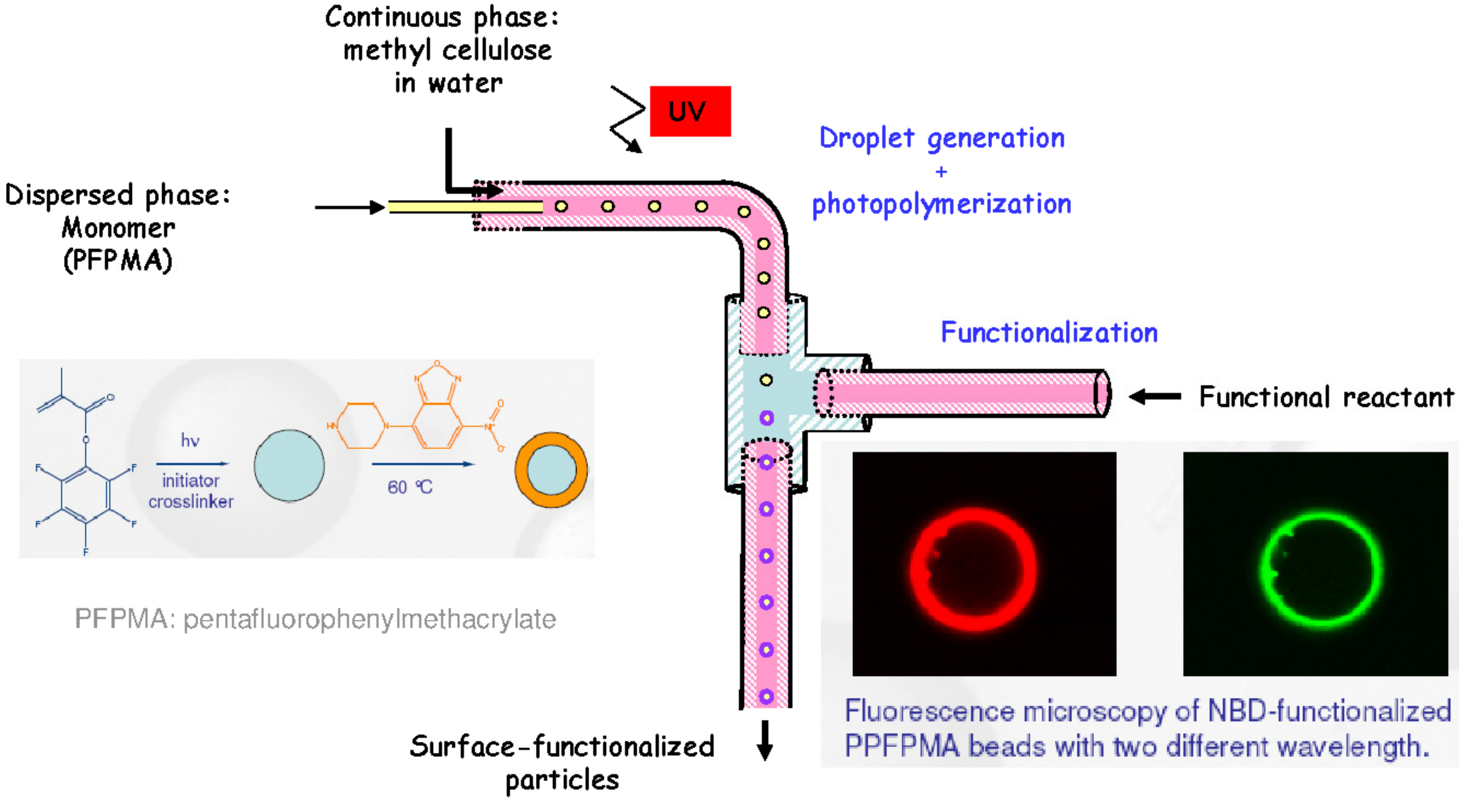
→

Surface-Enhanced Raman Scattering (SERS)



J.M. Köhler et al., J. Mater. Sci., 48 (5) (2013) 2158-2166.

- **Surface-functionalized particles**
  - **Two-stages flow process**

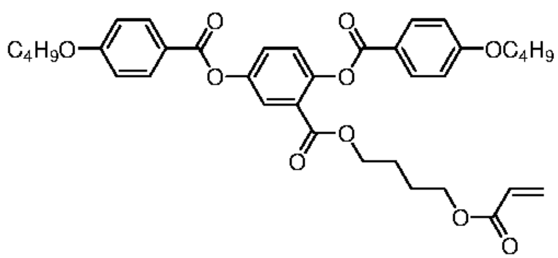


PFPMA: pentafluorophenylmethacrylate

Fluorescence microscopy of NBD-functionalized PPFPMA beads with two different wavelength.

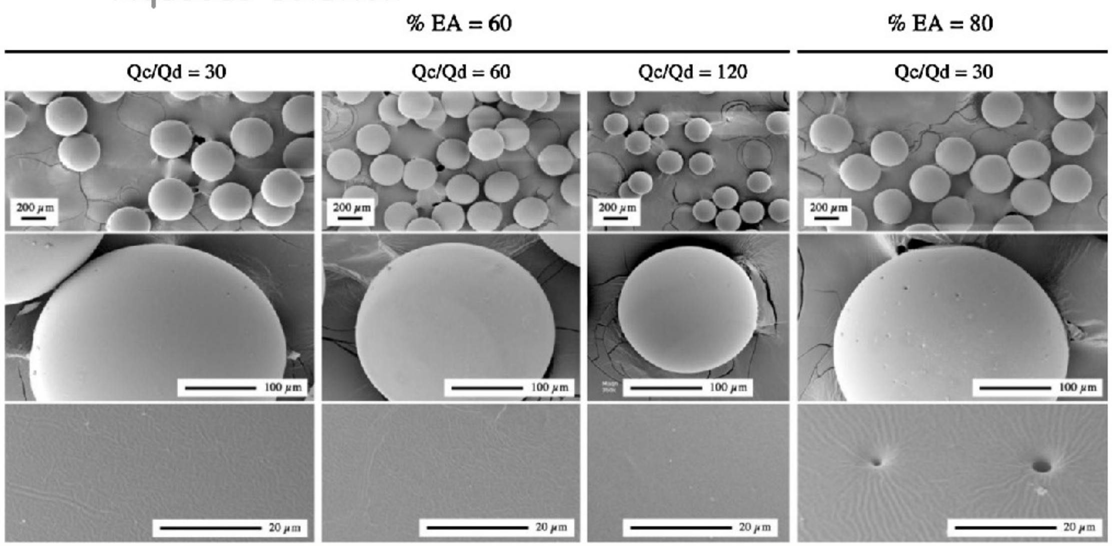
N. Metz et al., Proc. of ACS meeting, Boston, 2007

- Thermal actuators
  - Liquid crystalline elastomer particles
    - Dispersed phase
      - LC-monomer (isotropic phase)
      - Crosslinker
      - Photoinitiator
    - Continuous phase
      - Silicon oil
    - Polymerization
      - In the nematic phase



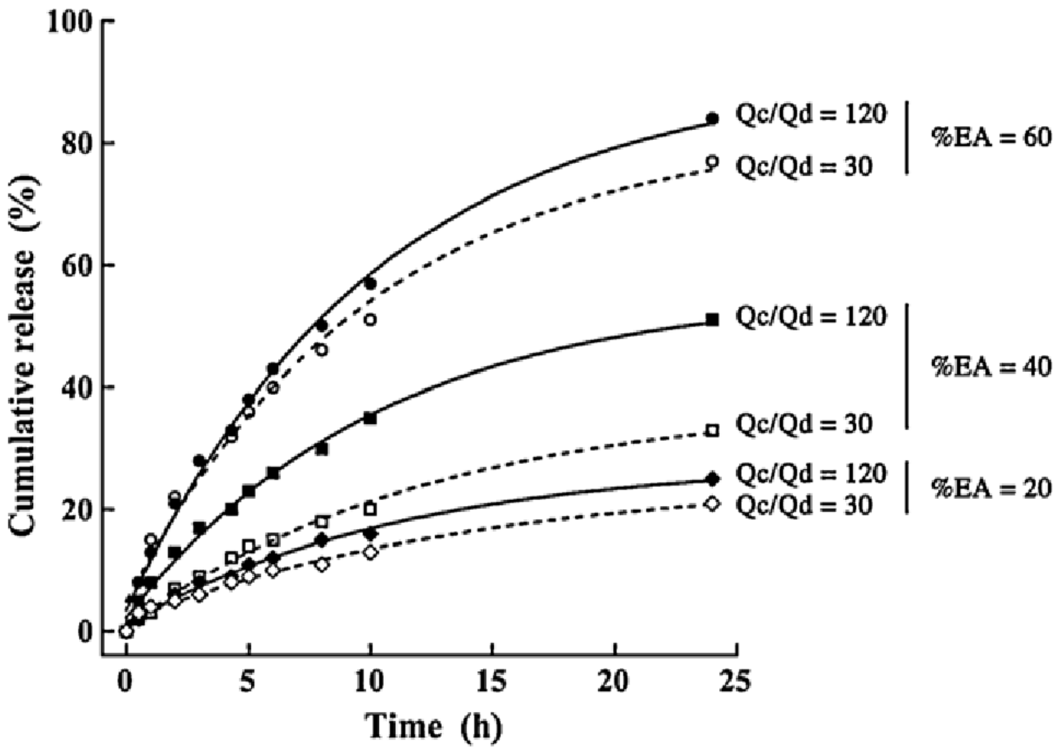
C. Ohm et al., Adv. Mater., 21 (2009) 1-4, Adv. Funct. Mater., 20 (2010) 4314-4322, Soft Matter, 7 (2011) 2340-2344.

