Membrane emulsification: an innovative continuous process to create highly uniform capsules/particles

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Loughborough University

Chemical Engineering Department

PRESENTATION LAYOUT

- **How can we produce drops and turn them into particles?**
- **Conventional ways to produce drops**
- **Drop by Drop devices to produce drops**
  - **Microchannel & Membrane emulsification**
- **Specific encapsulations – from drops to particles**

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PARTICLE FORMULATION BACKGROUND

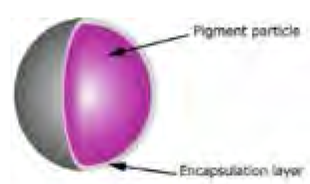
- **Highest value products - complex formulated systems**

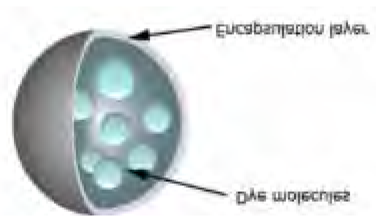
- **To produce uniform particles**
  - **- novel methods for producing**
  - **- novel formulations**

- **Droplets with D >10 μm have become increasingly popular**

- **Additional treatment of the droplets is needed to produce particles**



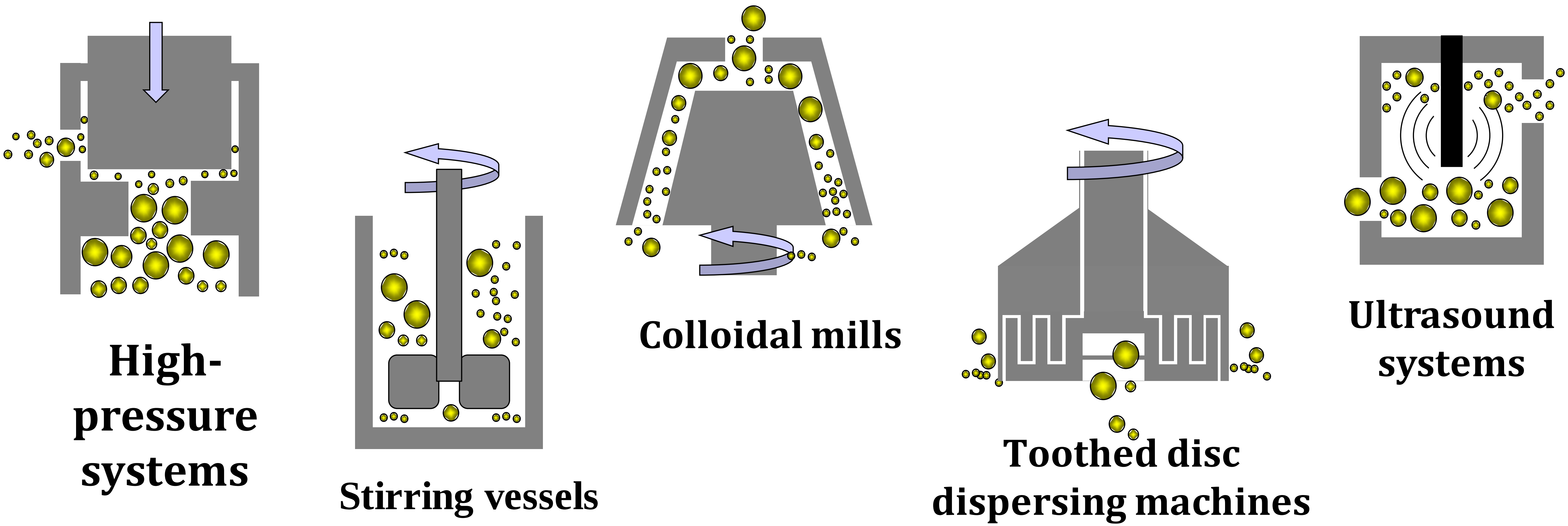





IF WE COULD CREATE A DROP THEN WITH THE ADITIONAL TREATMENT WE COULD GET THE SPHERICAL PARTICLE

HOW TO MAKE A DROP?

MAKING EMULSIONS - CONVENTIONAL WAY



Karbstein H. and Schubert H. 1995

They all apply **more energy** than needed for the production of droplets, and give droplets with **wide size distribution** if larger droplets are wanted.

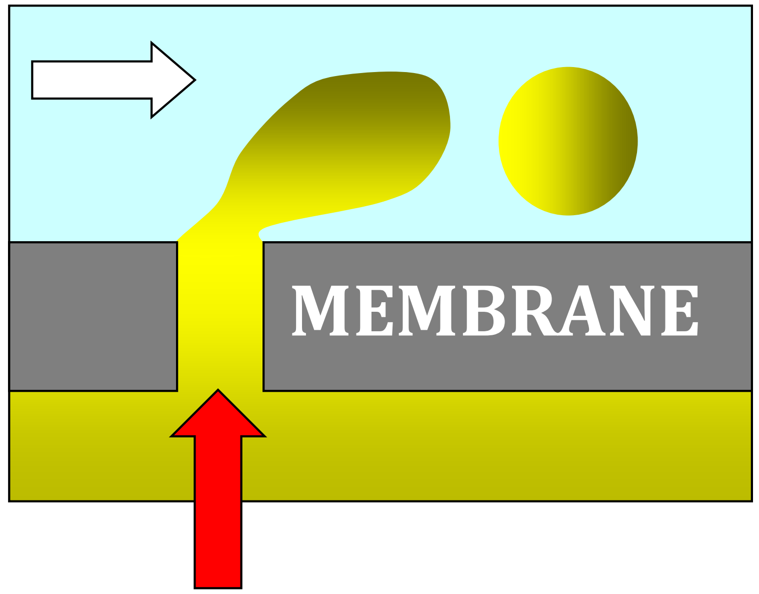
MAKING EMULSIONS - DROP-BY-DROP

Microchannel emulsification

Injection of dispersed phase through microgrooves.

Kawakatsu et. al. 1997

Membrane emulsification



Injection of dispersed phase through membrane.

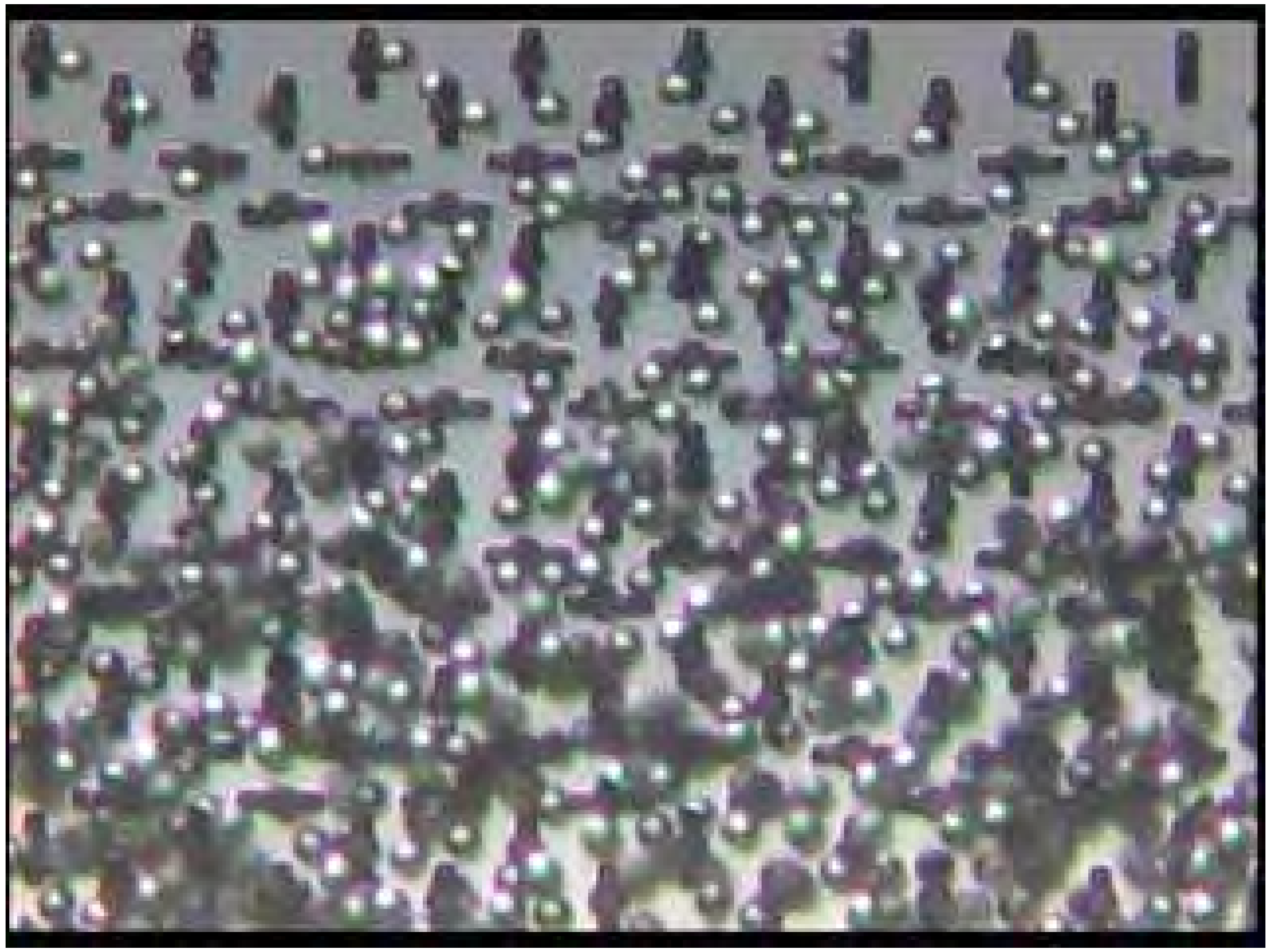
Patent - Asher and Tsien 1980

Nakashima et. al. 1991

They use **low energy** per unit volume and give **monosized** distribution.