- **Drug loaded microcarrier**
  - **Plain particles**
    - **Dispersed phase**
      - Ethyl acrylate + Bifunctional acrylate monomer + Photoinitiator
      - Hydrophobic model drug (ketoprofen)
    - **Continuous phase**
      - Aqueous solution



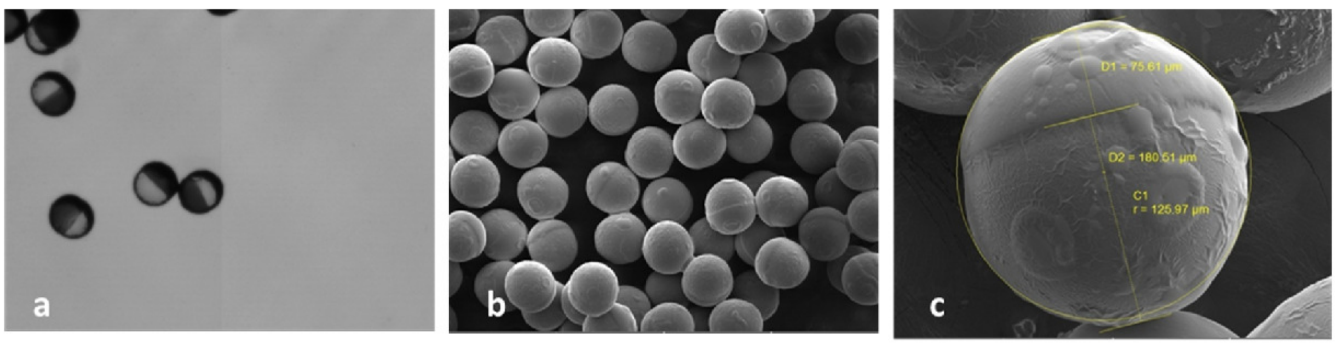
I.U. Ikram et al., Int. J. Pharm., 441 (1) (2013) 809-817.

- **Drug loaded microcarrier (cont'd)**
  - **Plain particles**



I.U. Ikram et al., Int. J. Pharm., 441 (1) (2013) 809-817.

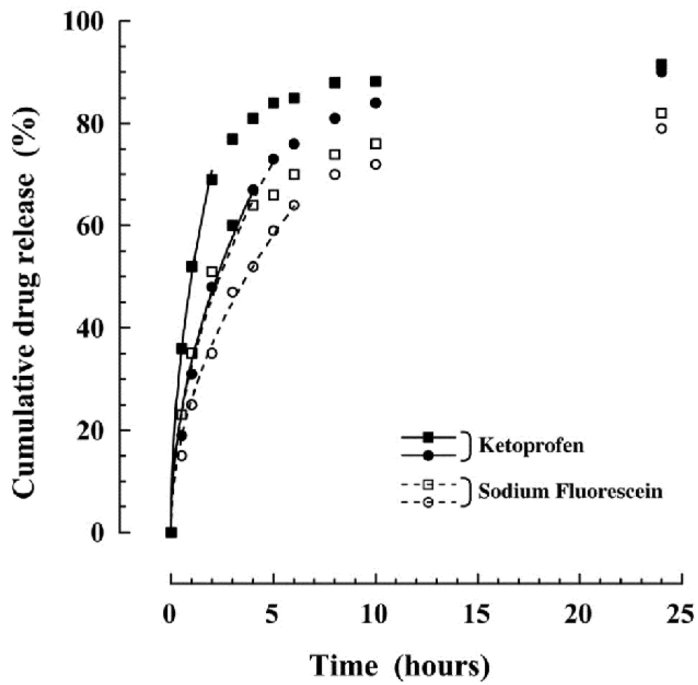
- **Drug loaded microcarrier (cont'd)**
  - **Janus particles**
    - **Dispersed phase 1**
      - Methyl acrylate + Bifunctional acrylate monomer + Photoinitiator
      - Hydrophobic model drug (ketoprofen)
    - **Dispersed phase 2**
      - Acrylamide + Photoinitiator + crosslinker
      - Hydrophilic model drug (sodium fluorescein)
    - **Continuous phase**
      - Silicon oil

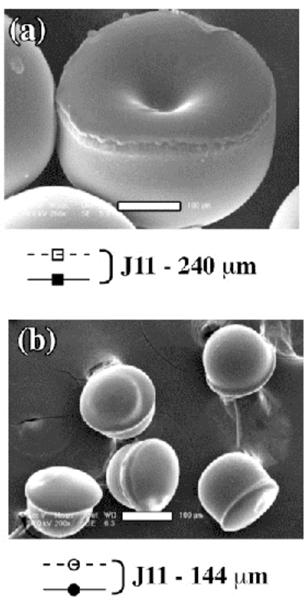


I.U. Ikram et al., Int. J. Pharm., DOI: 10.1016/j.ijpharm.2014.06.035.

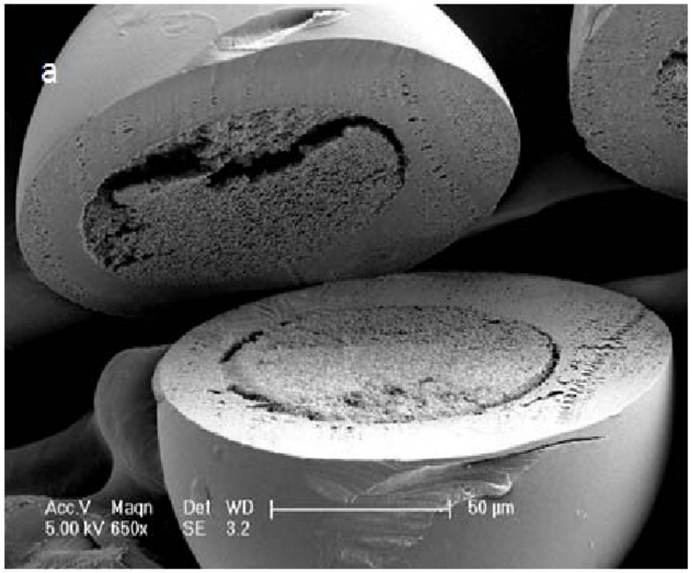
2. Microparticles

- Drug loaded microcarrier (cont'd)
  - Janus particles
    - Release properties @ PH 6.8 in USP phosphate buffer solution





- **Drug loaded microcarrier (cont'd)**
  - **Core-shell particles**
    - Ketoprofene loaded poly(methyl acrylate) core
    - Ranitidine HCl loaded poly(acrylamide) shell

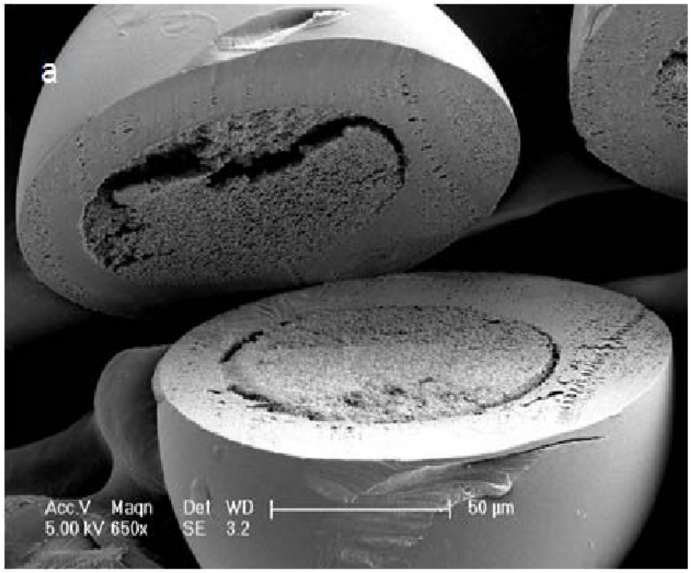


~100µm core-shell microparticle

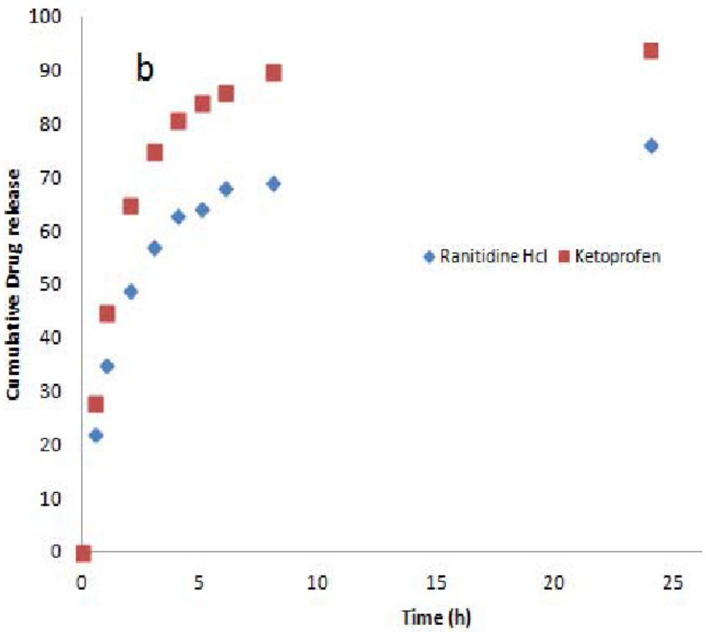
I.U. Ikram et al., Int. J. Pharm., DOI: 10.1016/j.ijpharm.2014.06.035.

2. Microparticles

- **Drug loaded microcarrier (cont'd)**
  - **Core-shell particles**
    - Ketoprofene loaded poly(methyl acrylate) core
    - Ranitidine HCl loaded poly(acrylamide) shell



~100µm core-shell microparticle



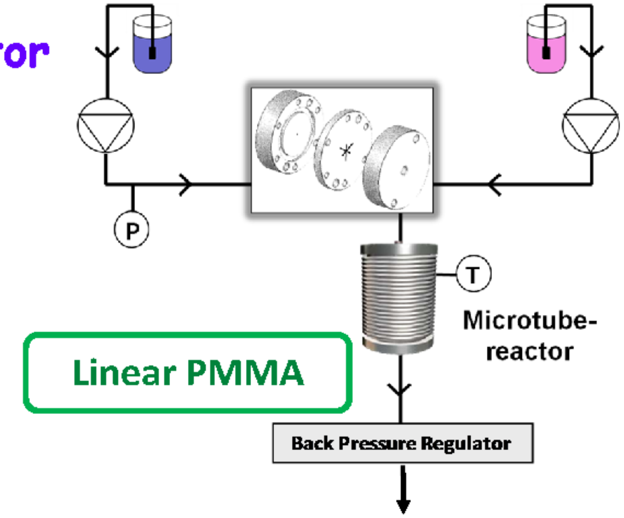
I.U. Ikram et al., Int. J. Pharm., DOI: 10.1016/j.ijpharm.2014.06.035.

Outline

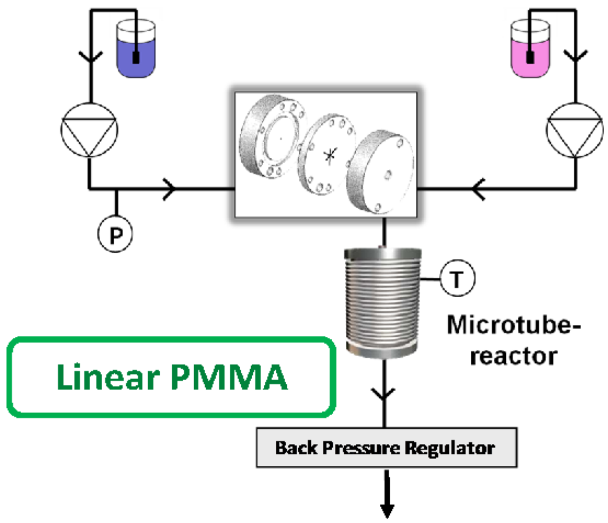
- 1. Introduction
- 2. Microparticles by capillary-based emulsification
  - Experimental setup
  - Applications
- **3. Nanoparticles**
  - **Micromixer-assisted nanoprecipitation**
  - Elongational-flow emulsification
- 4. Conclusion

3. Nanoparticles / Nanoprecipitation

- **Continuous-microflow process**
  - ➢ **Micromixer+Microtubular reactor**

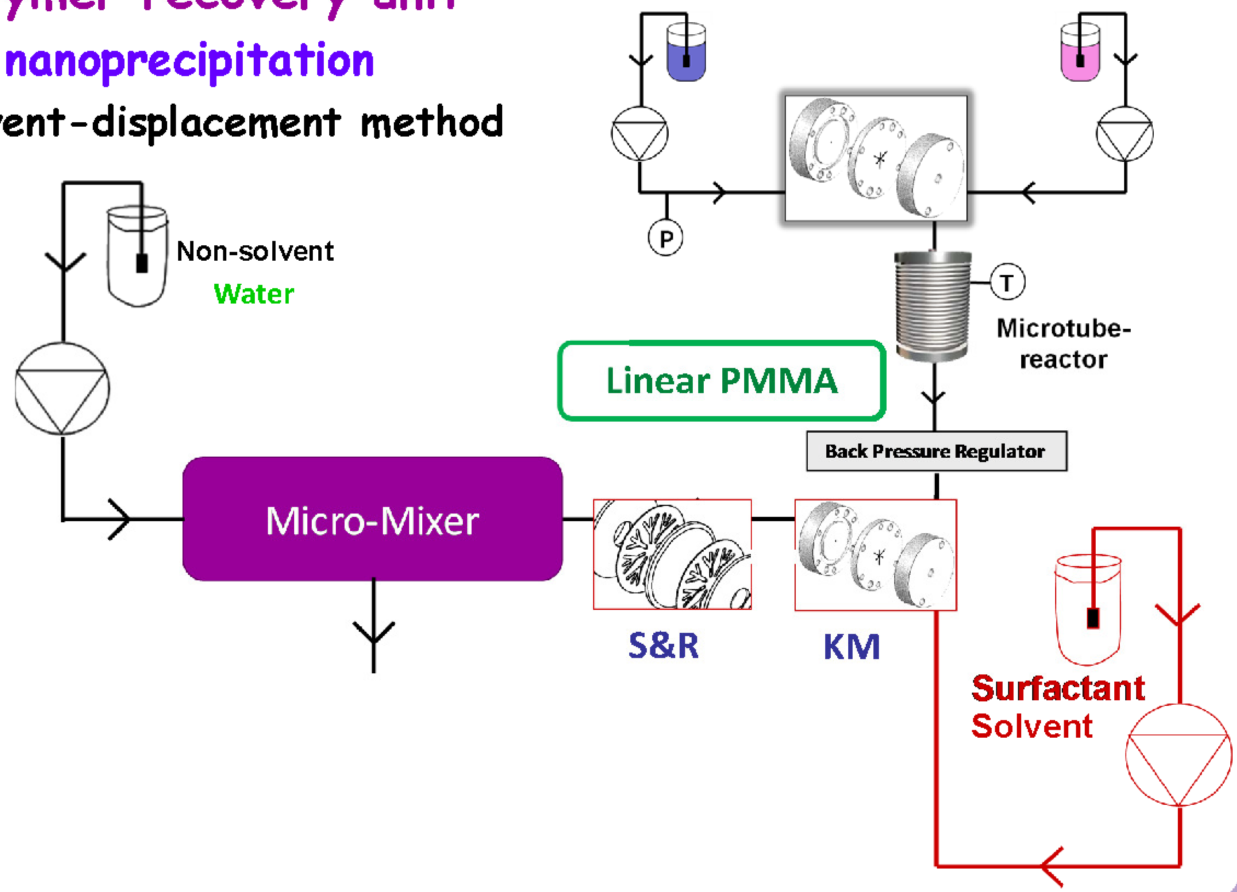


- **Inline polymer recovery unit**
  - **Online nanoprecipitation**
    - Solvent-displacement method



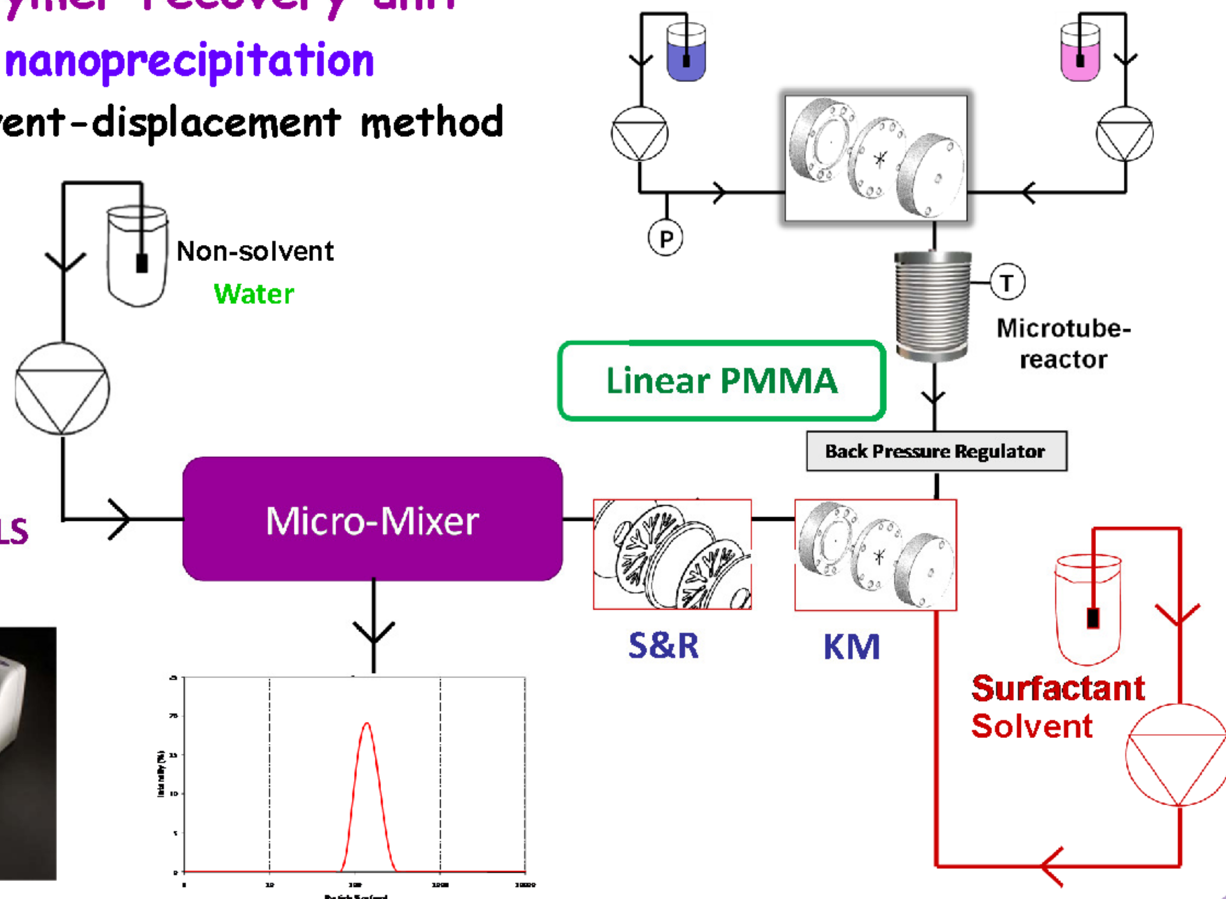
3. Nanoparticles / Nanoprecipitation

- **Inline polymer recovery unit**
  - **Online nanoprecipitation**
    - Solvent-displacement method