MAKING EMULSIONS - DROP-BY-DROP

Microchannel emulsification



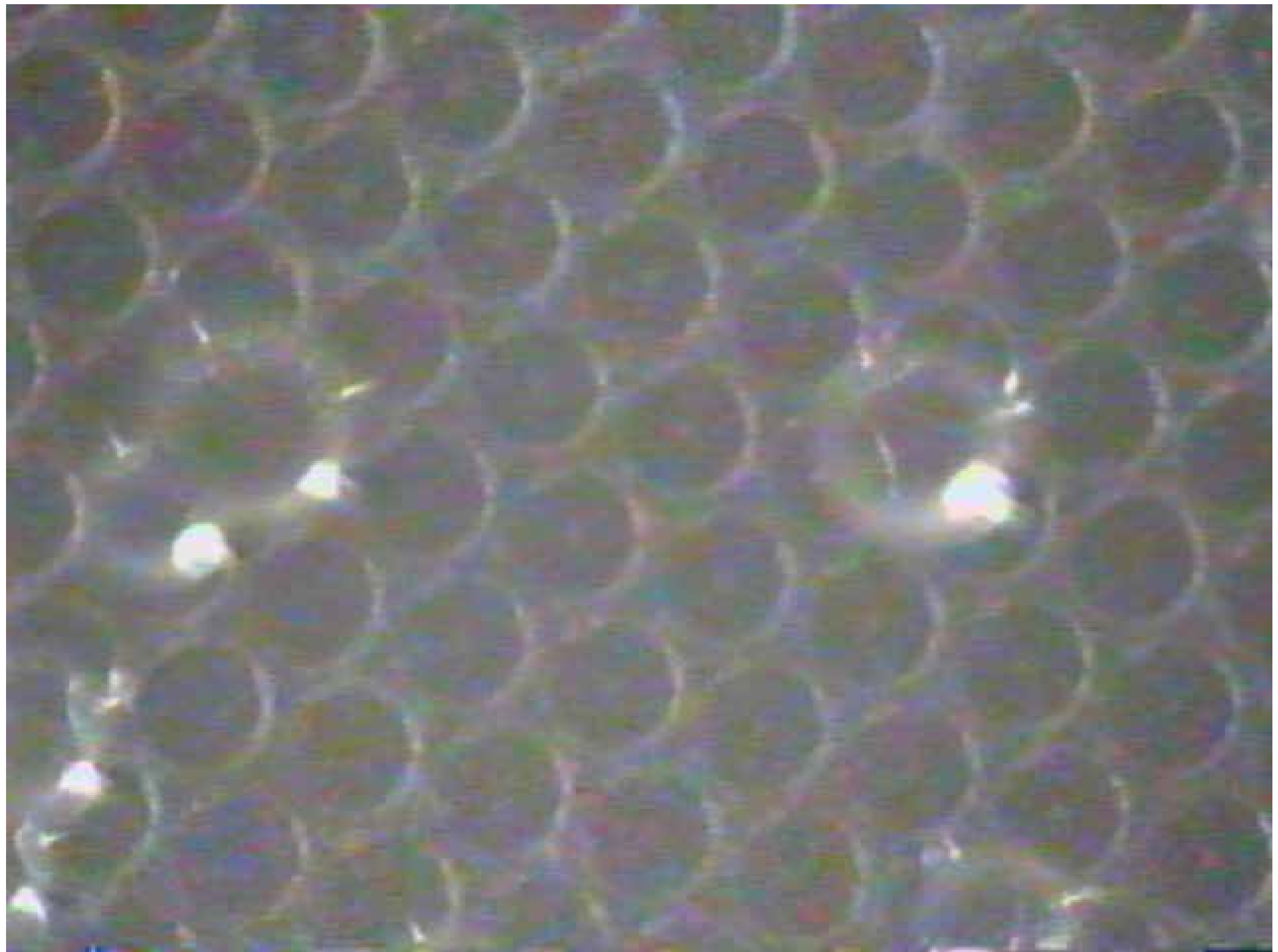
Apply shear
No change in droplet size

Dragosavac 2012

Membrane emulsification

NO shear

Hydrophilic nickel membrane



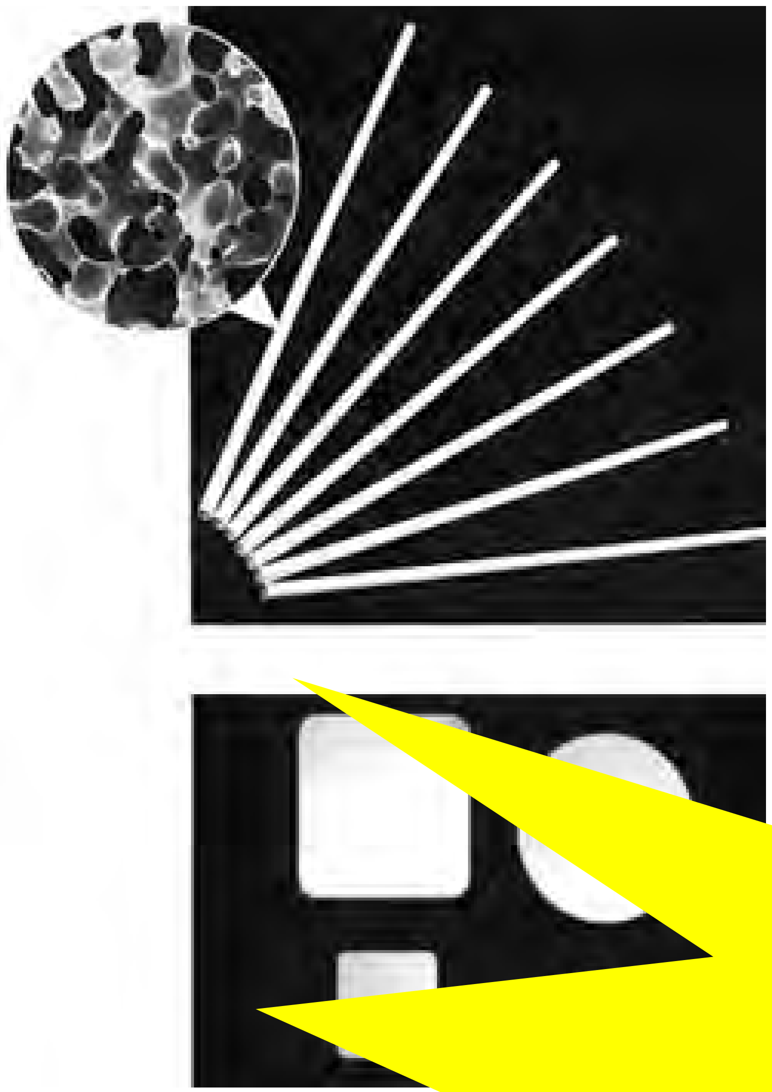
D_{50}=200 µm

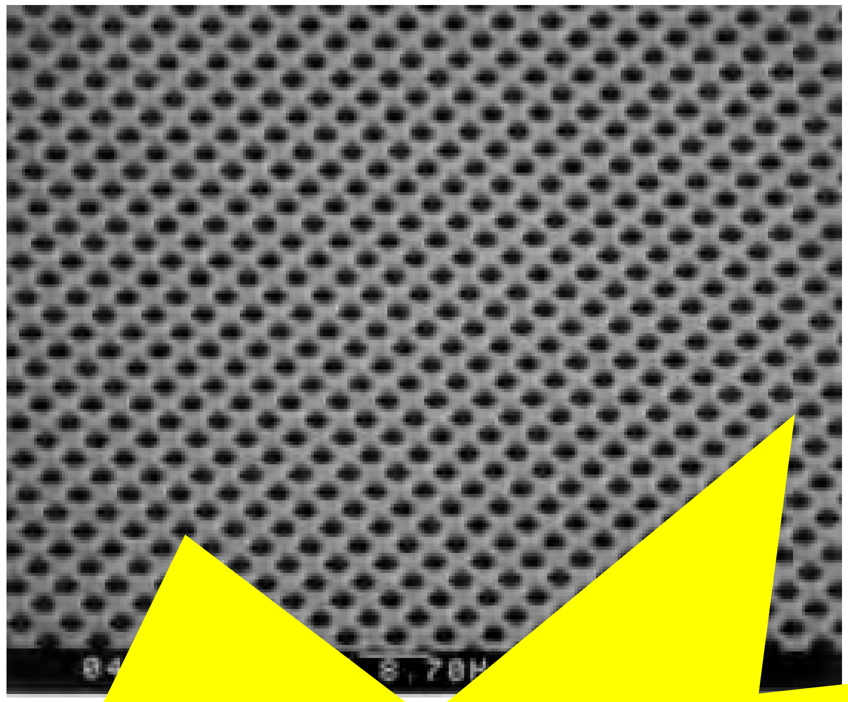
Apply shear
smaller droplets obtained

Kosvintsev 2008

MEMBRANE EMULSIFICATION

MEMBRANES AVAILABLE AT THE MARKET





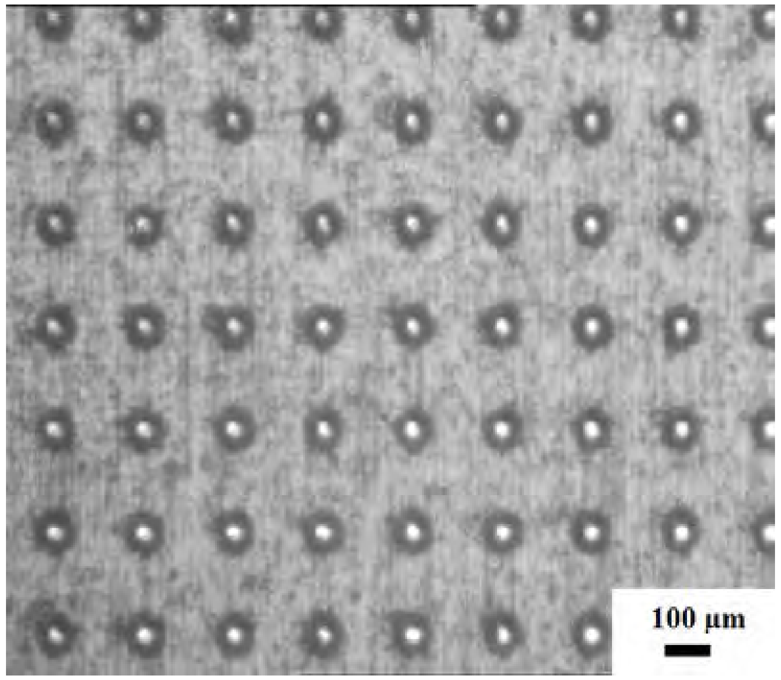
Ceramic membranes
TAMI industries (France)
Various other producers
Drop size
0.3 - 40 μm

Fragile

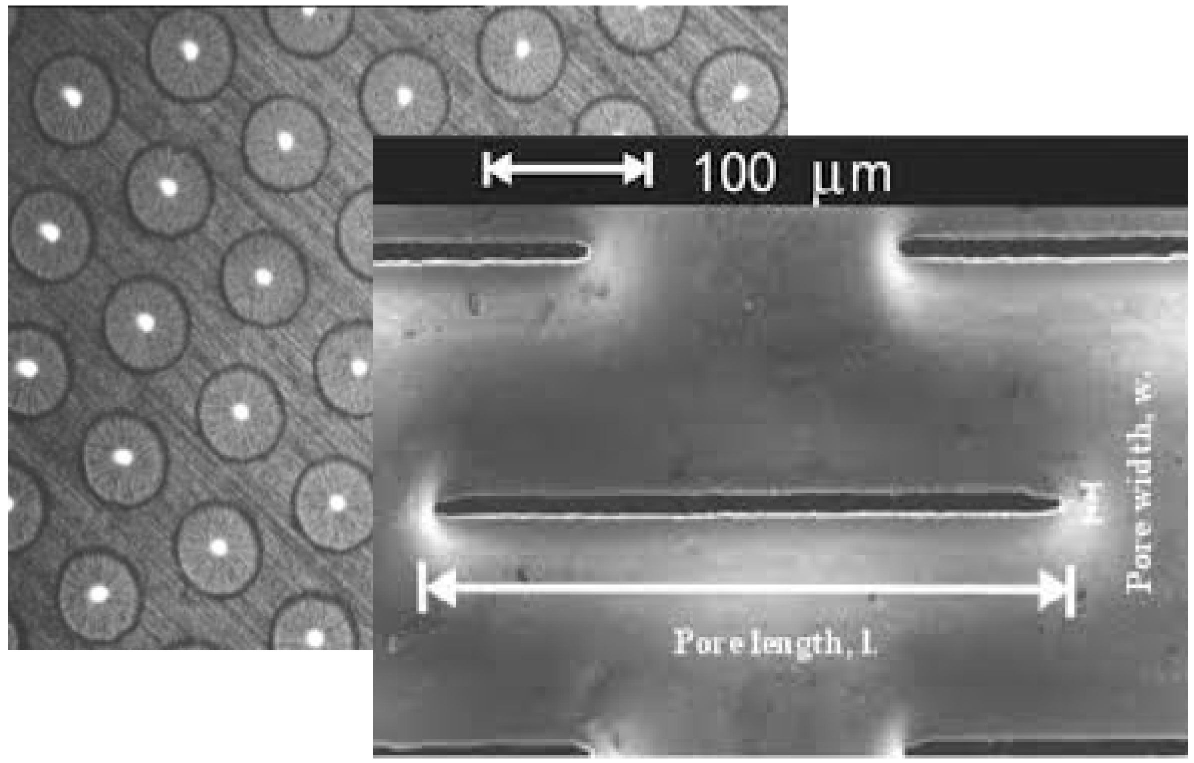
SPG memb
SPG Technology Co.,L
Japan
Drop size
0.2 - 40 μm

METAL MEMBRANES

Stainless steel membranes



Nickel membranes

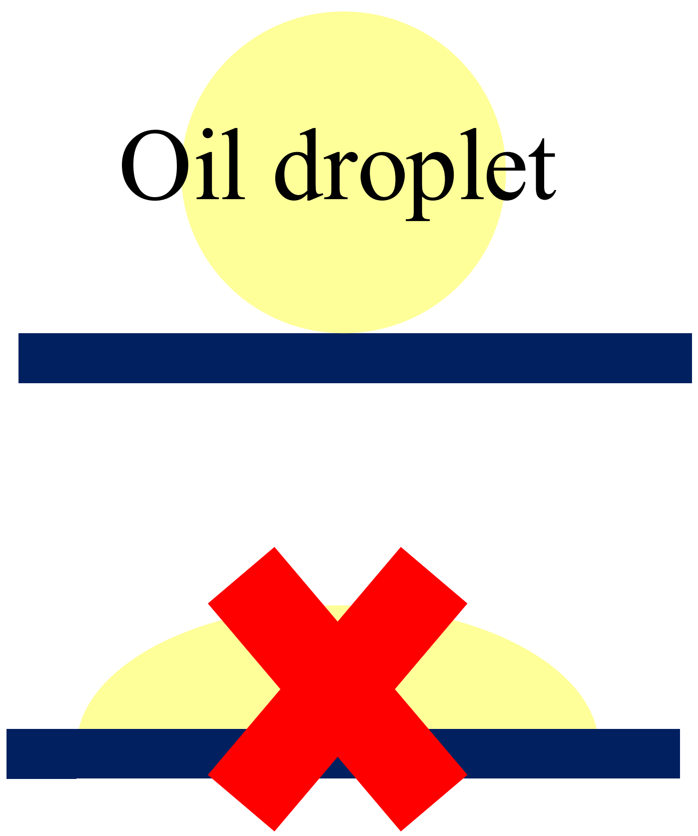


used at Loughborough

MEMBRANE SURFACE

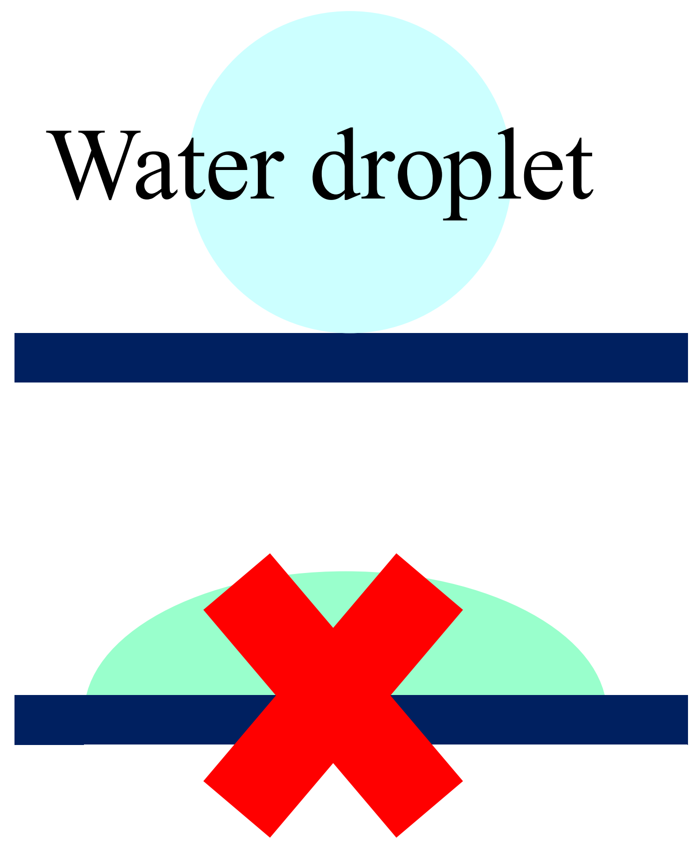
O/W and W/O/W

Hydrophilic surface



W/O and O/W/O

Hydrophobic surface



MODELLING

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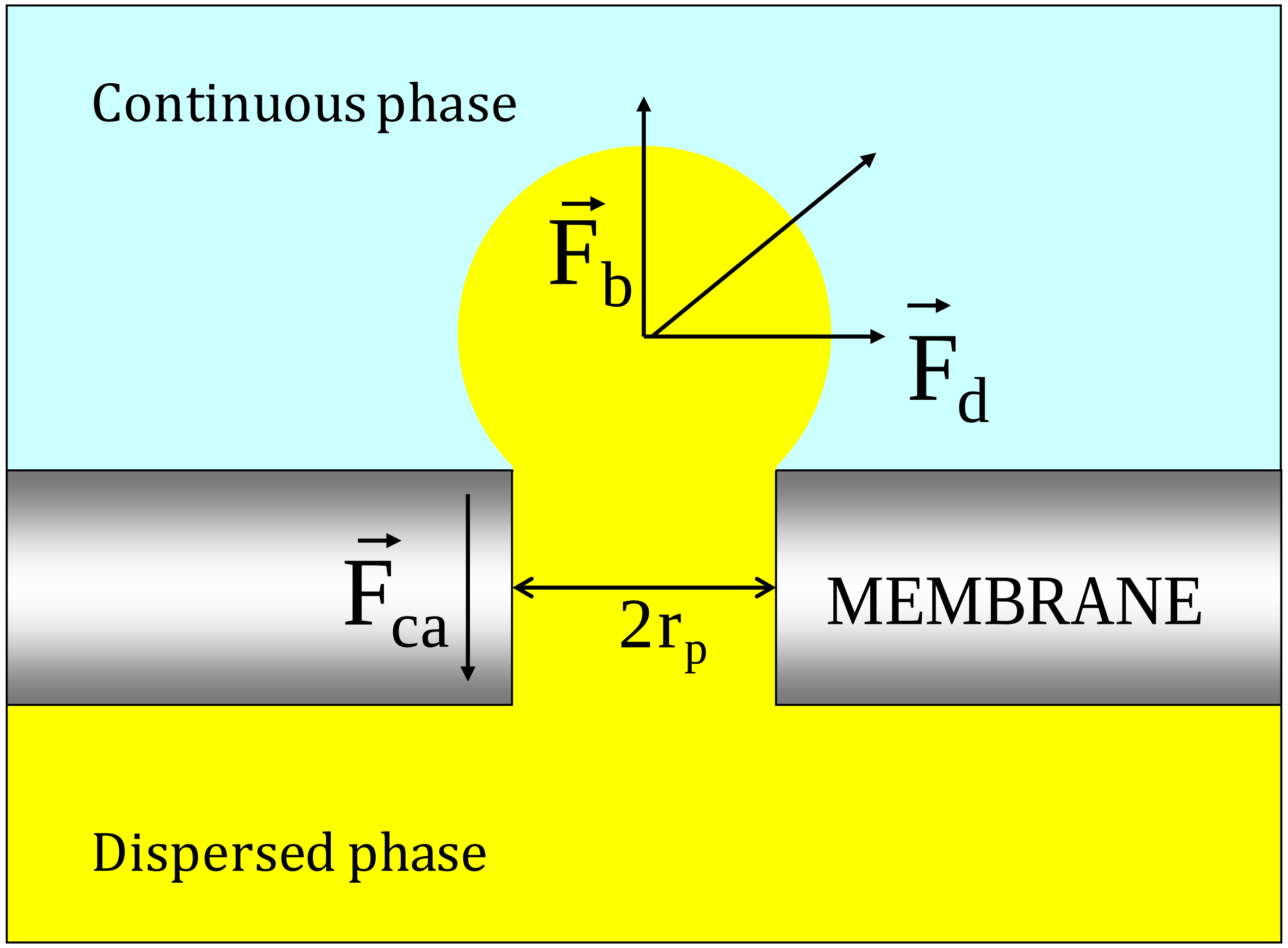
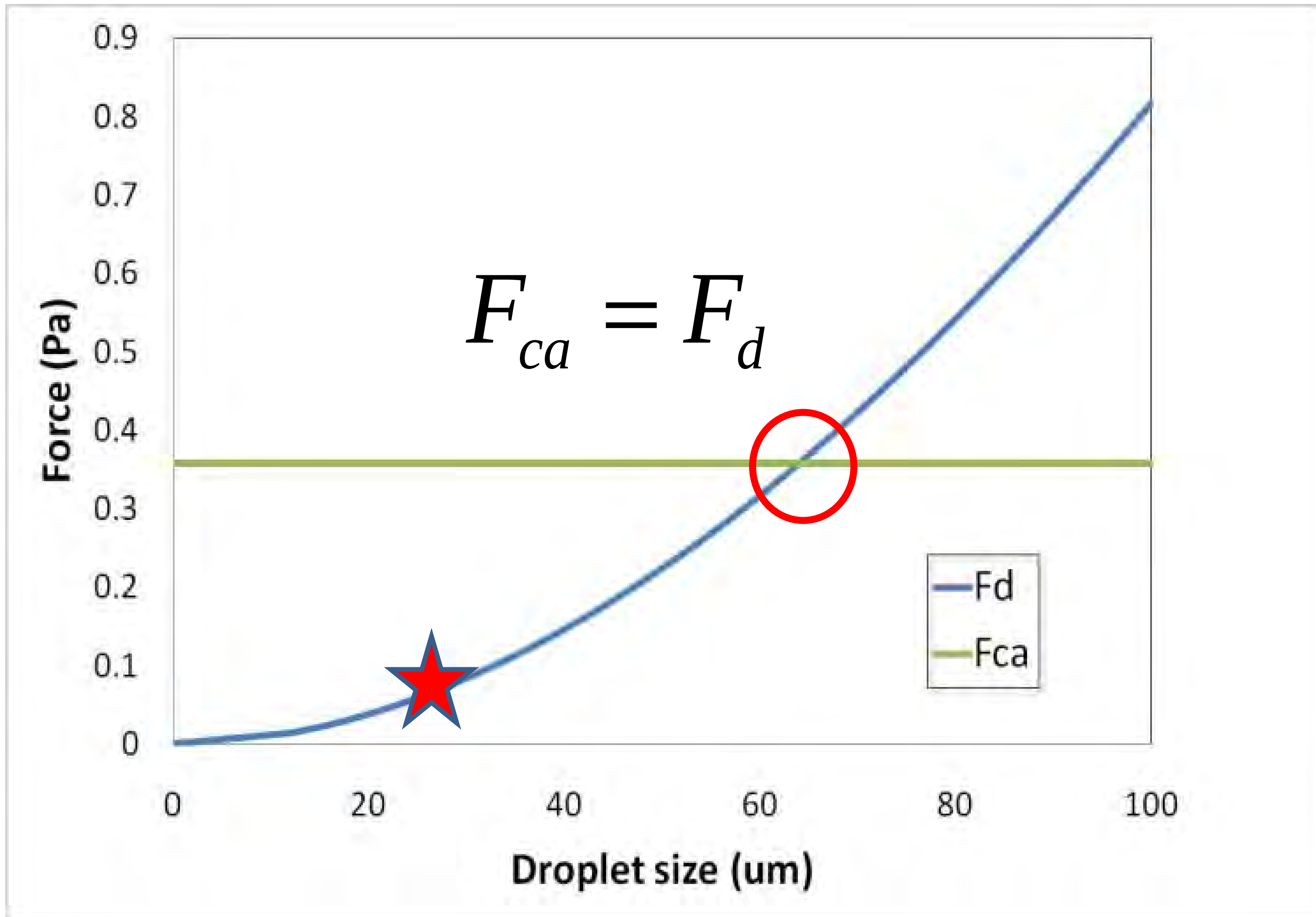
FORCE BALANCE MODEL