3. Nanoparticles / Nanoprecipitation

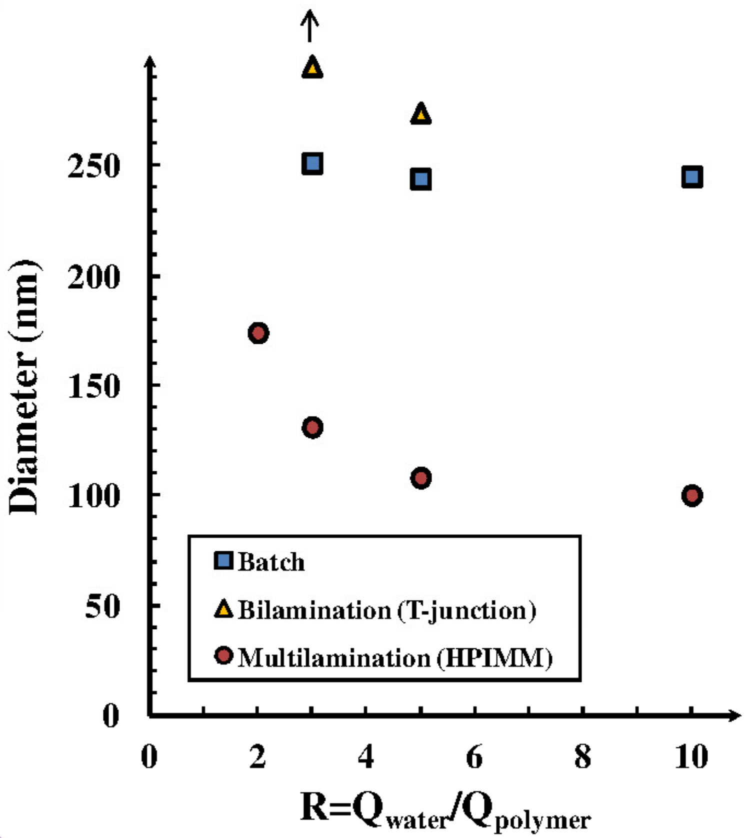
- **Inline polymer recovery unit**
  - **Online nanoprecipitation**
    - Solvent-displacement method

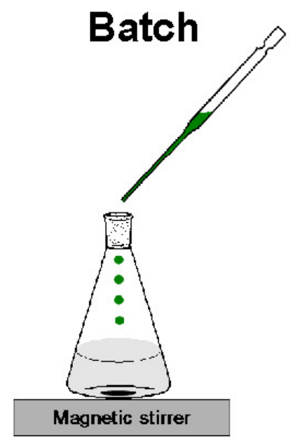


Nanosizer – DLS
(173nm)

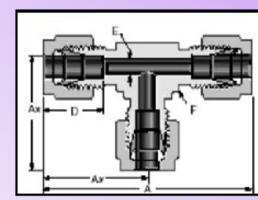
3. Nanoparticles / Nanoprecipitation

- **Influence of micromixers**





T-Junction



HPIMM

Polymer Concentration: 1%

Polymer Flow Rate: 0.8mL/min

Unpublished/Under submission results

3. Nanoparticles / Nanoprecipitation

▪ Batch vs. continuous-flow

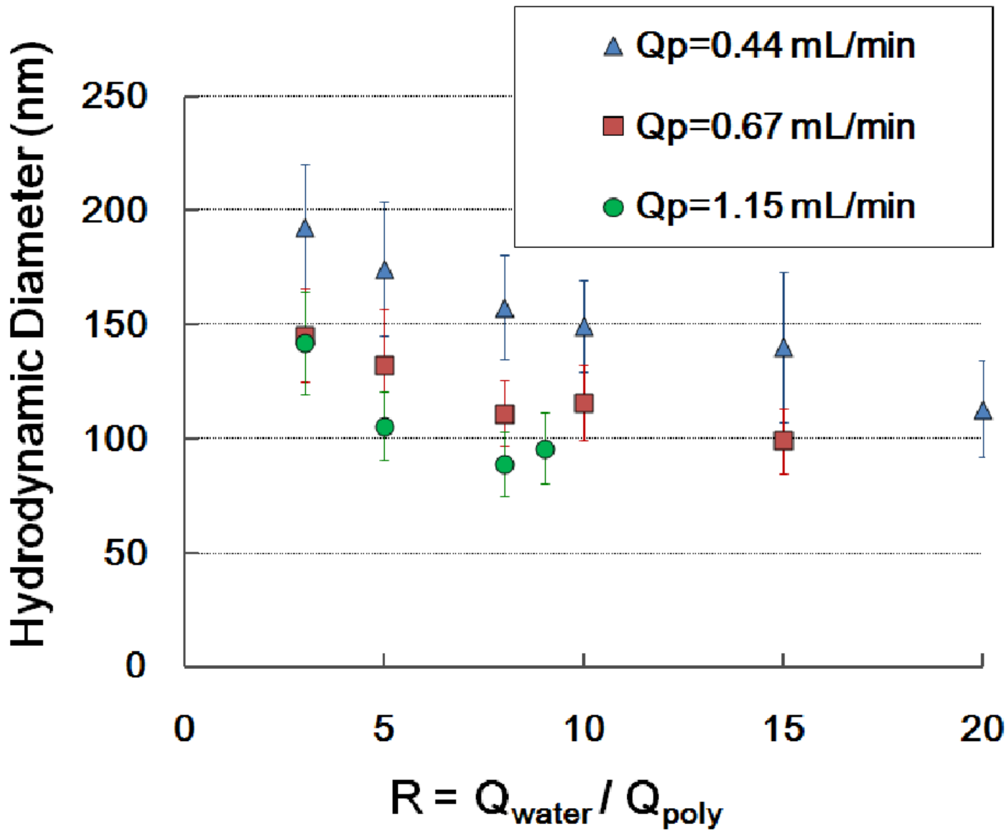
Good dispersion
[Polymer] < 1%

Aggregation
[Polymer] > 1%

%P	R	Batch Diam.Int 1 (nm)	Batch Width.Int 1 (nm)	Micro Diam.Int 1 (nm)	Micro Width.Int 1 (nm)
0,5	3	178	37	101	22
	5	179	44	83	17
	10	181	42	106	26
1	3	251	64	141	41
	5	244	72	111	35
	10	245	76	111	33
2	5	na	na	-	-
	8	na	na	146	41
	10	na	na	167	47
5	5	na	na	166	63
	8	na	na	190	46
	10	na	na	210	60

Unpublished/Under submission results

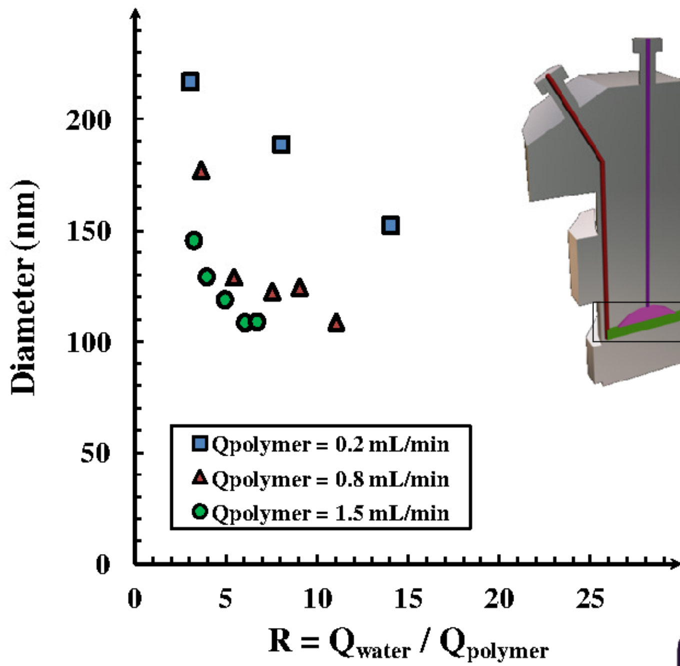
- **Effect of polymer solution flow rate**