F_{ca} - Capillary force

$$F_{ca} = f(\gamma, r_p)$$

F_d - Drag force

$$F_d = f(\tau_{max}, r_p, d)$$

$$\tau_{max} = 0.825 \eta \omega r_{trans} \frac{1}{\delta}$$

Kosvintsev et al. 2008

Dragosavac et al. 2008

$$\pi d_p \gamma = 9 \pi \tau_{max} d_d \sqrt{\left(\frac{d_d}{2}\right)^2 - r_p^2}$$

$$d_d$$

SHEAR STRESS ON THE MEMBRANE SURFACE

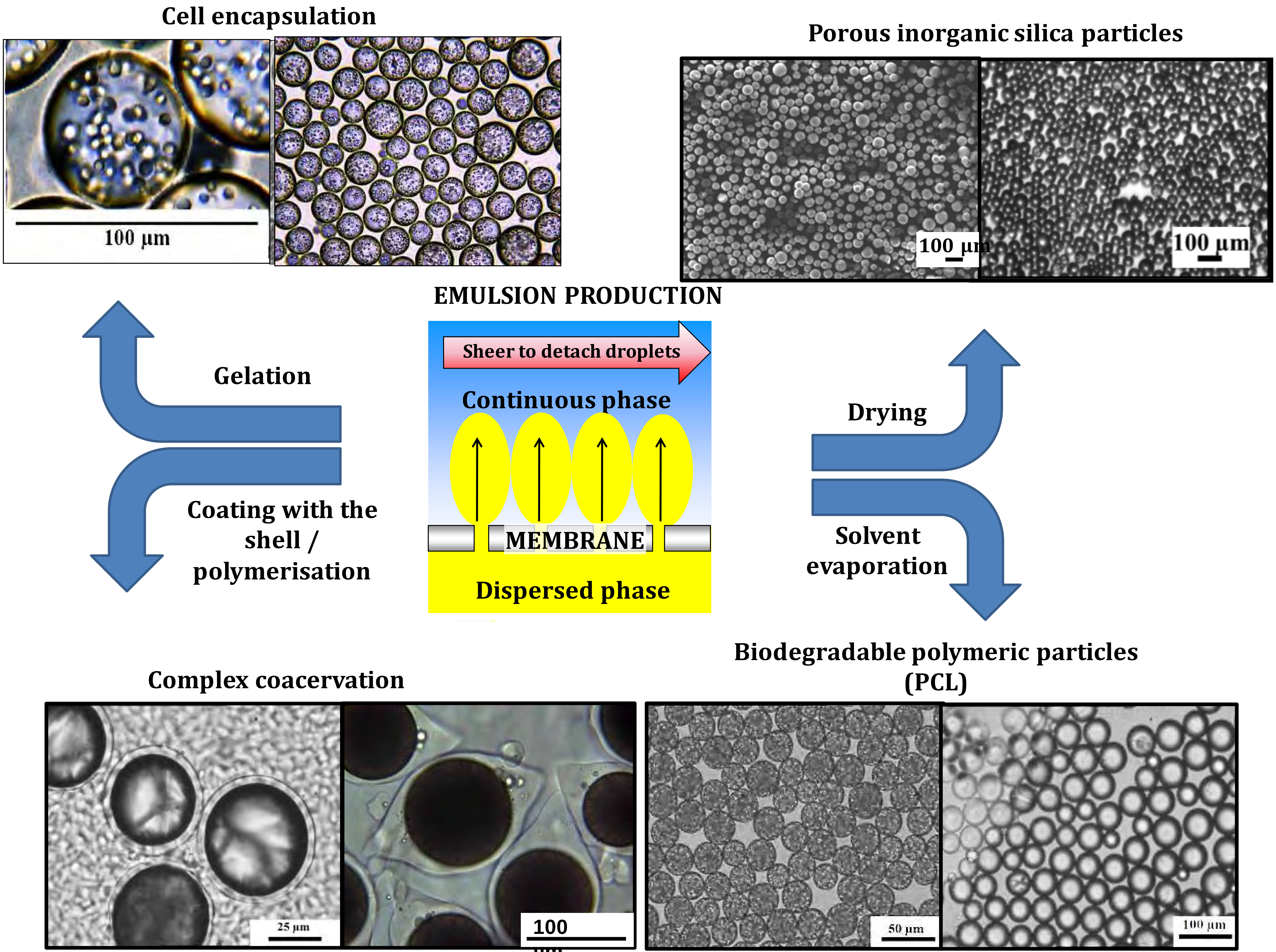
Movements of continuous phase:

- **STIRRING**
- **CROSS FLOW**
- **PULSATIONS OF THE CONTINUOUS PHASE**

Movements of the membrane:

- **VIBRATIONS**
- **ROTATIONS**
- **TORSIONAL MOVEMENTS**

SOME OF THE PARTICLES PRODUCED UP TO DATE AT LOUGHBOROUGH



COMPLEX COACERVATION
O/W emulsion

Motivation for the work:

Currently batch production
High polydispersity of the product and usually too big droplet size

Need for pig gelatine alternative

Piacentini, Emma, et al. "Microencapsulation of oil droplets using cold water fish gelatine/gum arabic complex coacervation by membrane emulsification." *Food research international* 53.1 (2013): 362-372.

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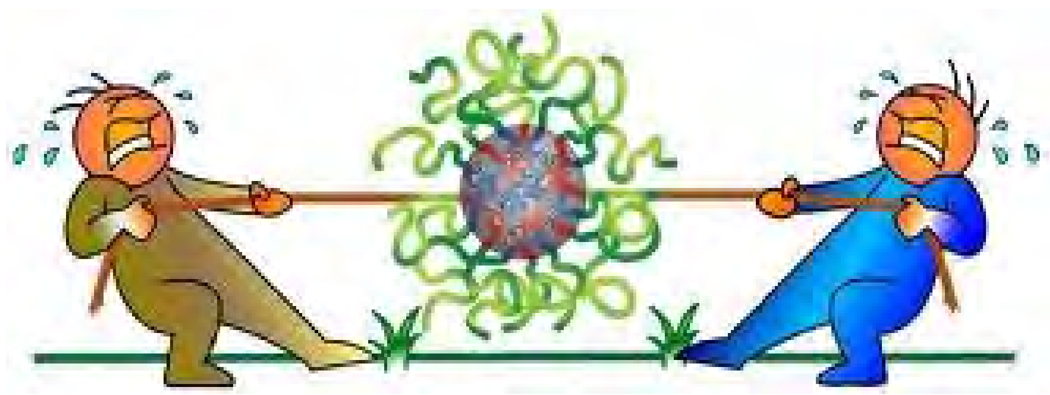
COMPLEX COACERVATION

1. **Drop production in hydrocolloids solution**

2. **Coacervation (phase separation) implying the formation of a coacervate phase – pH adjustment**

3. **Wall formation by aggregation of the hydrocolloid around droplets of the emulsified hydrophobic material – time, room temperature**

4. **Wall-hardening, which is generally achieved by cross-linking the hydrocolloid forming the wall**



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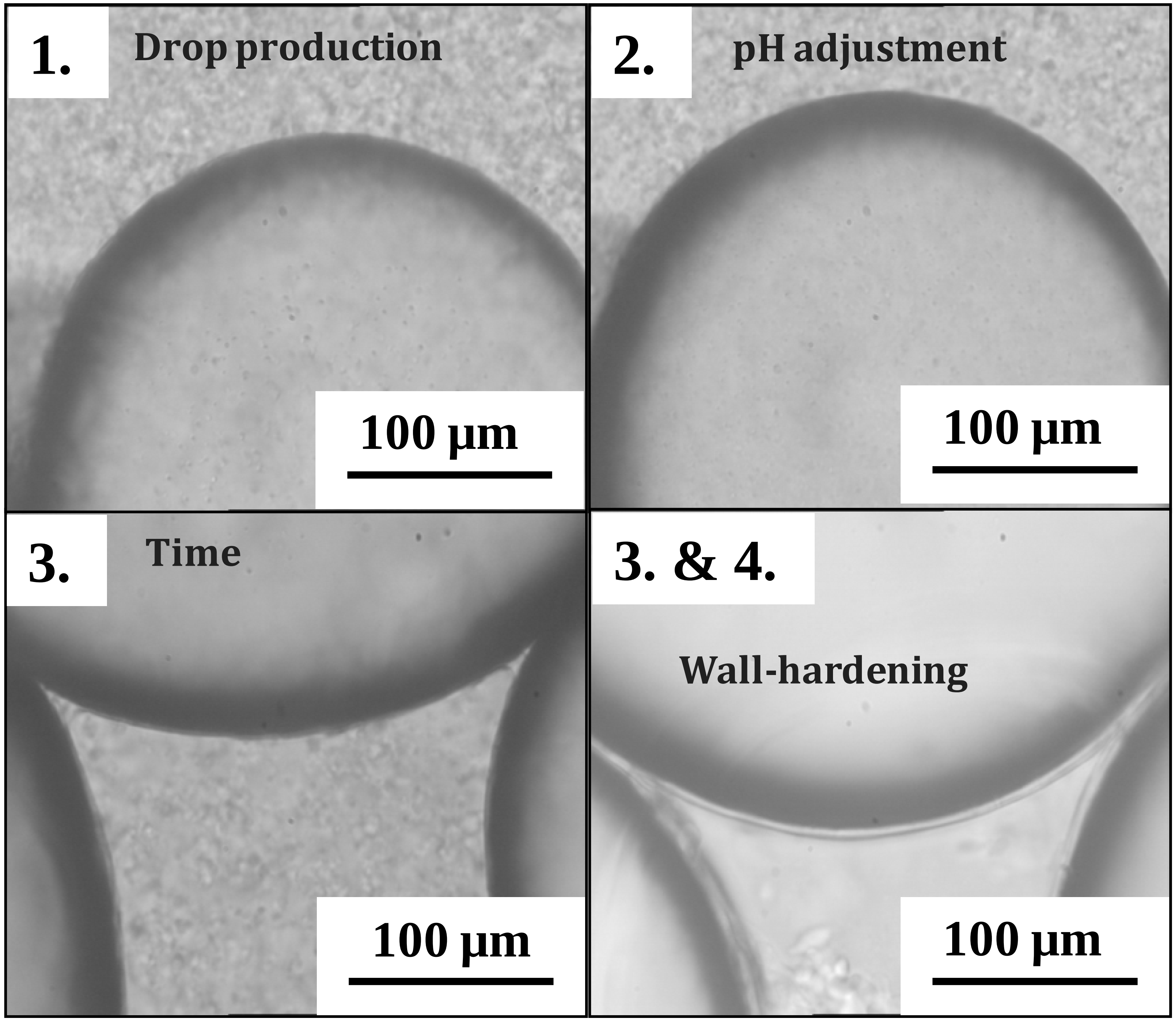
COMPLEX COACERVATION



COMPLEX COACERVATION – Oil encapsulation

FISH GELATINE CAPSULES

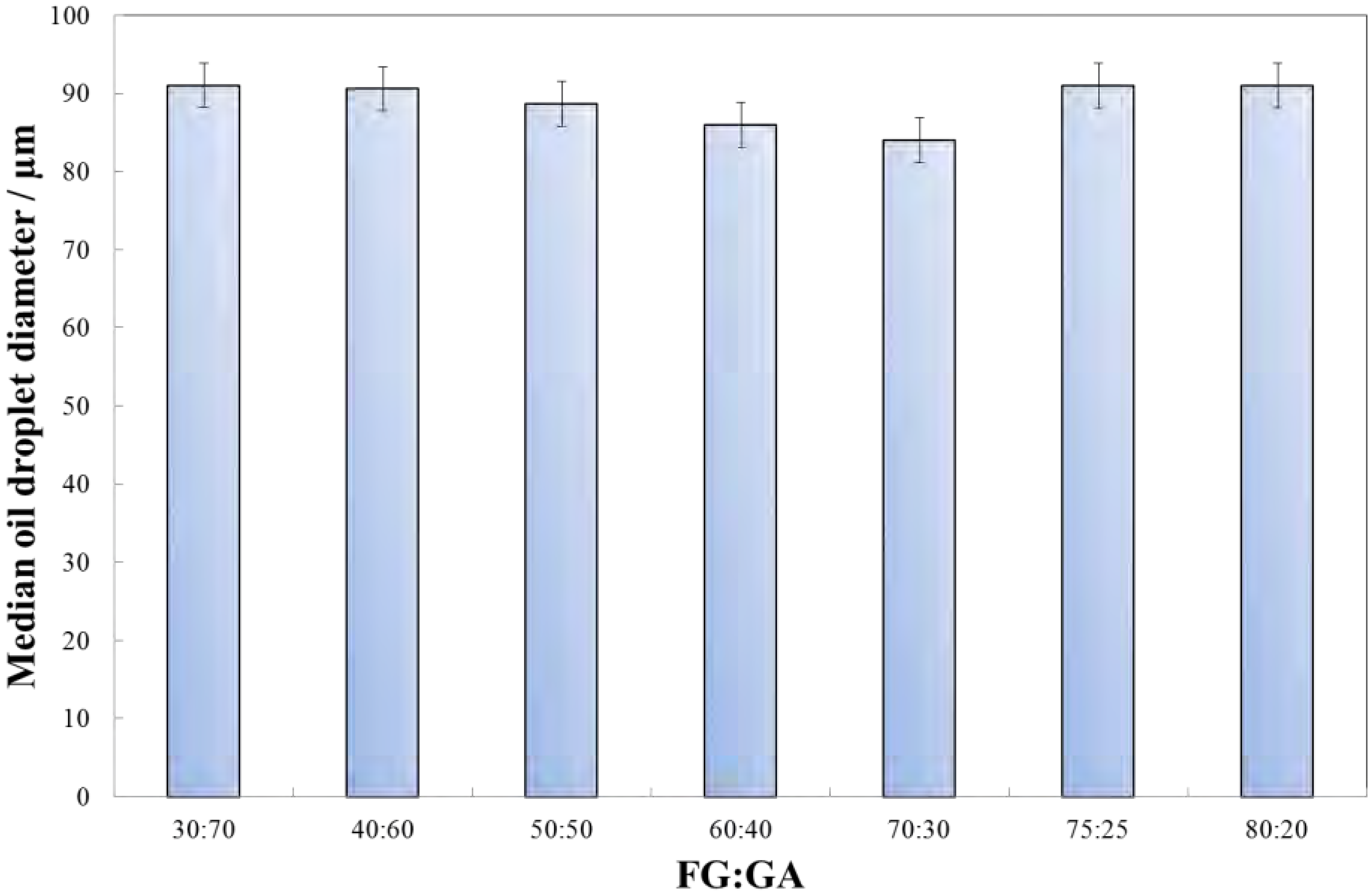
WHY FISH GELATINE?