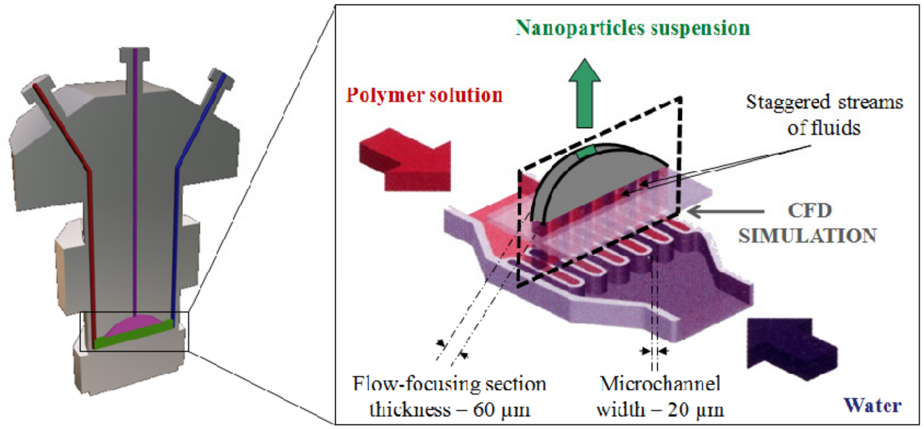


Bally et al., Macromol. React. Eng., 5 (11-12) (2011) 542–547

3. Nanoparticles / Nanoprecipitation

- **Influence of the flow rate of the polymer solution**

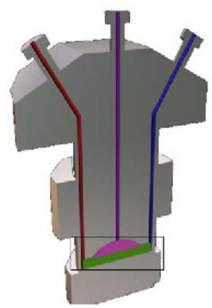




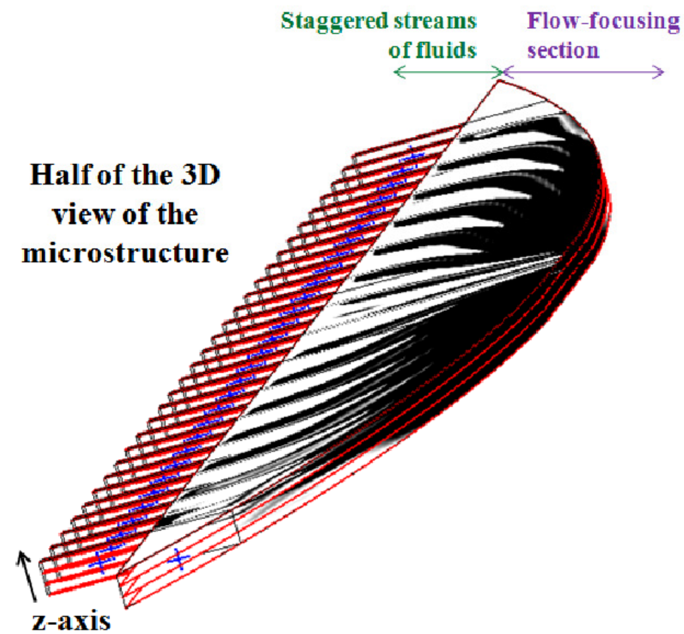
Number of channel / fluid:15

Further CFD simulations of the flow-focusing section

- Numerical simulations of the flow-focusing section



Black point = point where particle formation may occur

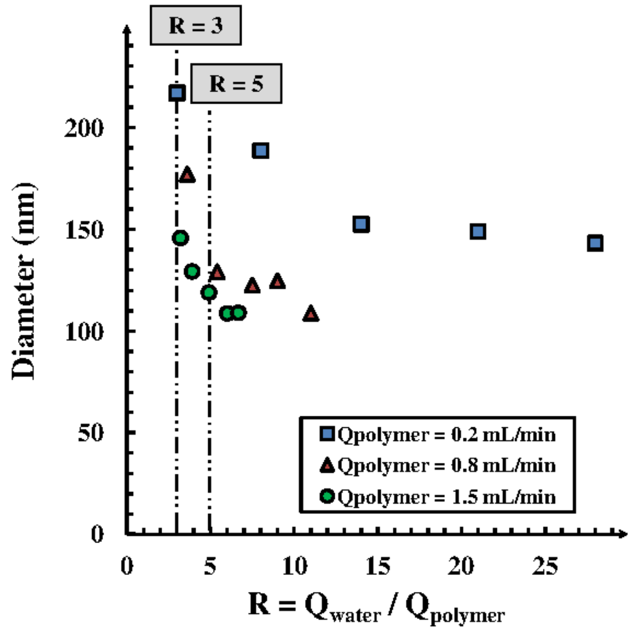


$$\text{Mixing criterion} = \frac{\text{Black mesh points}}{\text{Total number of mesh points}} \times 100$$

F. Bally et al., Polymer, 53 (22) (2012) 5045-5051.

- **Numerical simulations of the flow-focusing section**

$$\text{Mixing criterion} = \frac{\text{Black mesh points}}{\text{Total number of mesh points}} \times 100$$



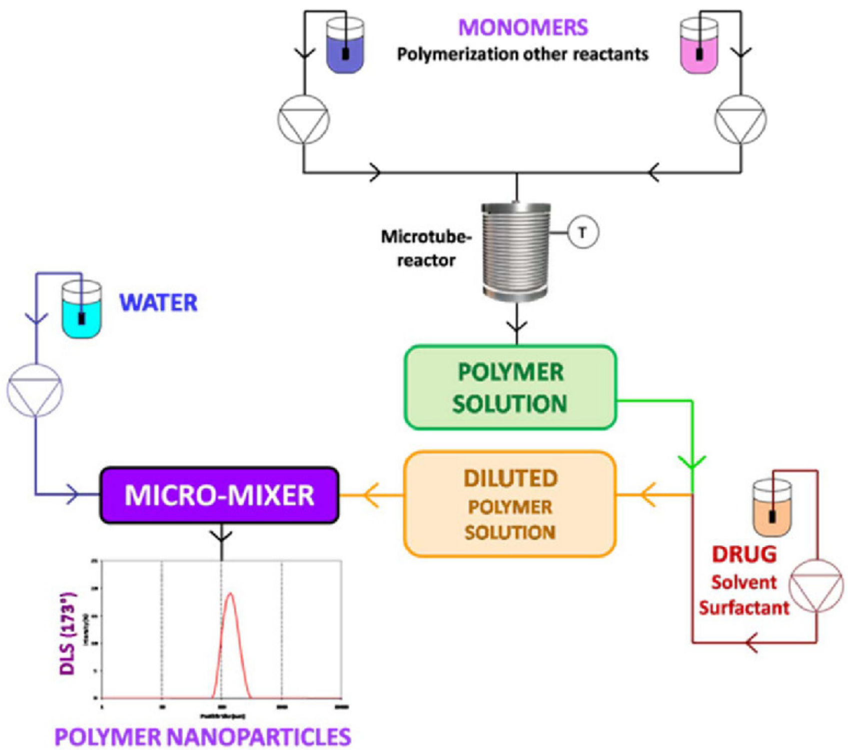
$Q_{polymer}$ (mL/min)	R = 3	R = 5
0.2	51 %	61 %
0.8	67 %	71 %
1.5	73 %	77 %

Mixing criterion to predict the particle size evolution (at constant R)

F. Bally et al., Polymer, 53 (22) (2012) 5045-5051.

3. Nanoparticles / Nanoprecipitation

- **Application: drug-loaded polymer nanoparticles**



Polymer: PMMA (0.5 - 2 wt.%)

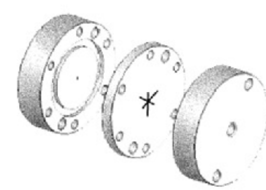
Q_p = 1 mL/min

Drug: Ketoprofen (0.5 wt.%)

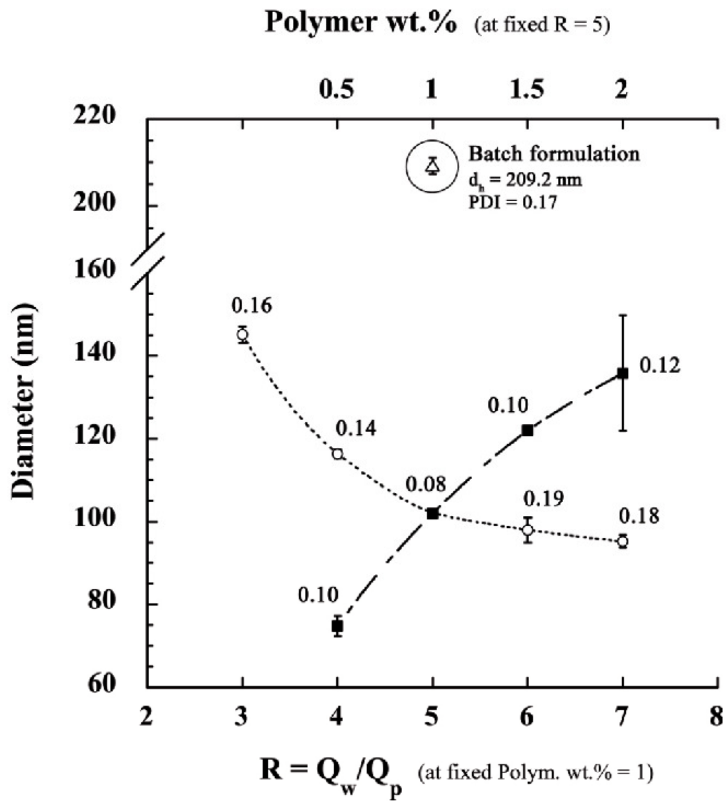
Solvant: THF

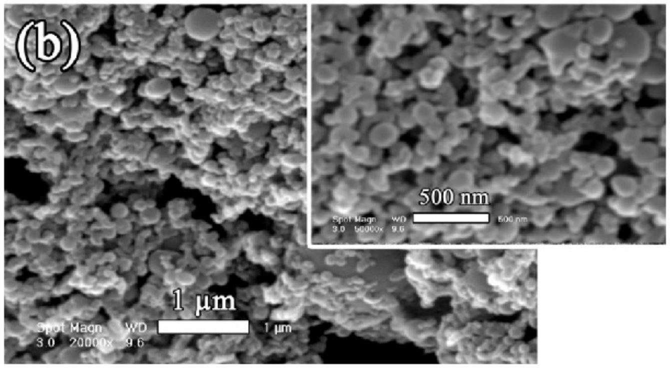
Surfactant: Cremophor (0.5 wt.%)