- ROOM TEMPERATURE - less energy compared to alternative gelatine types and
- New possibilities for encapsulation of VOLATILE COMPOUNDS
- Increased CONSUMER consent for religious or diet reasons and health safety

Piaccentini et al., 2013

ITM-CNR @ University of Calabria, Rende

DIFFERENT RATIOS OF FG:GA – PARTICLE SIZE



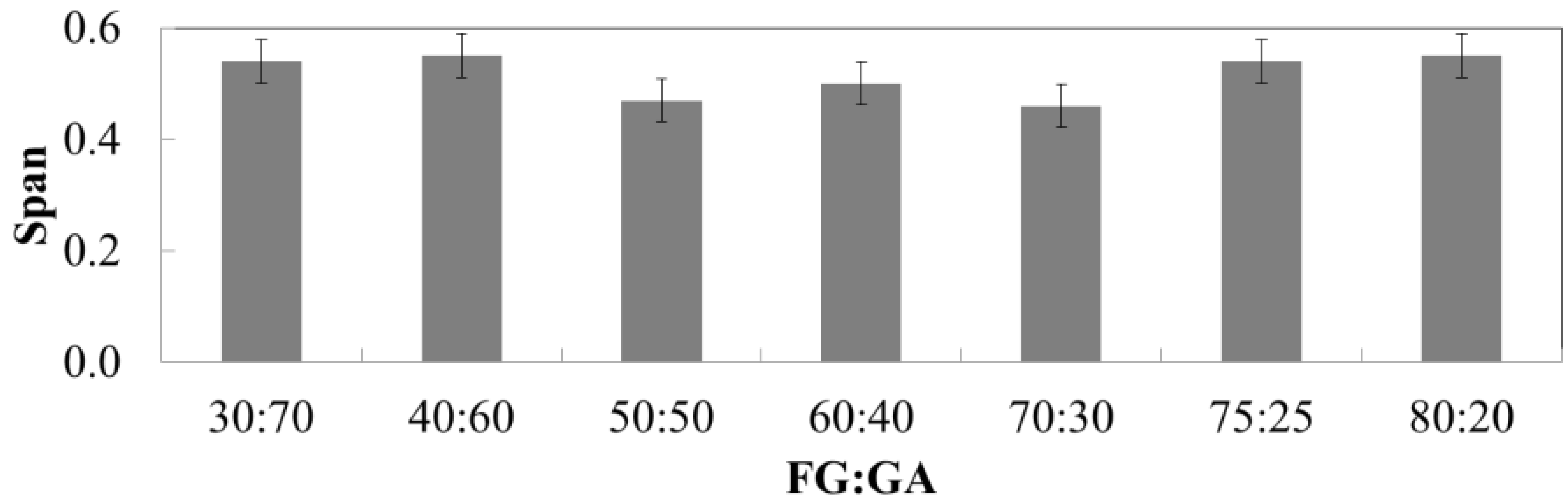
Shear = 6 Pa
Injection rate =1 L h^{-1}

pH=3.5

Room temperature

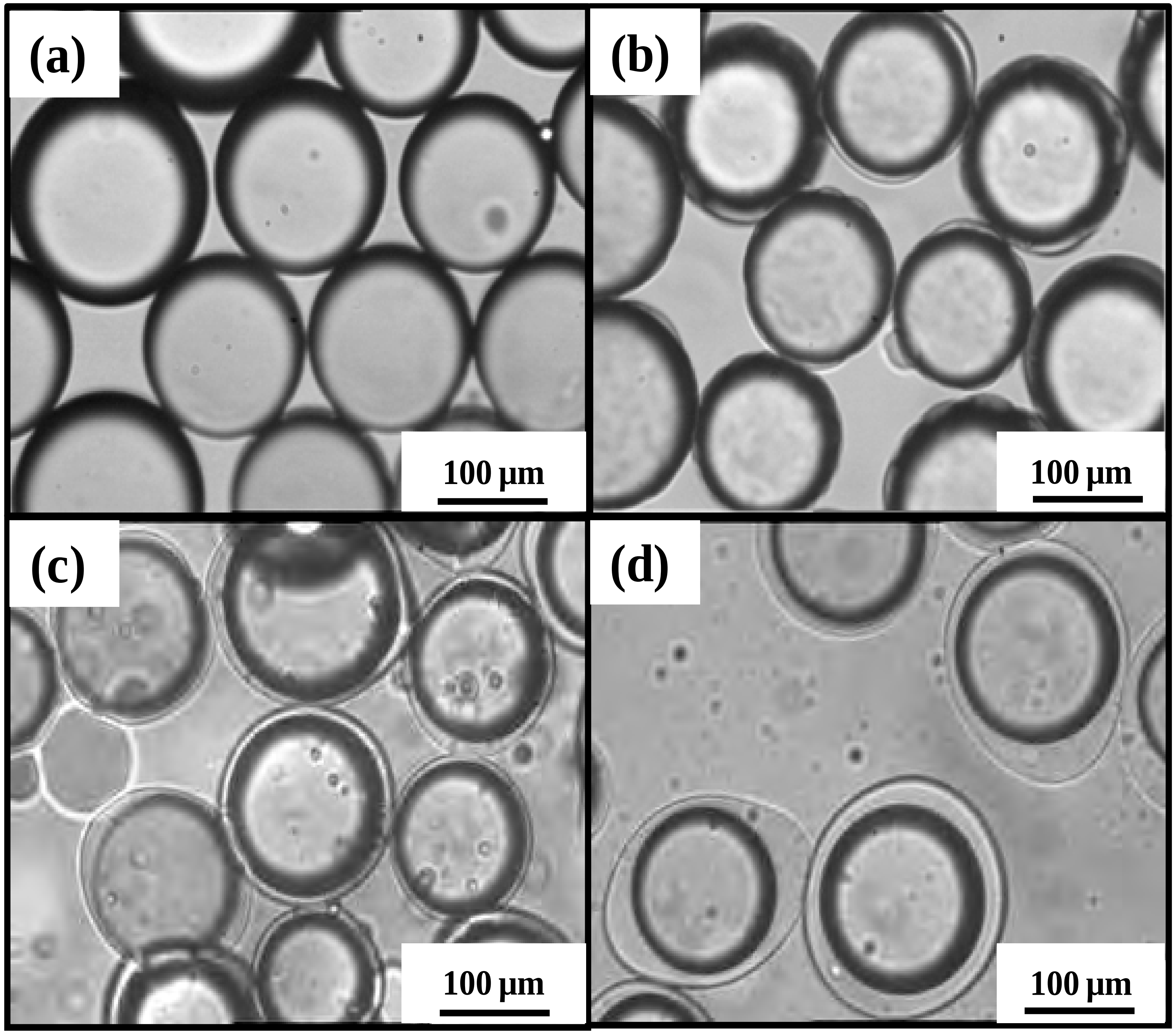
$$Span = \frac{D_{90} - D_{10}}{D_{50}}$$