Micromixer: KM



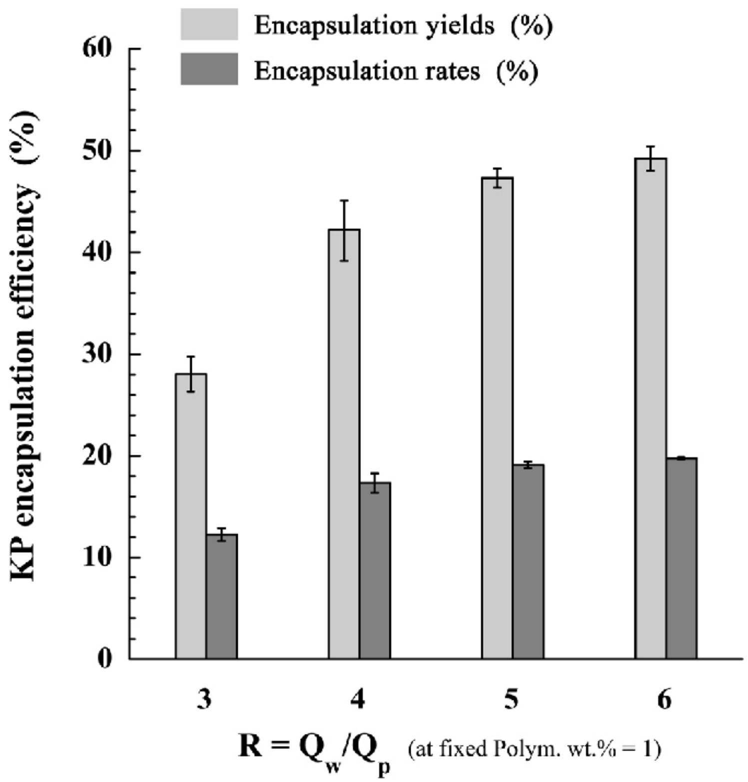
- **Application: drug-loaded polymer nanoparticles (cont'd)**
  - **Effect of R and polymer concentration**





N. Anton et al., Soft Matter, 8 (2012) 10628-10635.

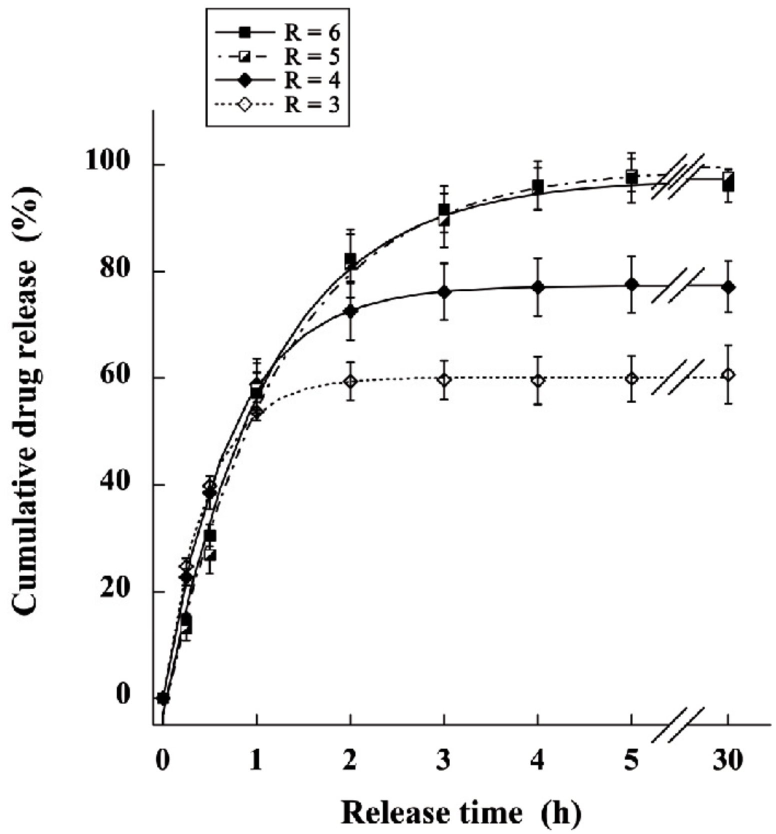
- **Application: drug-loaded polymer nanoparticles (cont'd)**
  - **Encapsulation properties**



N. Anton et al., Soft Matter, 8 (2012) 10628-10635.

3. Nanoparticles / Nanoprecipitation

- **Application: drug-loaded polymer nanoparticles (cont'd)**
  - **Release kinetics**



N. Anton et al., Soft Matter, 8 (2012) 10628-10635.

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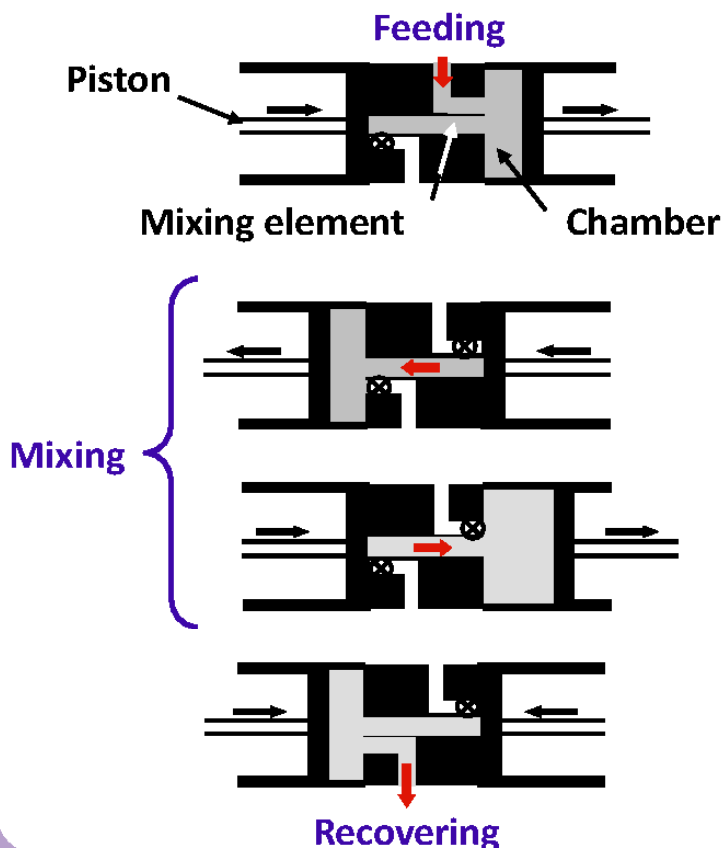
▪ The elongational-flow RMX® device



Characteristics:

• Adjustable volume: between 5 and 200 cm^3

• Temperature controlled

• Pressure drop: of the order of 5 - 20 bars
➔ v_h: 25 - 50 $m.s^{-1}$

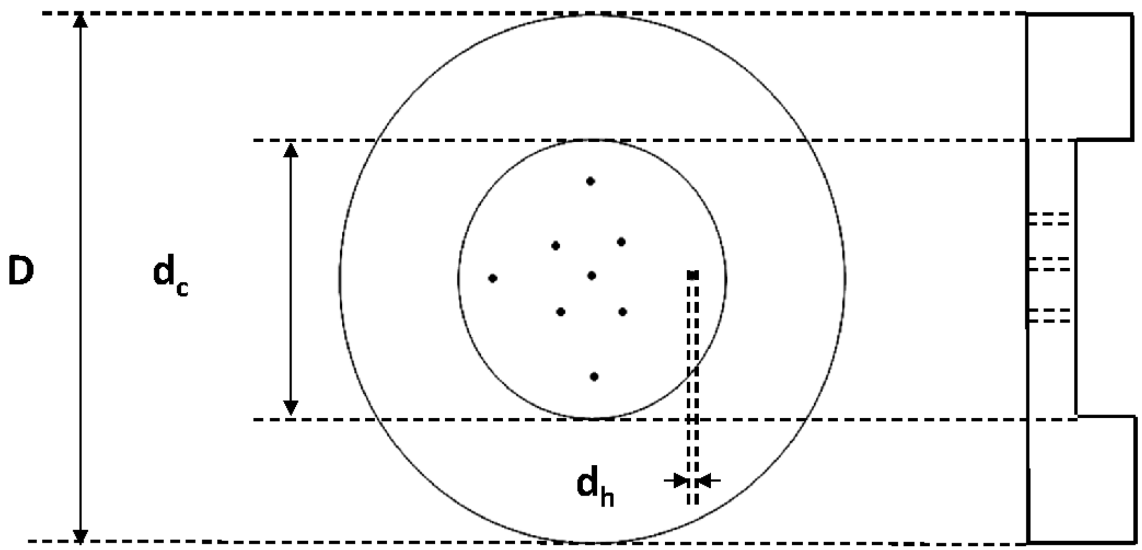
• Tightness to liquids and gases

• Easy feeding of components even for reactive systems and easy sampling during the process

• Strong elongational-flow component

Patent ULP n°07/02493

- **The elongational-flow RMX® device (cont'd)**
  - ***Mixing element geometry***



Number of holes (n): between 1 and 30

Diameter of holes: between 200 and 1000 µm

(d_h << d_c)

$$CF = \frac{d_c^2}{n\, d_h^2}$$

- **The elongational-flow RMX® device (cont'd)**
  - **Materials**
    - Continuous phase: deionized water
    - Dispersed phase: methyl methacrylate (MMA)
    - Surfactant: sodium dodecylsulfate (SDS)
    - Ostwald ripening inhibitor: hexadecane (HD)
    - Initiator: lauroyle peroxide (LPO)

Reference conditions:

85% Water

15% MMA

[SDS] = 4 g/l

[HD] = 4% wt./MMA

Reference mixing element:

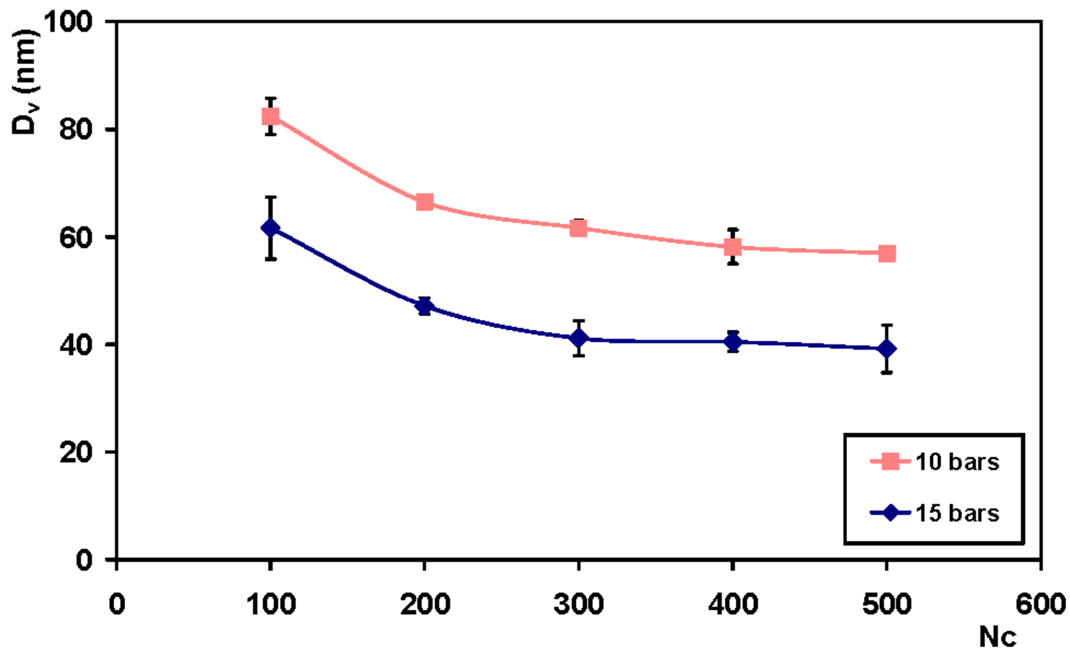
3 holes

of 500 µm

Droplet size distribution was determined by Dynamic Light Scattering (DLS)

3. Nanoparticles / Elongational-flow

- **RMX: influence of pressure drop**



Conditions:

Pressure drop

Cycles

ME: 3 holes of 500 µm

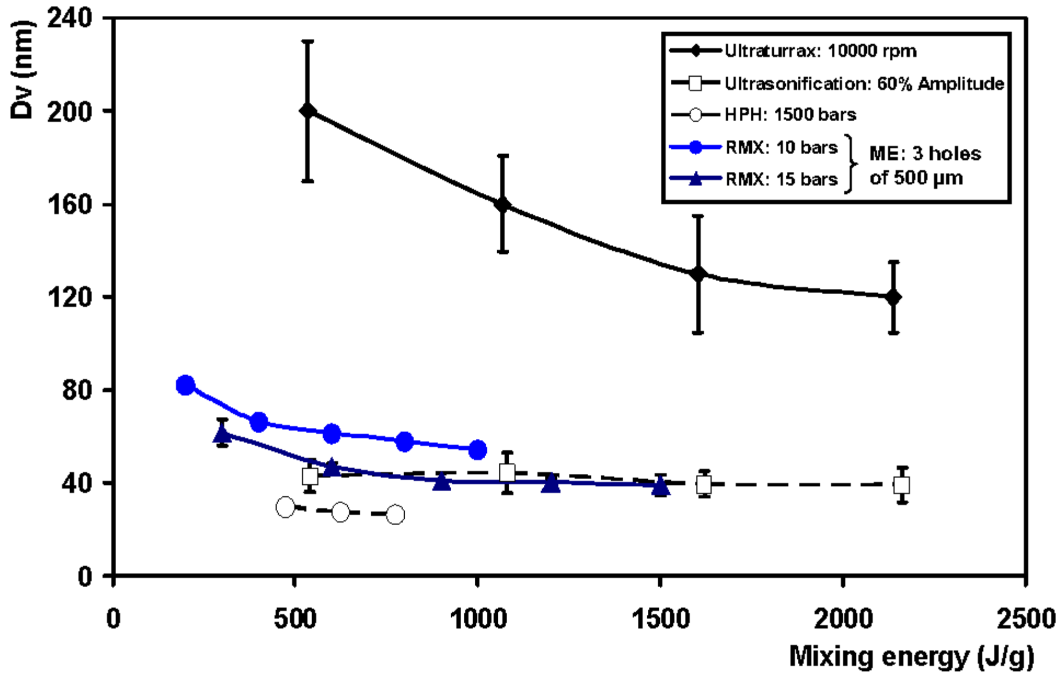
PDI < 0.2

➔ **Limiting and tunable droplet size**

I. Souilem et al., Chem. Eng. Technol., 35 (9) (2012) 1692–1698.

3. Nanoparticles / Elongational-flow

- **RMX: comparison with other emulsification devices**



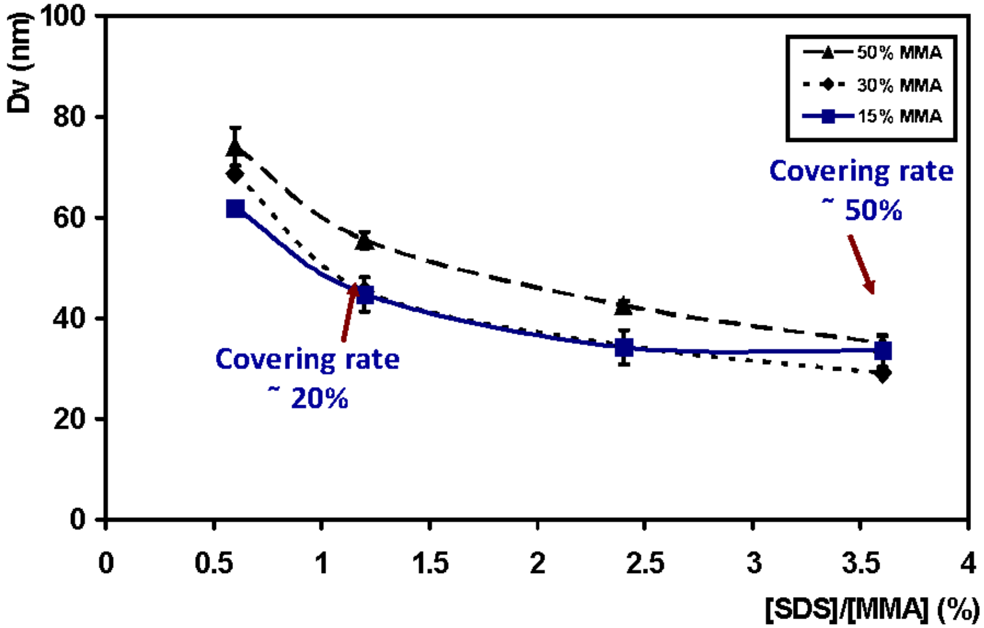
Efficiency of RMX:

- small size (comparable to US and HPH)
- improved reproducibility

$$E\left(J.g^{-1}\right)=\frac{P\times Q\times t}{m}$$

I. Souilem et al., Chem. Eng. Technol., 35 (9) (2012) 1692–1698.

▪ RMX: influence of SDS & MMA concentrations



Conditions:

Water

MMA

[SDS]

[HD] = 4% wt./MMA

ΔP = 15 bars

500 cycles

ME: 3 holes of 500 µm

➔ Small droplet size even at high monomer fractions

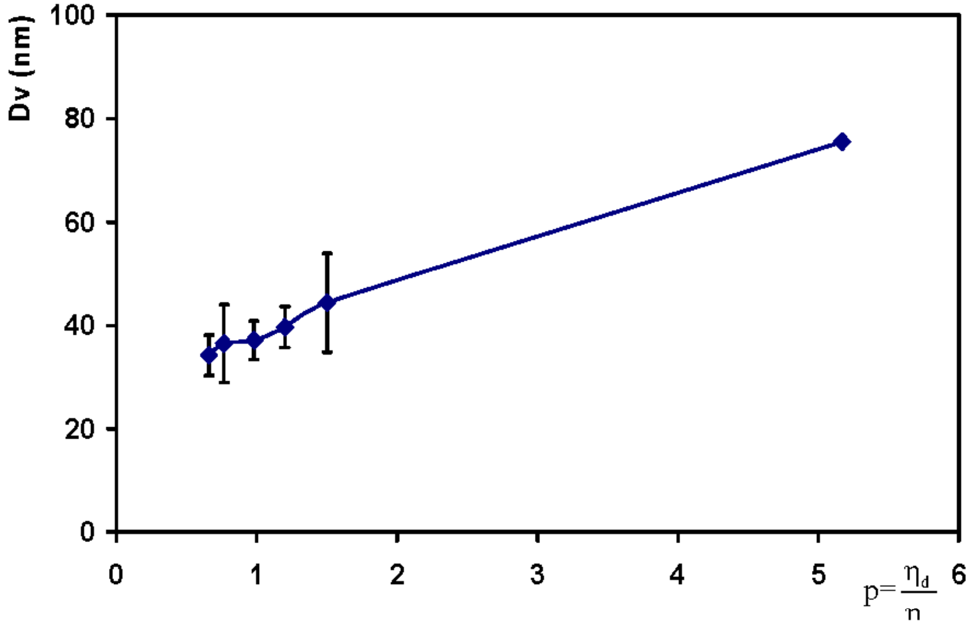
BUT lower emulsion stability

➔ Covering rate ≈ 20%

Emulsion stable (at least for few hours)