Piaccentini et al., 2013



DIFFERENT RATIOS OF FG:GA FOR MICROCAPSULES

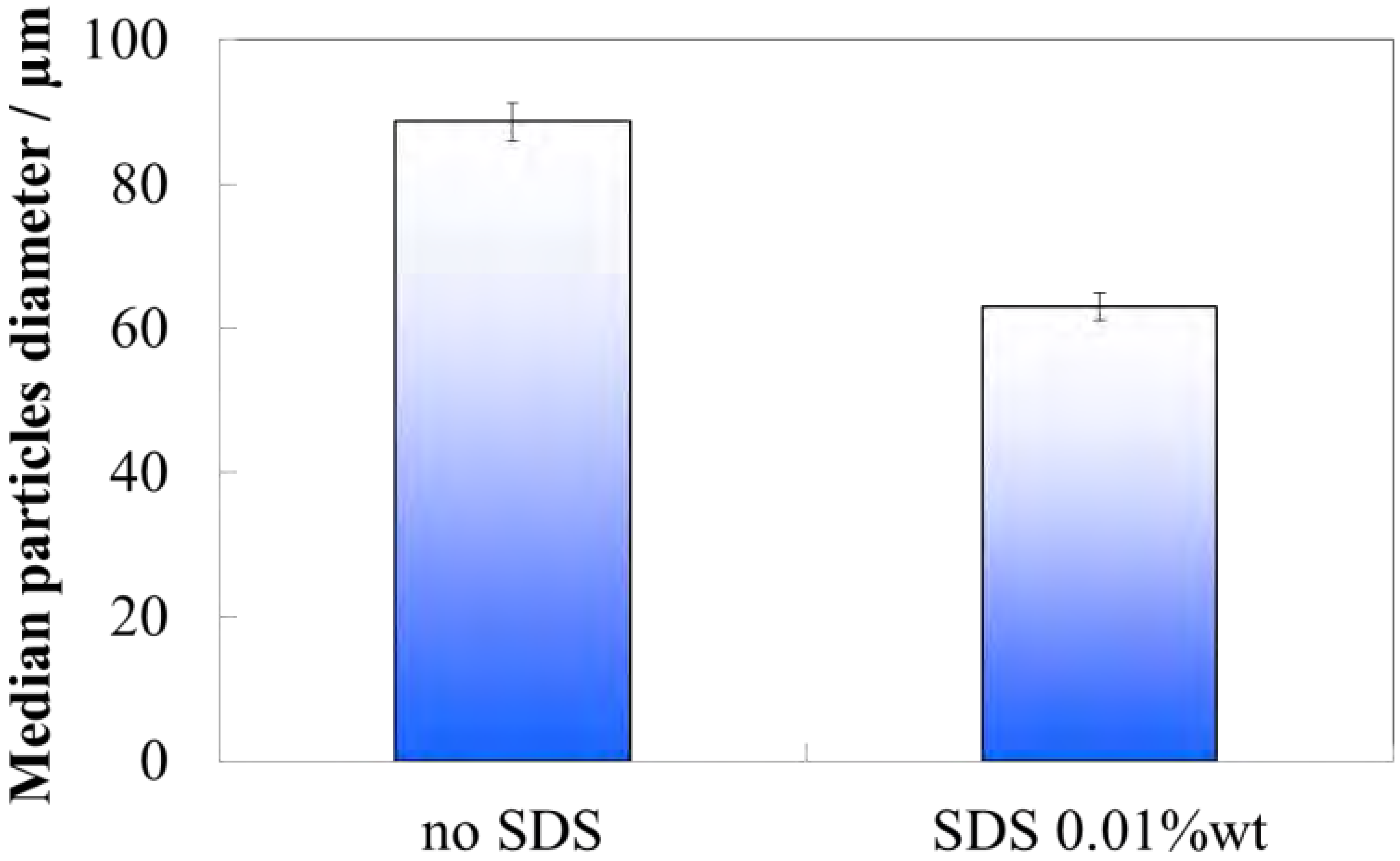
ROOM TEMPERATURE



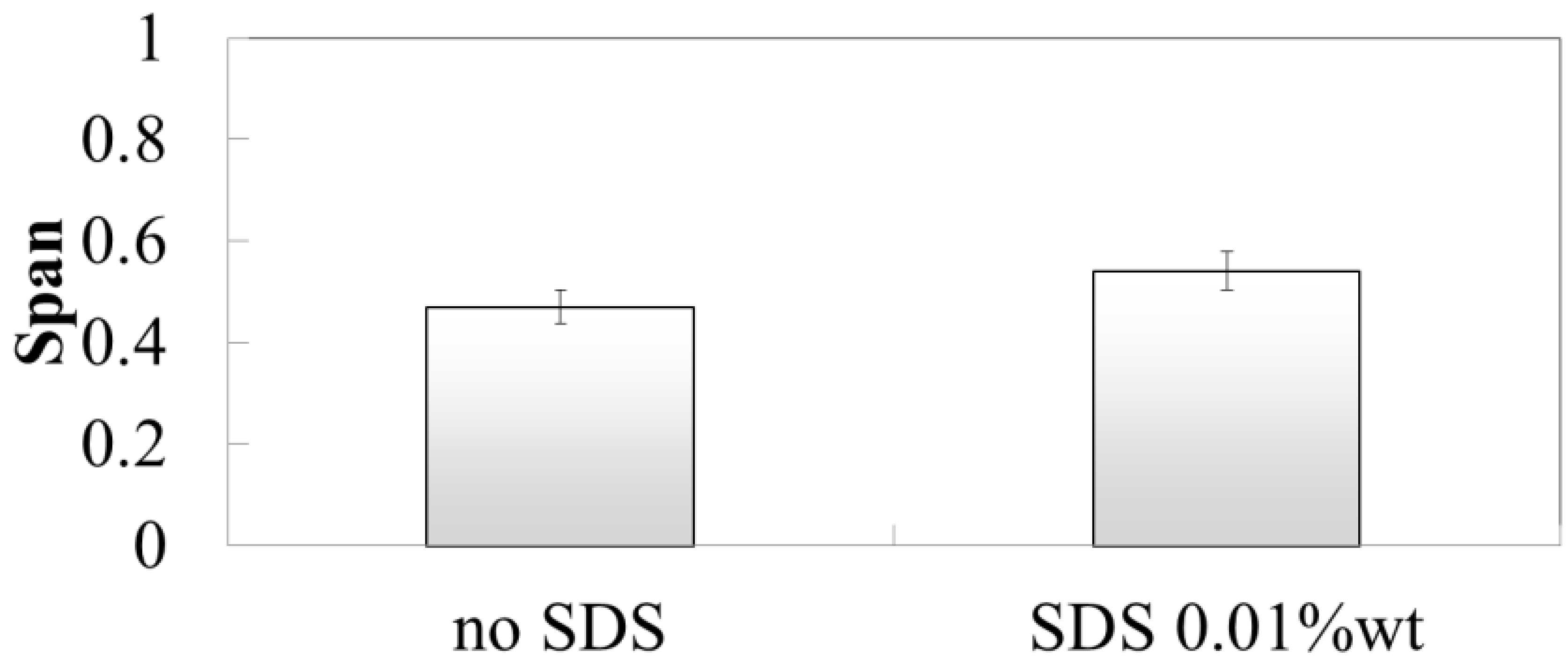
Piaccentini et al., 2013

FG:GA **(a) 30:70; (b) 40:60; (c) 80:20; and (d) 50:50.**

PARTICLE SIZE CONTROL WITH SURFACTANT ADDED

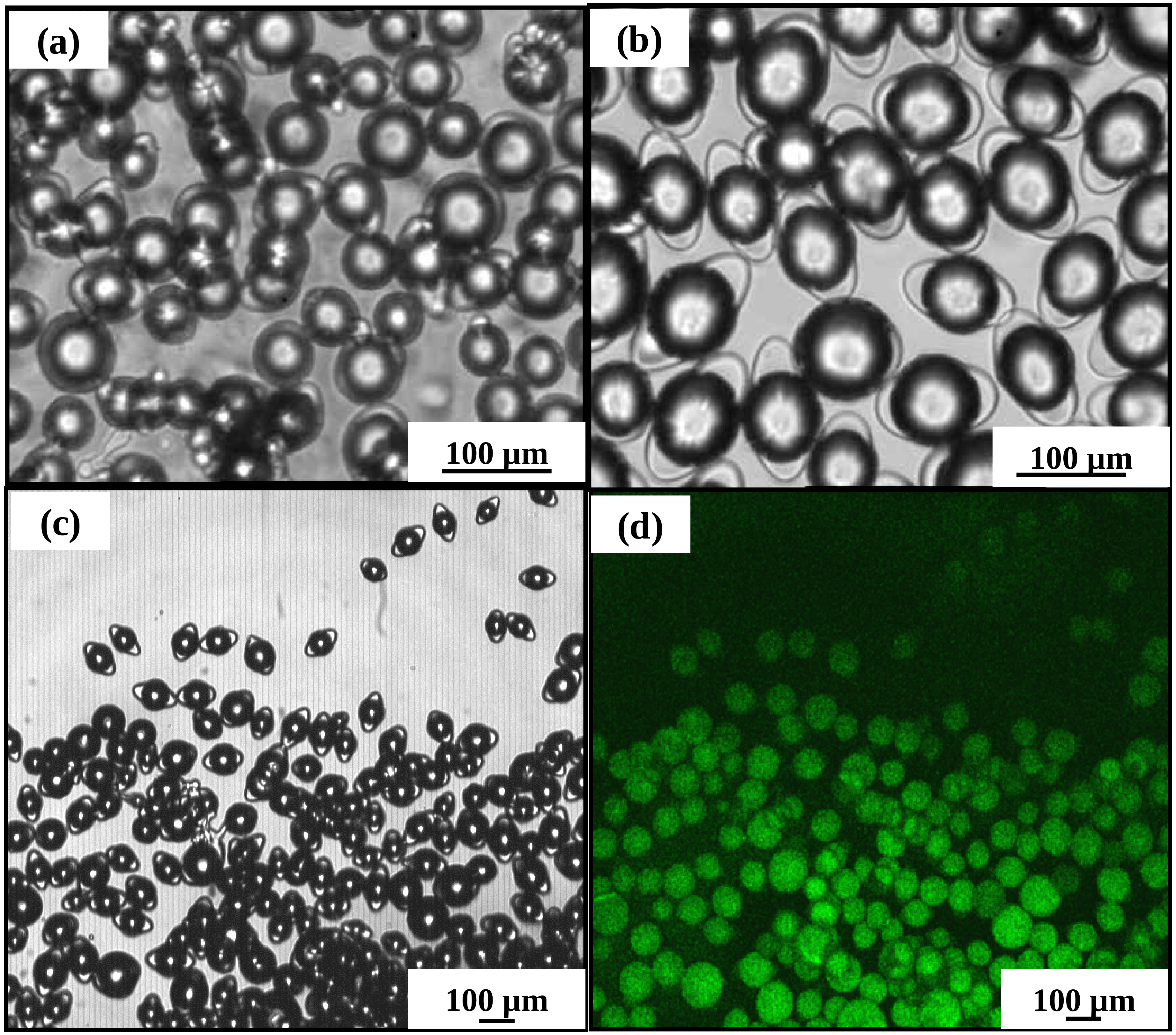


Shear = 6 Pa
Injection rate =1 L h^{-1}
20 µm pore size



Piaccentini et al., 2013

FRAGRANCE OIL ENTRAPMENT



Freeze dried particles (to enable future volatile compound encapsulation)

Silica particles or diatomaceous earth added to produce free flowing particles

Piaccentini et al., 2013

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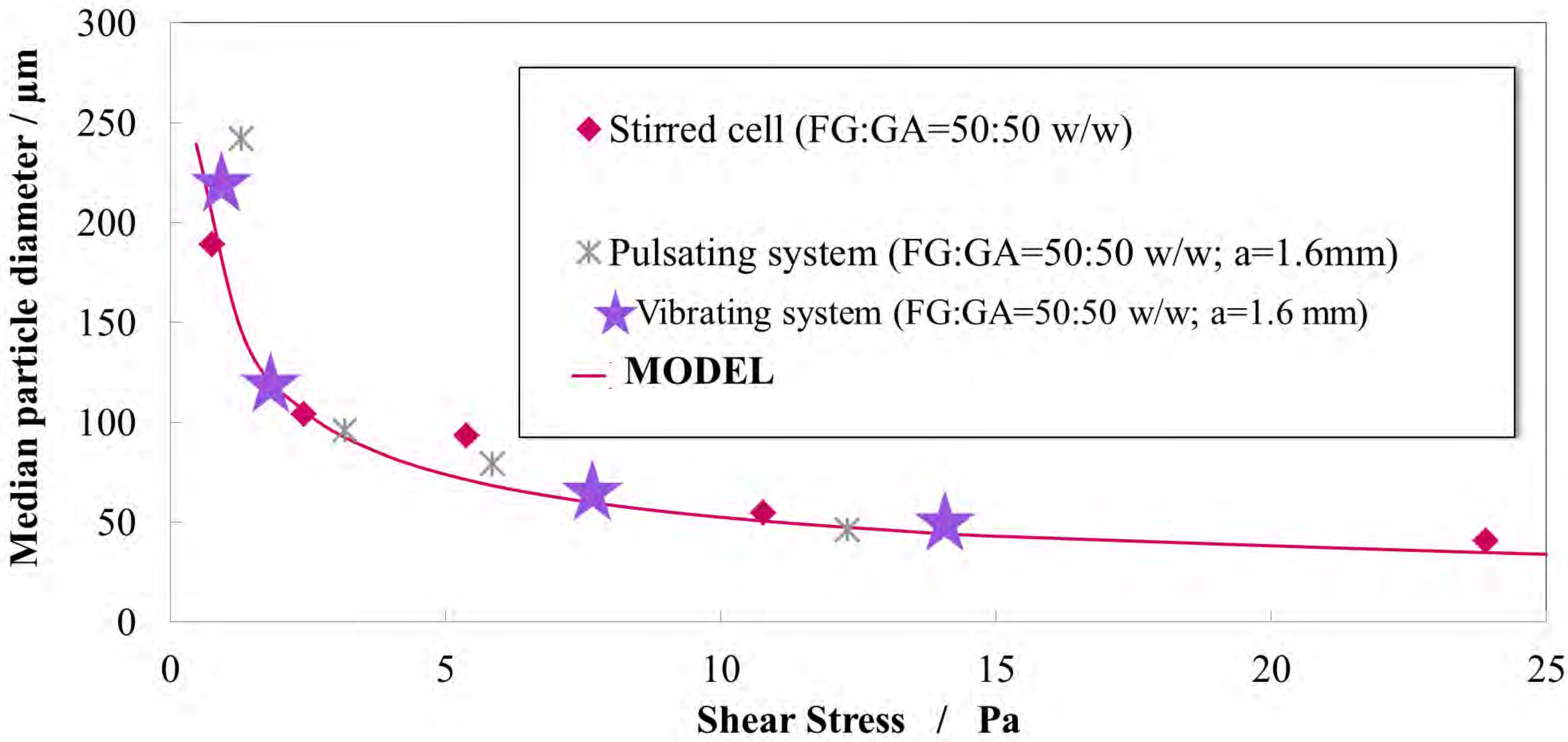
COMPLEX COACERVATION

DISPERSION CELL, PULSATING & VIBRATING SYSTEM

Dispersed phase: **Sunflower oil**
Continuous phase: **Fish gelatine (FG) and Gum Arabic (GA)**



Flow through the pulsed membrane = 3L h^{-1}

SPAN for all experiments below 0.5

Piaccentini et al., 2013

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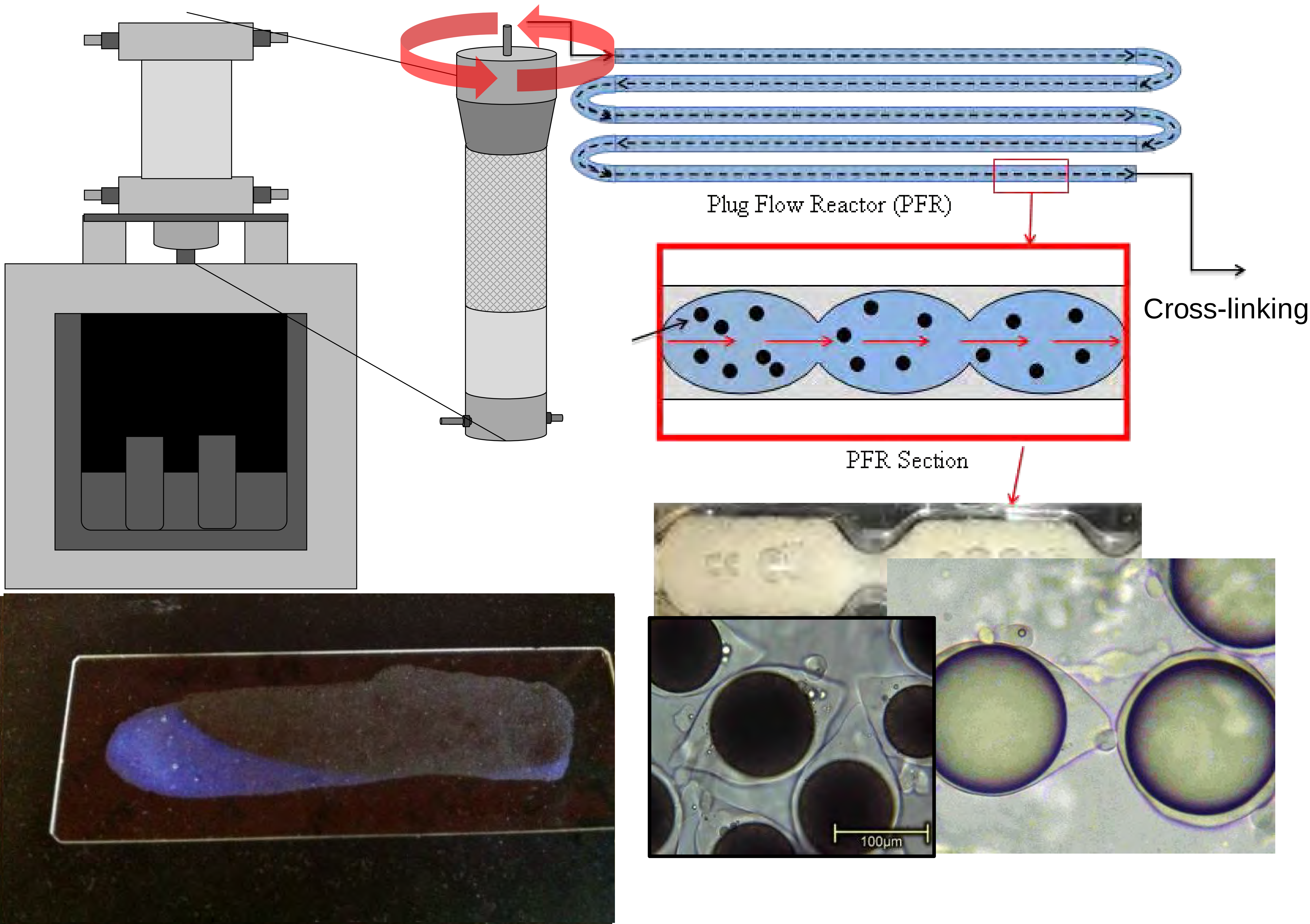
CURRENT WORK - COMPLEX COACERVATION

CONTINUOUS ENCAPSULATION/SHELL FORMATION

CONTINUOUS ENCAPSULATION/SHELL FORMATION



ANTYCANCER DRUG ENCAPSULATION
O/W & W/O/W

Motivation for the work:

Currently batch production
Low uniformity of the produced particles using conventional emulsification methods
Need for higher encapsulation efficiency

Anticancer drug - extremely expensive & temperature sensitive)

ENCAPSULATION OF WATER SOLUBLE PEPTIDE USING BIODEGRADABLE POLYMER

1. Dispersion phase – polymer (PLGA) mixed with DCM (volatile oil phase)

2. Mixing the peptide with previously prepared dispersion phase

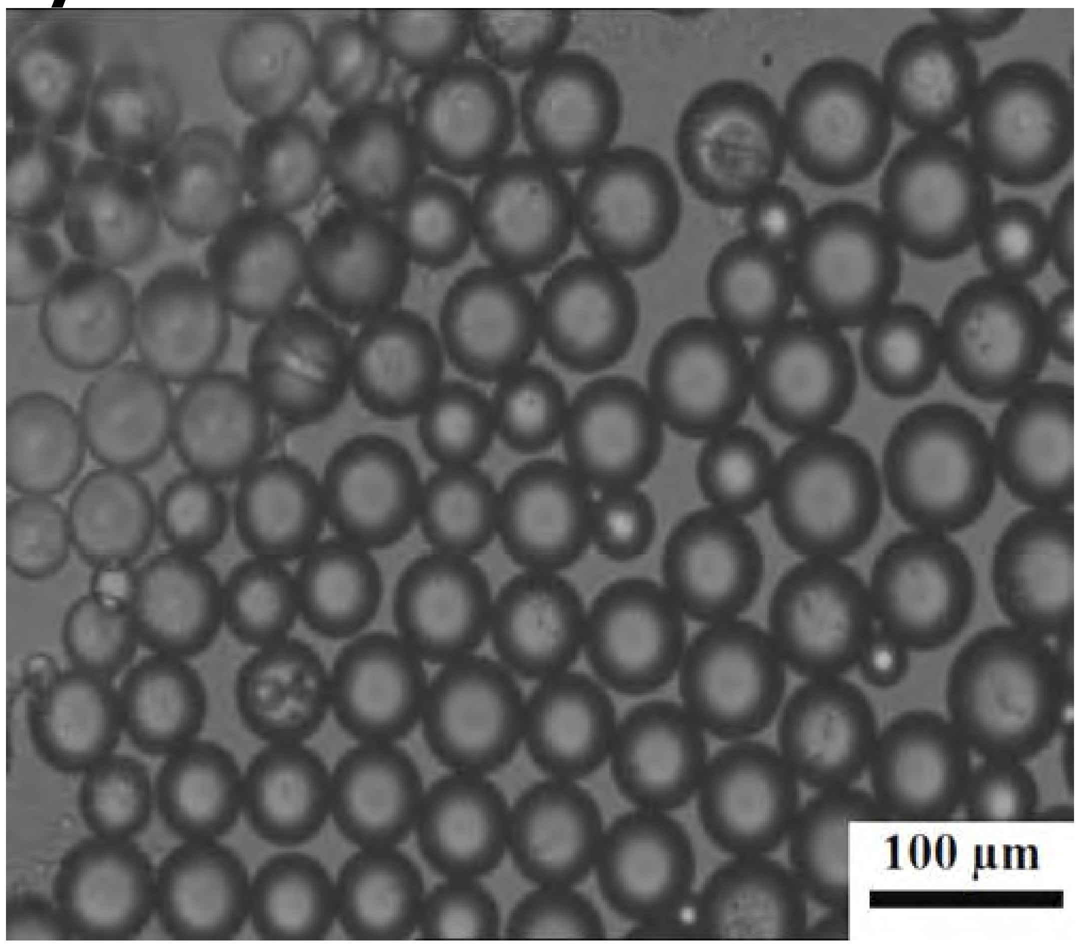
3. Injecting through the membrane into 1% PVA solution

4. DCM will evaporate from the particles leaving only peptide within the spherical PLGA particles

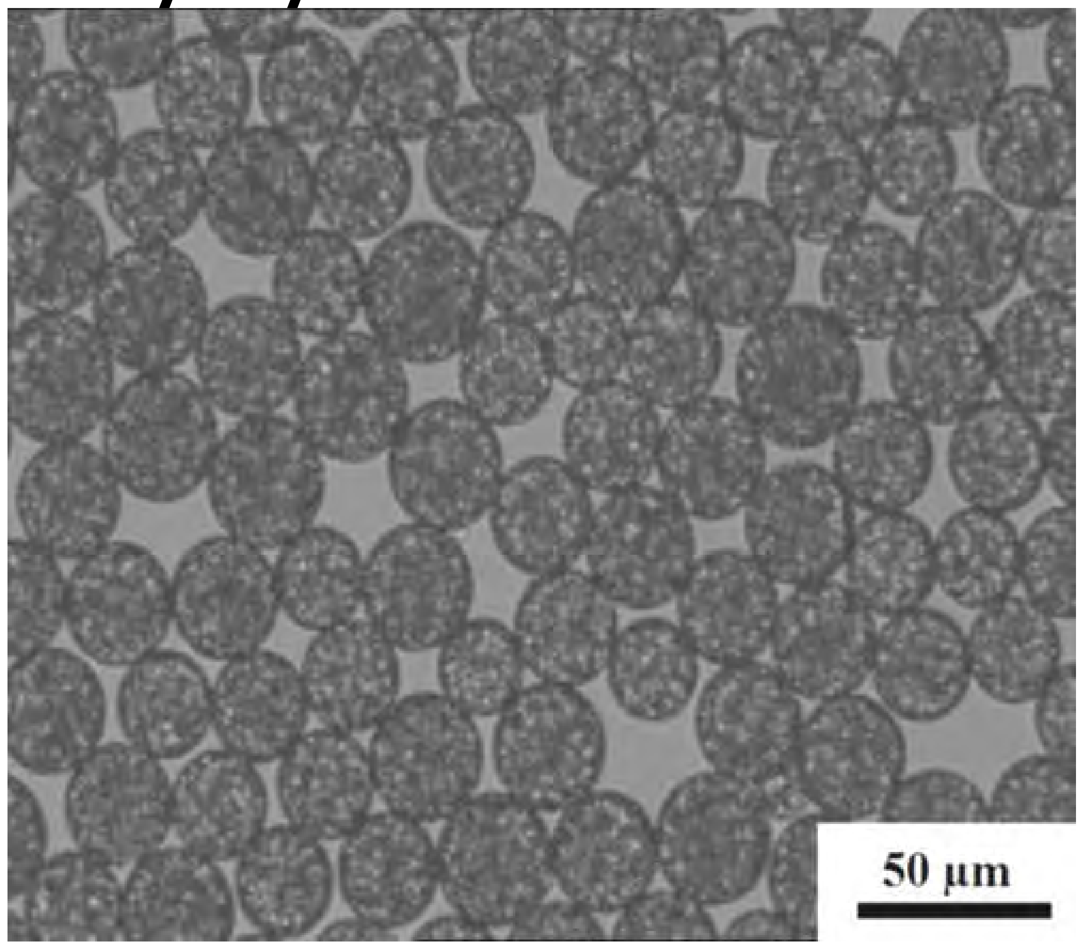
Micropore Technologies

ENCAPSULATION OF WATER SOLUBLE PEPTIDE USING BIODEGRADABLE POLYMER

O/W EMULSIONS



W/O/W EMULSIONS



HPLC - ENCAPSULATION EFFICIENCY (EE) OF PEPTIDE

ü Cancer treatment	POLYMER CONCENTRATION (%)	EE (%)
COSOLVENT METHOD (O/W)	10	40
	20	50
W/O/W	10	70
	20	85

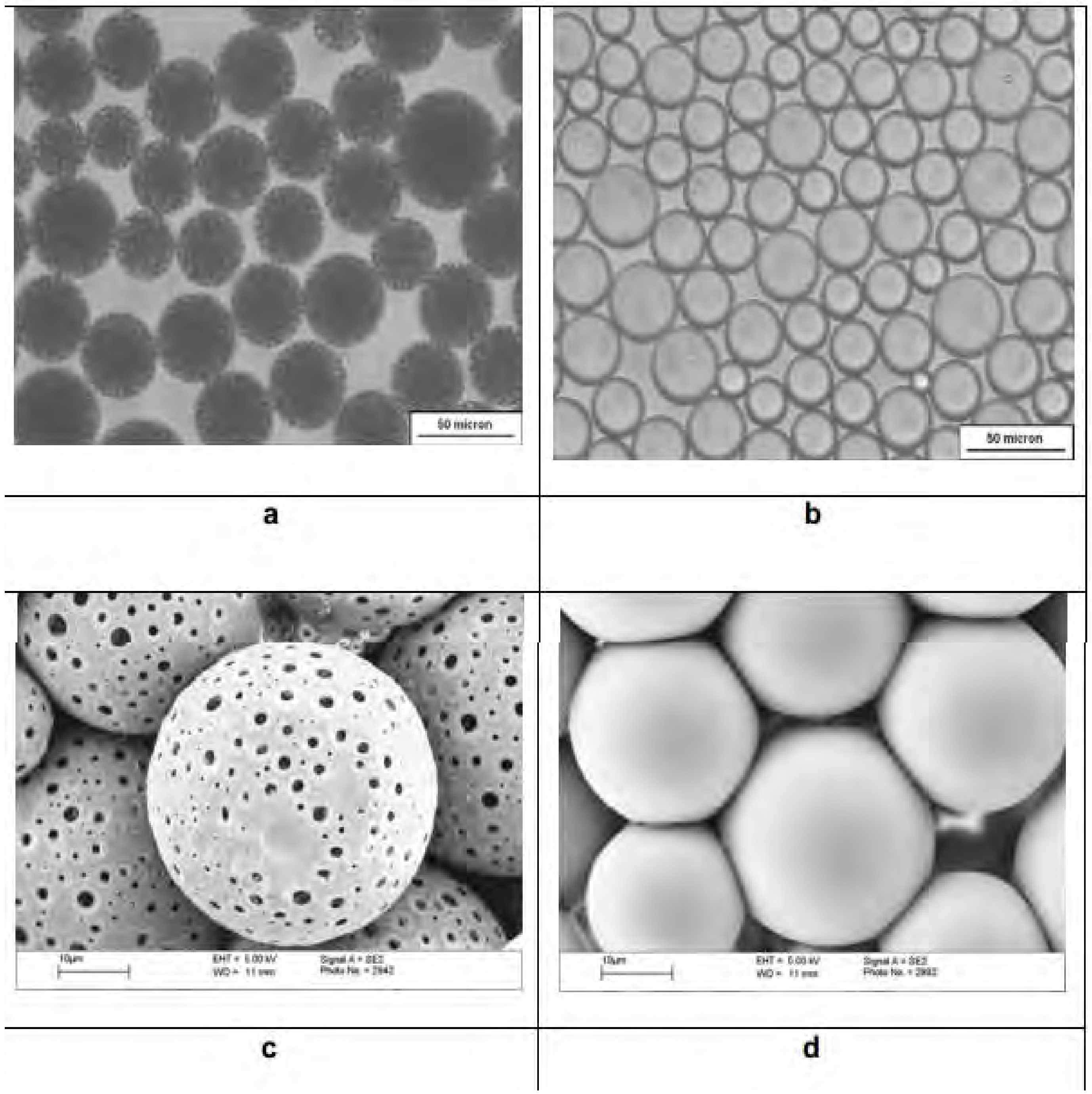
Commercially available
14 day kit
(~1g particles/ 70mg peptide)

~200£

Dragosavac 2012, Unpublished material

ENCAPSULATION OF WATER SOLUBLE PEPTIDE USING BIODEGRADABLE POLYMER

W/O/W EMULSIONS | O/W EMULSIONS



G. Gasparini et. al, 2010, Colloids and Surfaces B: Biointerfaces

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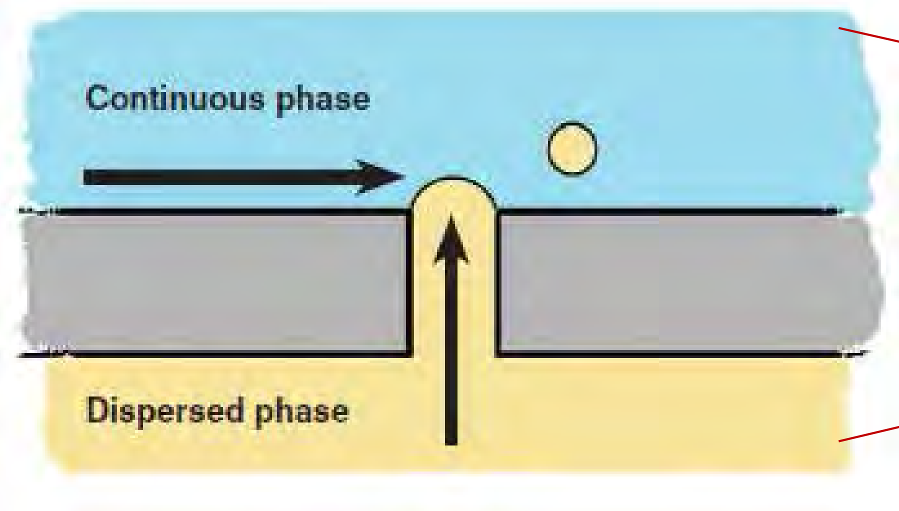
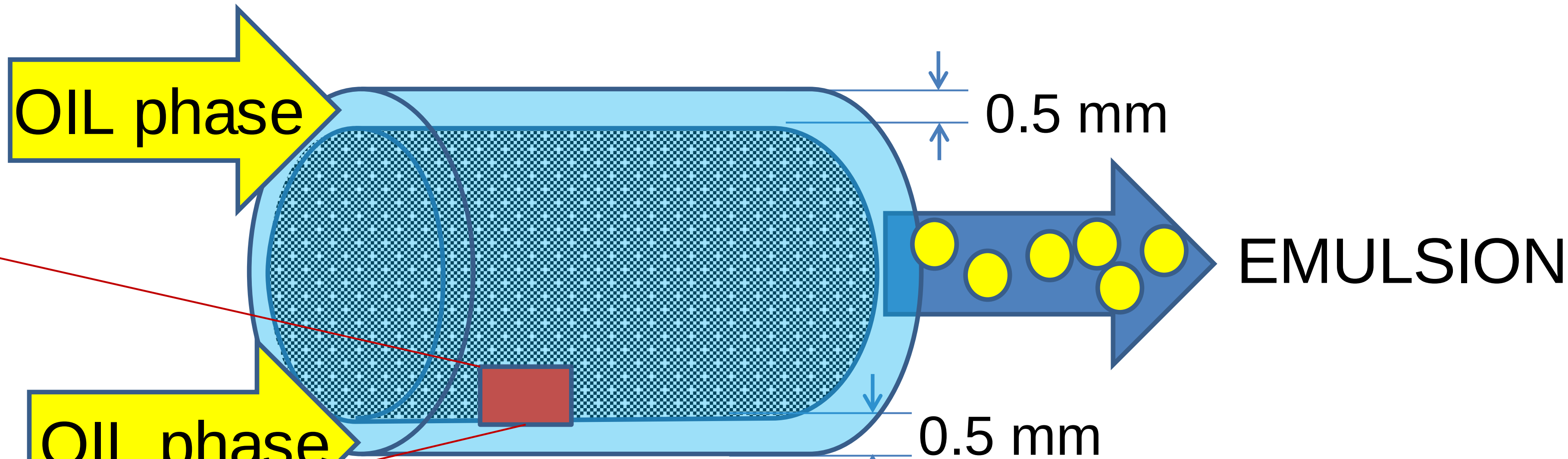
HIGH THROUGHPUT - SINGLE PASS SYSTEM

HIGH THROUGHPUT - SINGLE PASS SYSTEM





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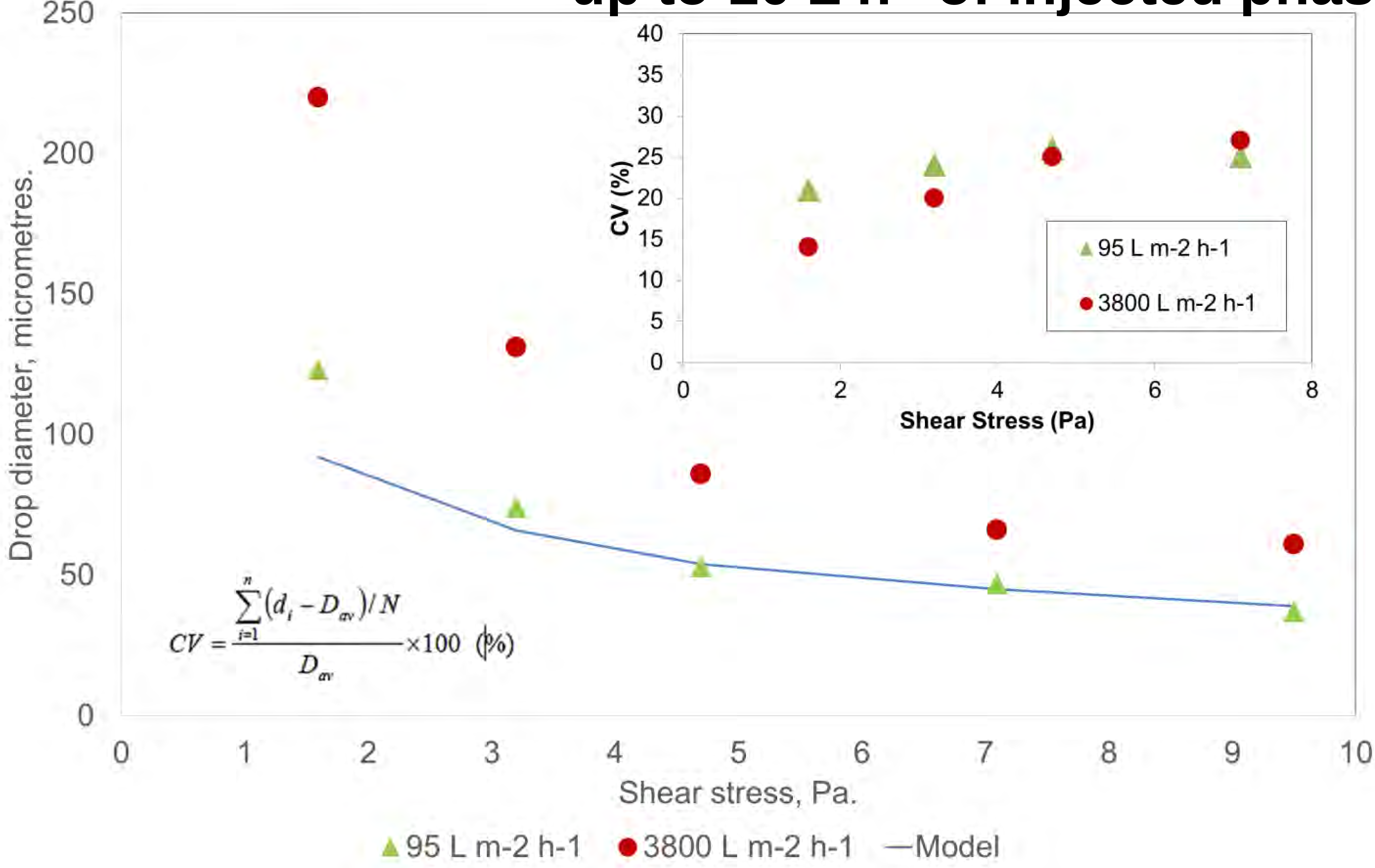
SINGLE PASS SYSTEM (9 mm insert)