I. Souilem et al., Chem. Eng. Technol., 35 (9) (2012) 1692–1698.

- **RMX: influence of dispersed phase viscosity**



Conditions:

85% Water

15% {MMA+ x%PMMA}

[SDS] = 4 g/l

[HD] = 4% wt./MMA

$$p=\frac{\eta_d}{\eta_c}$$

ΔP = 15 bars

500 cycles

ME: 3 holes of 500 µm

➔ **Faisability of nanoemulsions for high viscosity ratios**

I. Souilem et al., Chem. Eng. Technol., 35 (9) (2012) 1692–1698.

- **RMX: dimensional analysis**
  - **For the reference mixing element**
    - Reynolds number

$$\mathrm{Re} = \frac{\rho\, v_h\, d_h}{\eta_e}$$

    - Weber number

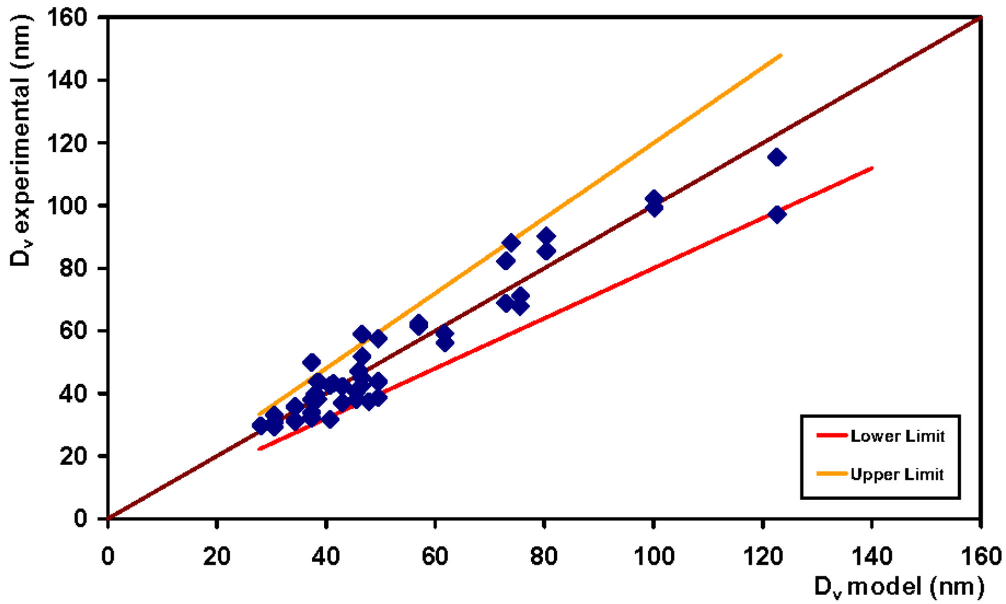
$$\mathrm{We} = \frac{\rho\, v_h^2\, d_h}{\sigma}$$

    - Dispersed to continuous phase viscosities ratio

$$p = \frac{\eta_d}{\eta_c}$$

3. Nanoparticles / Elongational-flow

- **RMX: dimensional analysis (cont'd)**
  - **For the reference mixing element**



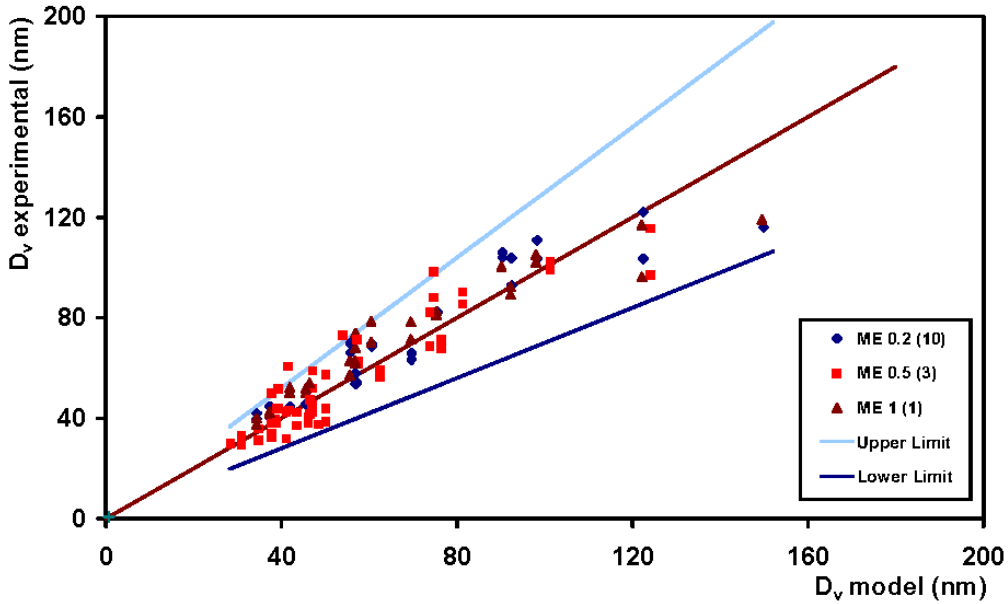
$$\frac{d}{d_h} = 2.05\text{x}10^{-9}\ Re^{1.79}\ We^{-1.74}\ p^{0.45}$$

Unpublished/Under submission results

- RMX: dimensional analysis (cont'd)
  - For different mixing elements (5 tested)
    - Contraction factor

$$CF = \frac{d_c^2}{n\,d_h^2}$$

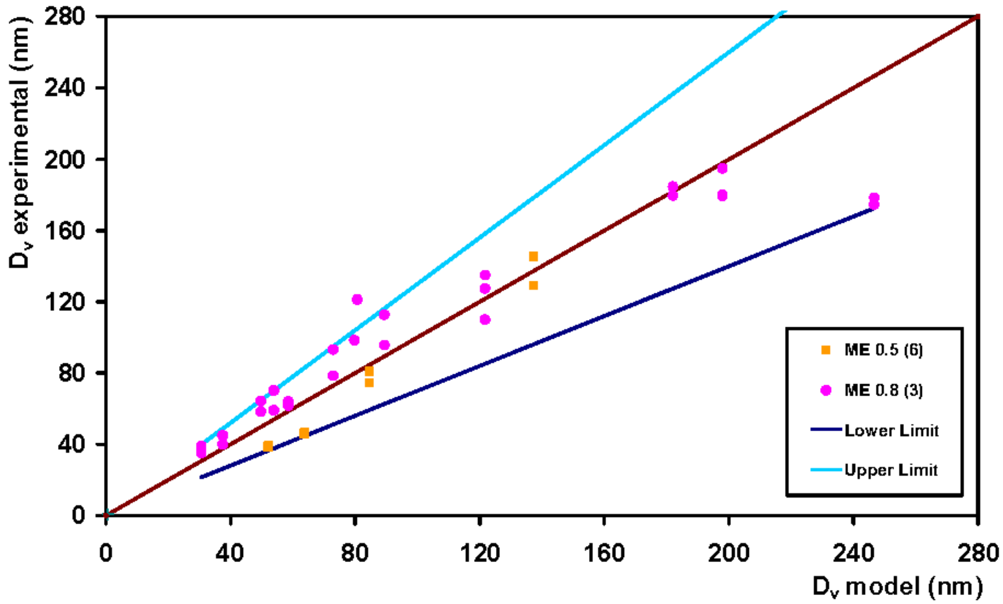
- **RMX: dimensional analysis (cont'd)**
  - **For different mixing elements (5 tested)**
    - **For CF > 1000**



$$\frac{d}{d_h} = 8.06x10^{-9}\ Re^{1.39}\ We^{-1.39}\ p^{0.45}\ CF^{1.76}$$

3. Nanoparticles / Elongational-flow

- **RMX: dimensional analysis (cont'd)**
  - **For different mixing elements (5 tested)**
    - **For CF < 1000**



$$\frac{d}{d_h} = 1.45x10^{-9}\ Re^{1.39}\ We^{-1.39}\ p^{0.45}\ CF^{4.05}$$

Unpublished/Under submission results

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4. Conclusion

- **Polymer particles**
  - **Easy tuning of particle size**
    - Microparticles
      - Few microns to hundreds of micrometers
    - Nanoparticles
      - 40 to 250 nm
  - **Narrow size distribution**
    - CV<5%, PDI<0.2
  - **Different shapes**
    - Sphere, Rod, Disk
  - **Composition- and morphology-controlled**
    - Core-shell, Composite, Capsules, Porous
  - **Tediously achievable in conventional processes**
    - Janus, Multi cores-shell, disk- and rod-like particles

4. Acknowledgements

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- C. Kientz

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- M. Schmutz (ICS)
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- M. Köhler (Ilmenau Univ.)

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The end

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