Dispersed phase Sunflower oil; continuous phase 2% Tween 20

up to 10 L h^{-1} of injected phase

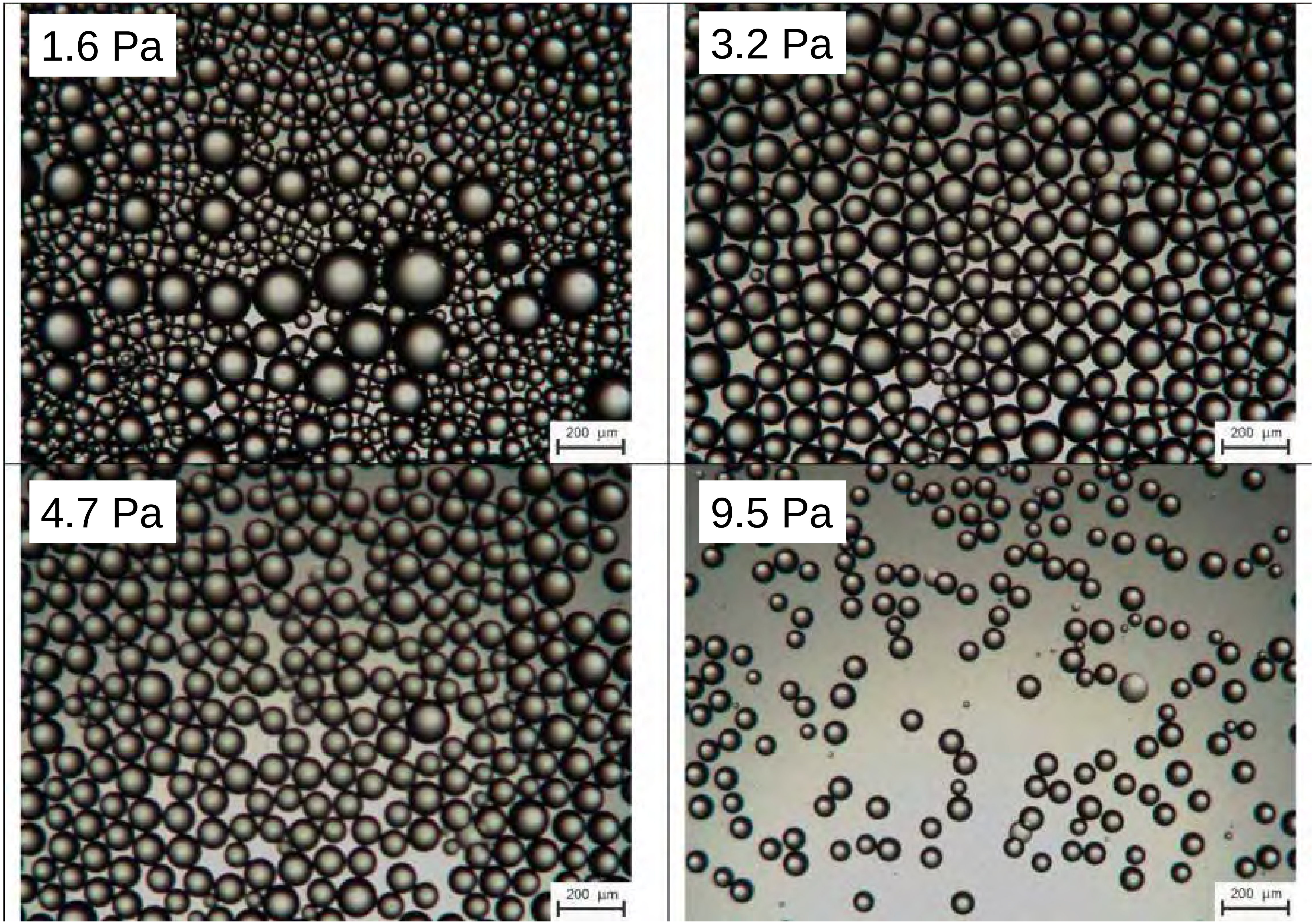


$$CV = \frac{\sum_{i=1}^{n}(d_i - D_{av})/N}{D_{av}} \times 100 \ (\%)$$

Drop diameter (solid markers) and CV (open markers) as a function of the shear stress

SINGLE PASS SYSTEM (9 mm insert)

Dispersed phase Sunflower oil; continuous phase 2% Tween 20

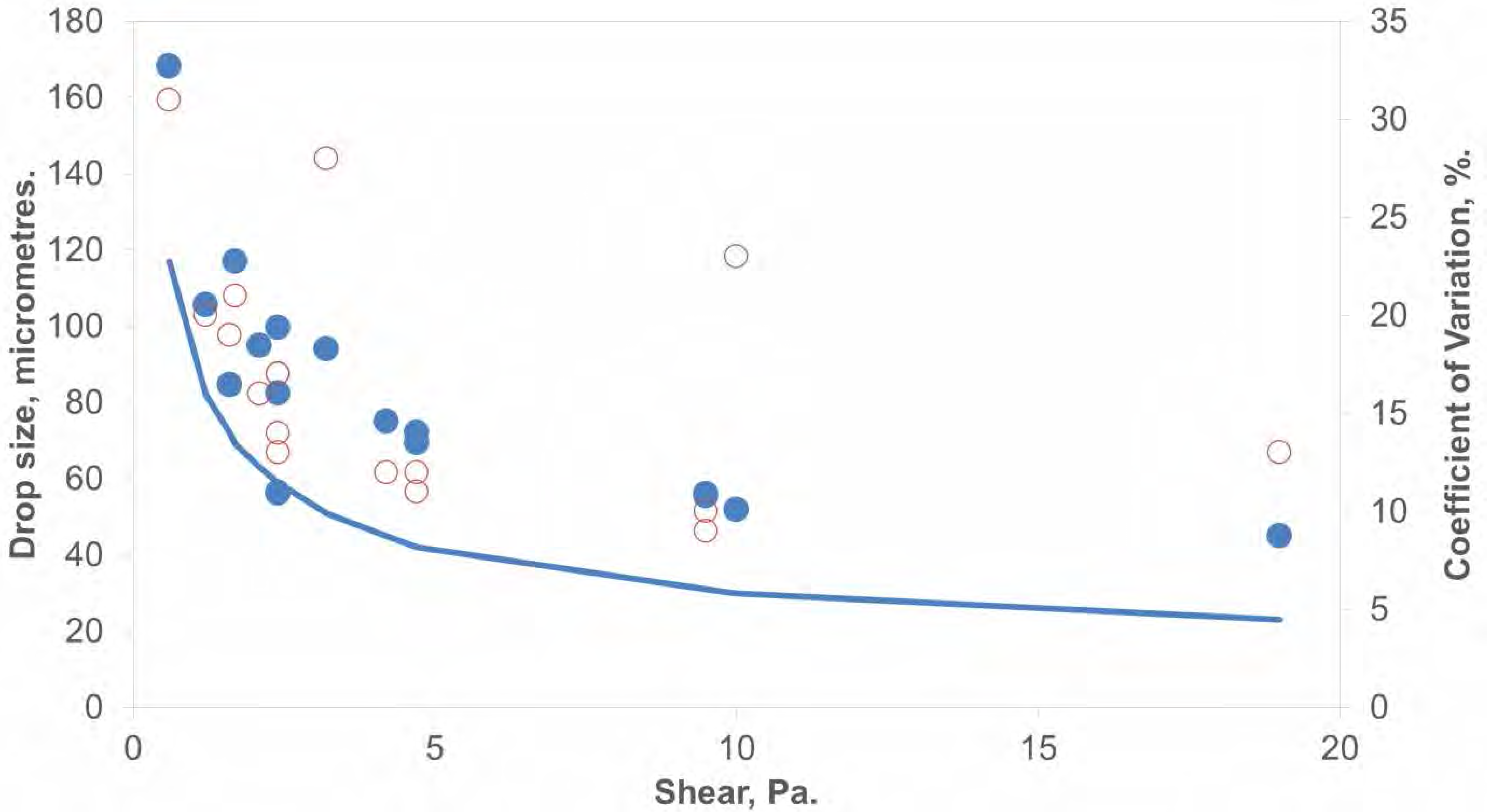


10 L h^{-1} of injected phase

SINGLE PASS SYSTEM (9 mm insert)

Dispersed phase 4% PCL in DCM; continuous phase 1% PVA

up to 10 L h^{-1} of injected phase



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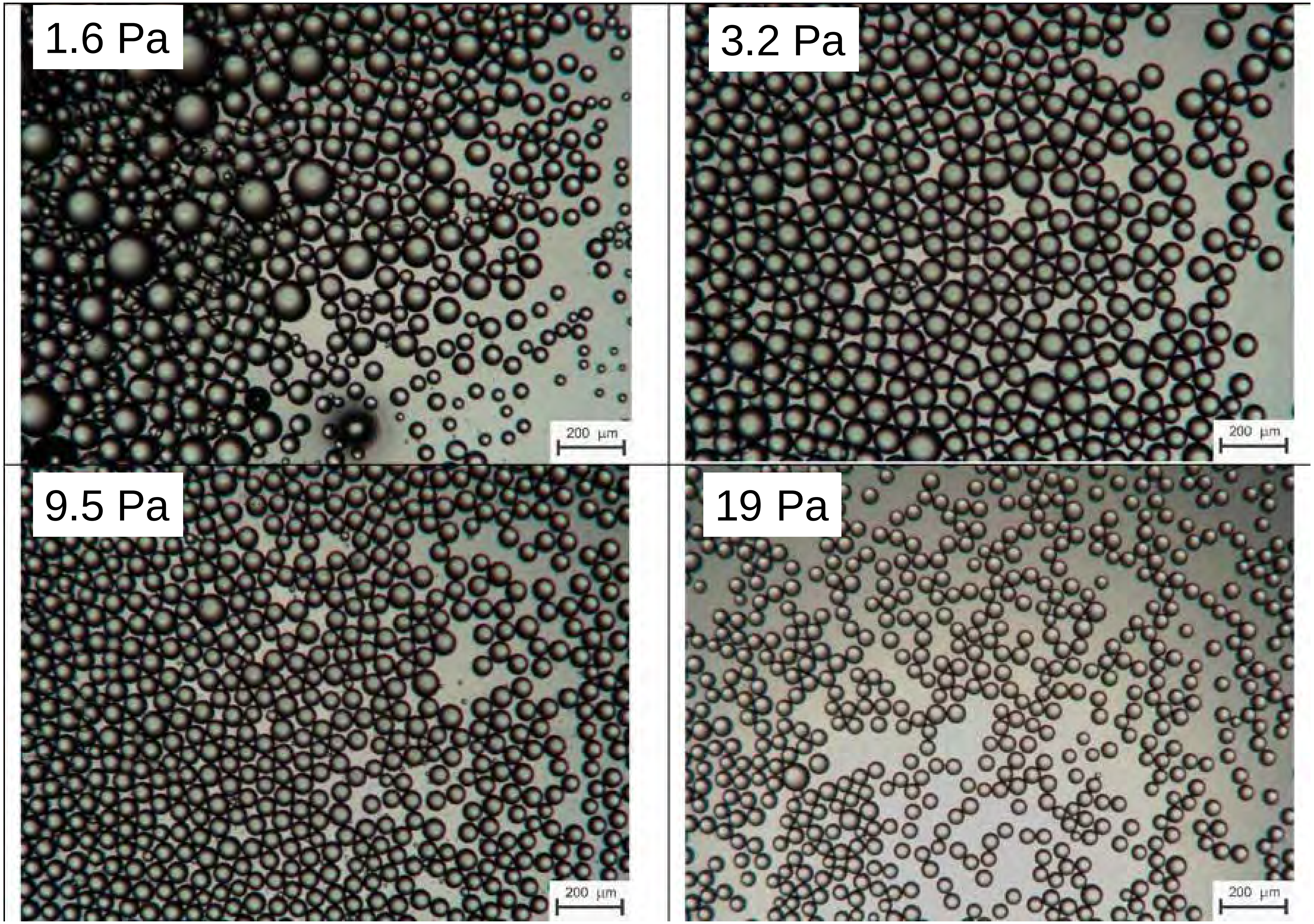

10 L h^{-1} of injected phase

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ENCAPSULATED YEAST CELLS
W/O emulsion

Aim to produce pH sensitive particles and exploit the pH to deliver the active ingredient (e.g. cells)

Morelli, Serena, R. G. Holdich, and Marijana M. Dragosavac. "Microparticles for cell encapsulation and colonic delivery produced by membrane emulsification." *Journal of Membrane Science* 524 (2017): 377-388.

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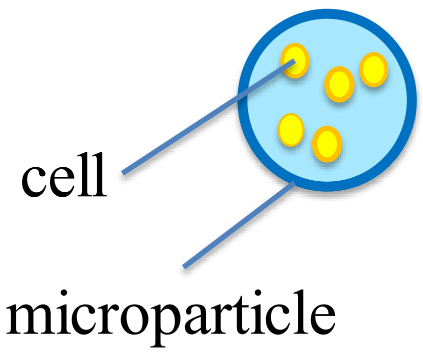
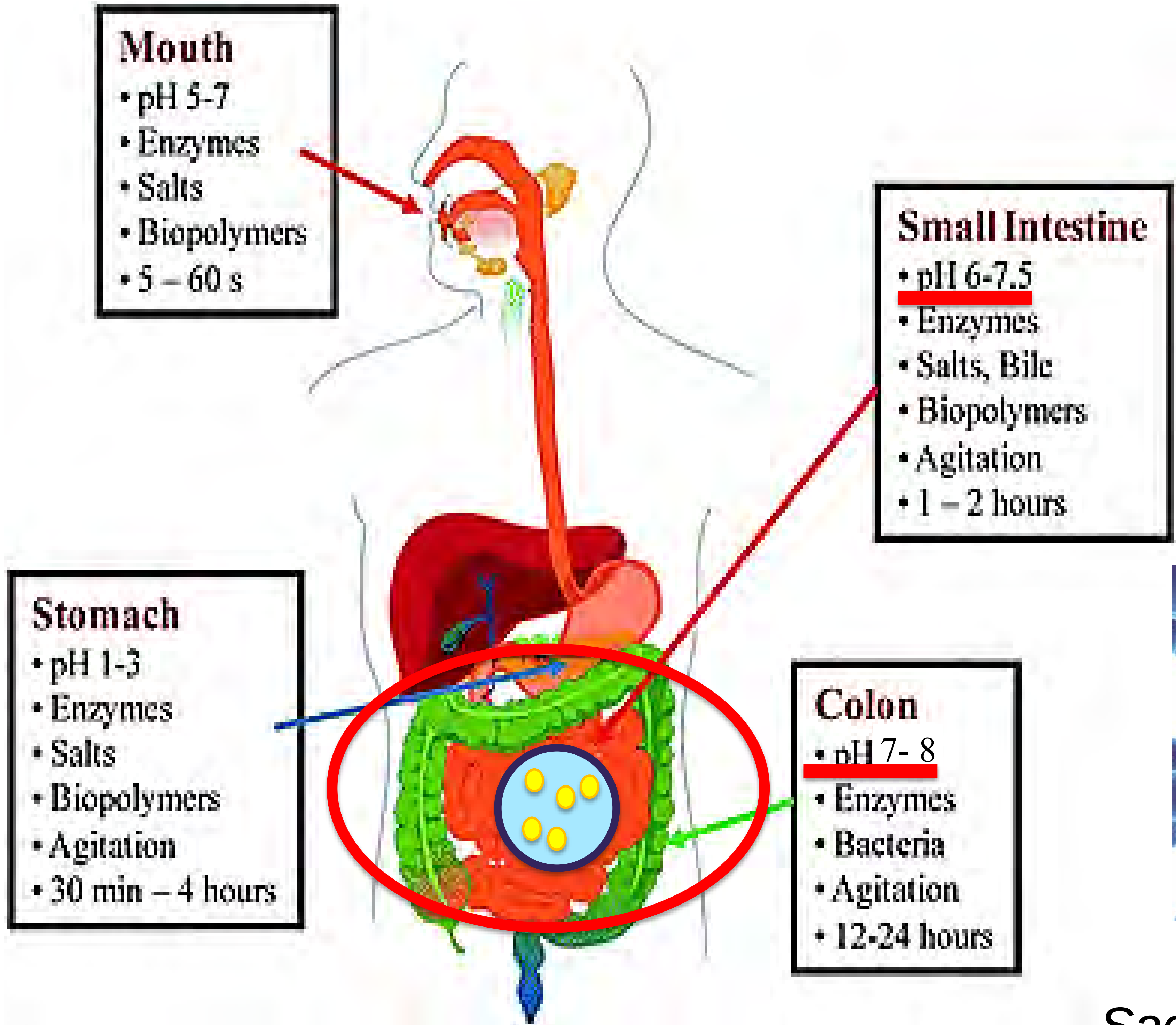
Intestine delivery of probiotic

- Release of probiotic into the small intestine- colon area, exploiting the pH 7- 8 existing

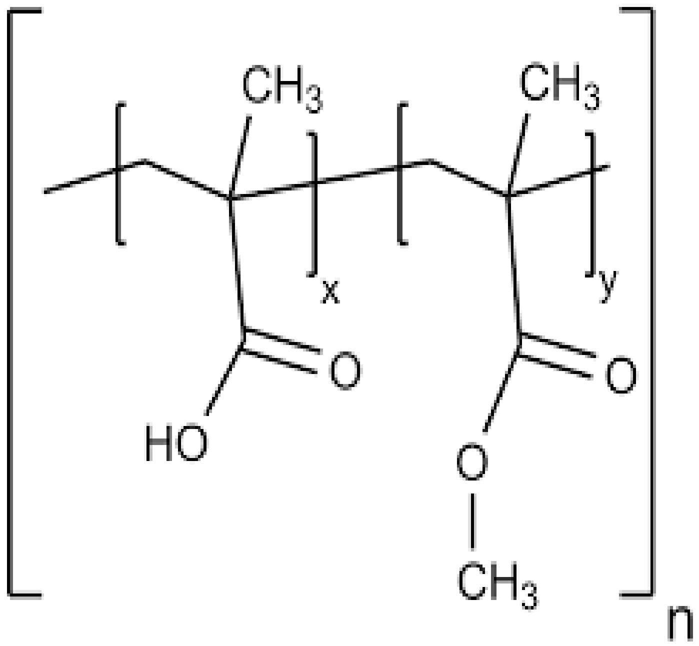




Yeast species *Saccharomyces boulardii* has shown probiotic activity

Eudragit S100 coating process

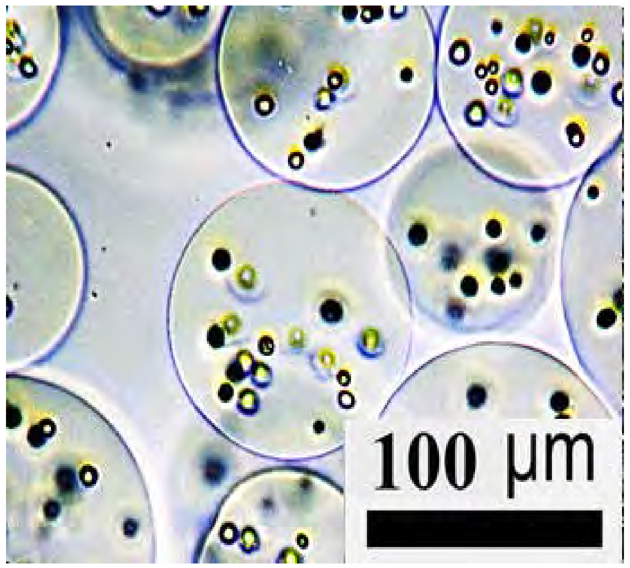
Oil in oil (o_1/ o_2) solvent evaporation method*:

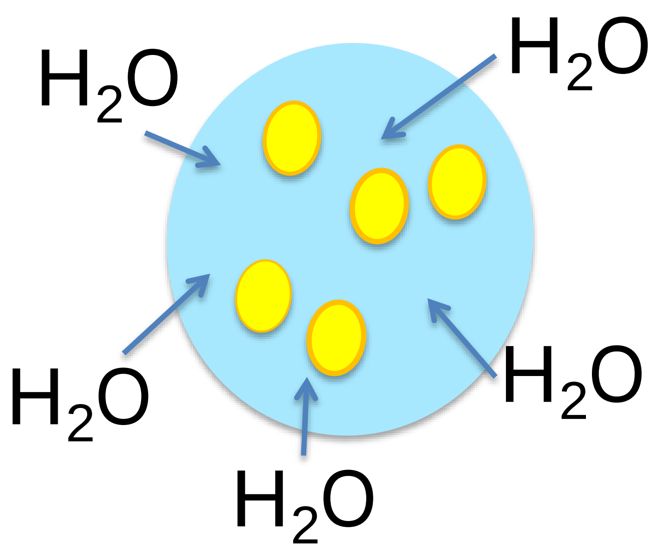


Eudragit S100 polymer

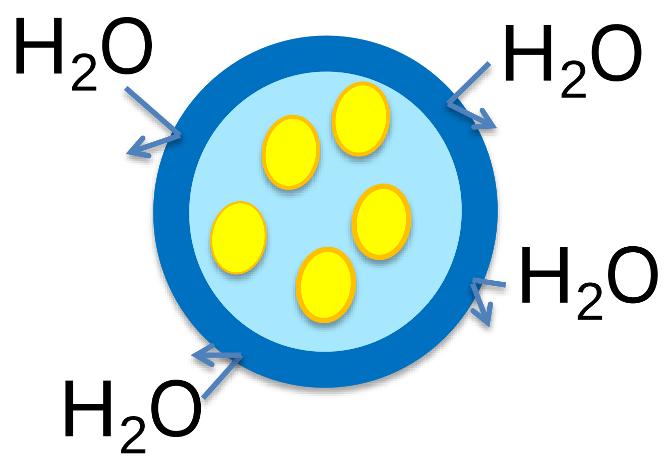
- Soluble at pH above 7
- Insoluble in water

Uncoated microparticles in water





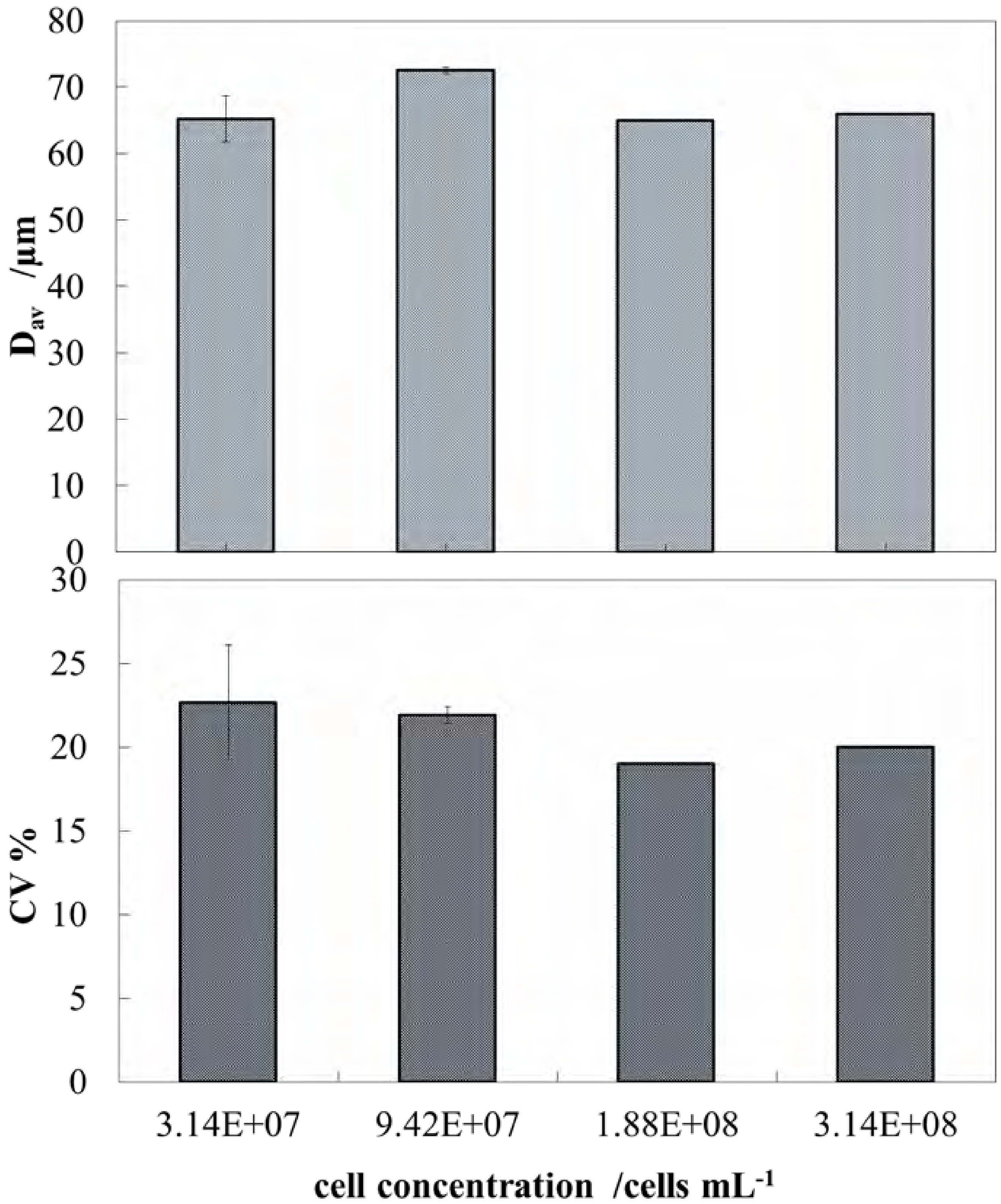
Coated microparticles in water

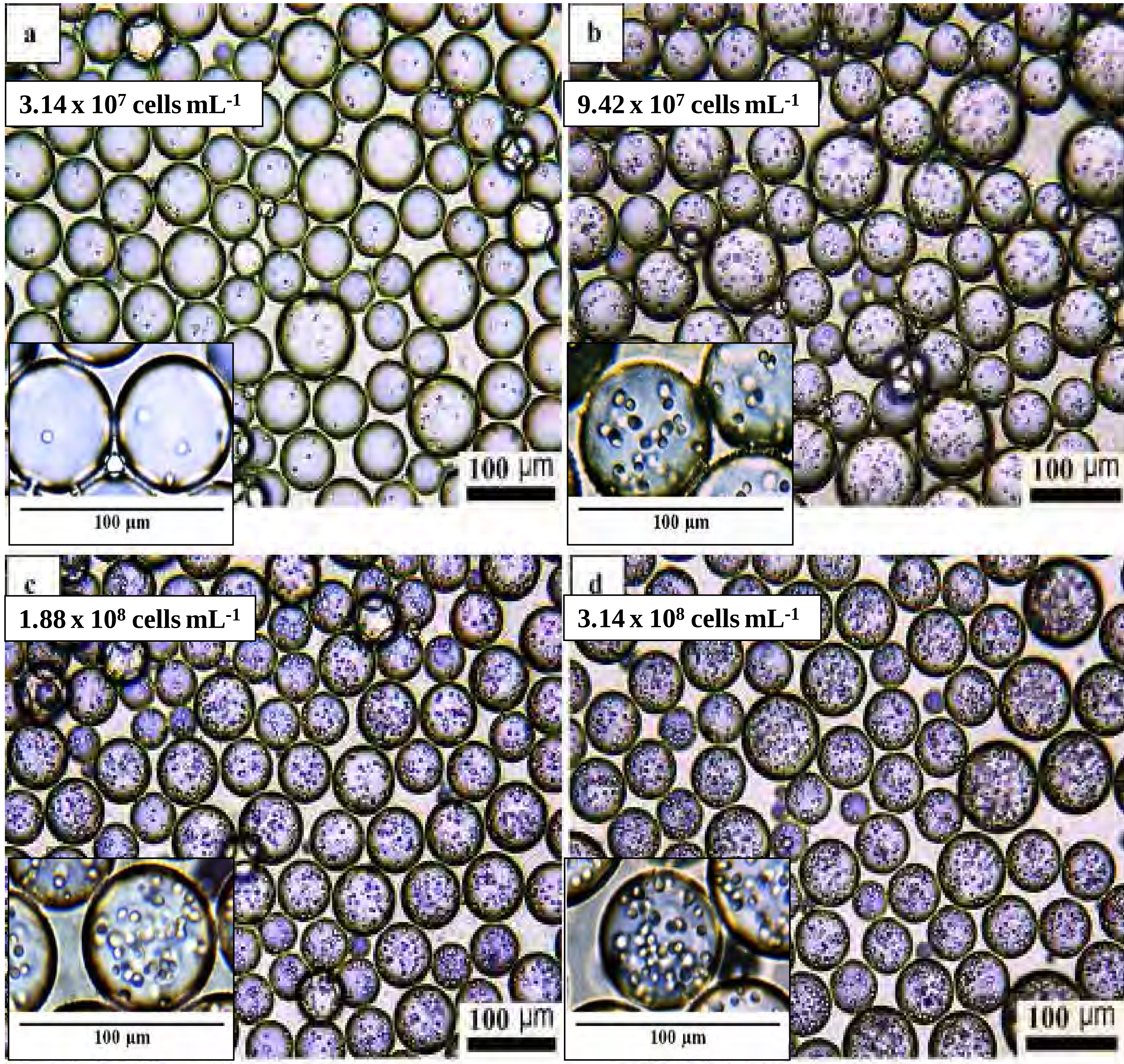


Coated microparticles resulted smaller in size than the uncoated ones - less able to swell

*Zhang, Lin, et al. "Eudragit® S100 coated calcium pectinate microspheres of curcumin for colon targeting." *Journal of microencapsulation* 28.7 (2011), 659-667.

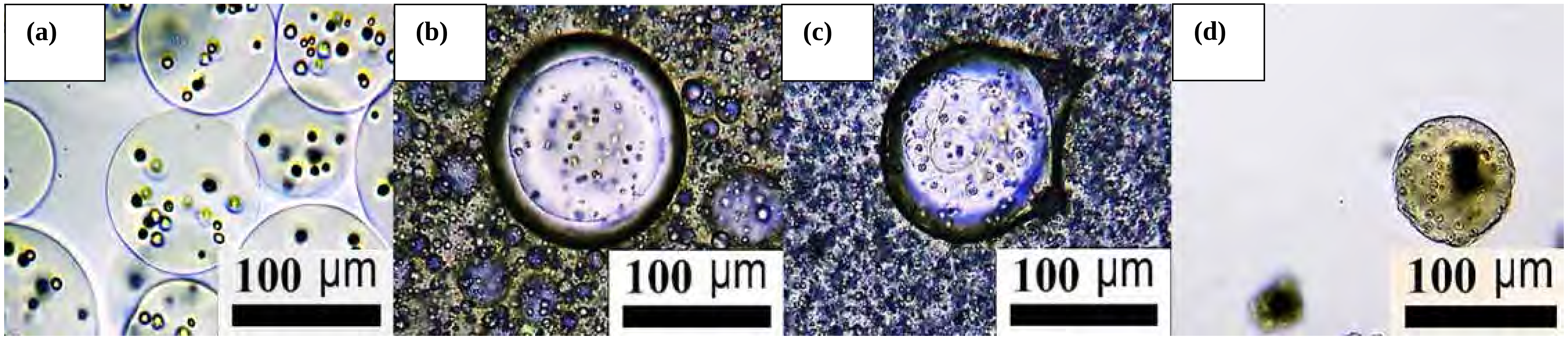
Influence of the cell concentration on emulsion characteristic





The amount of cell encapsulated does not affect the resulting droplet size and uniformity

Microparticles dissolution time and pH

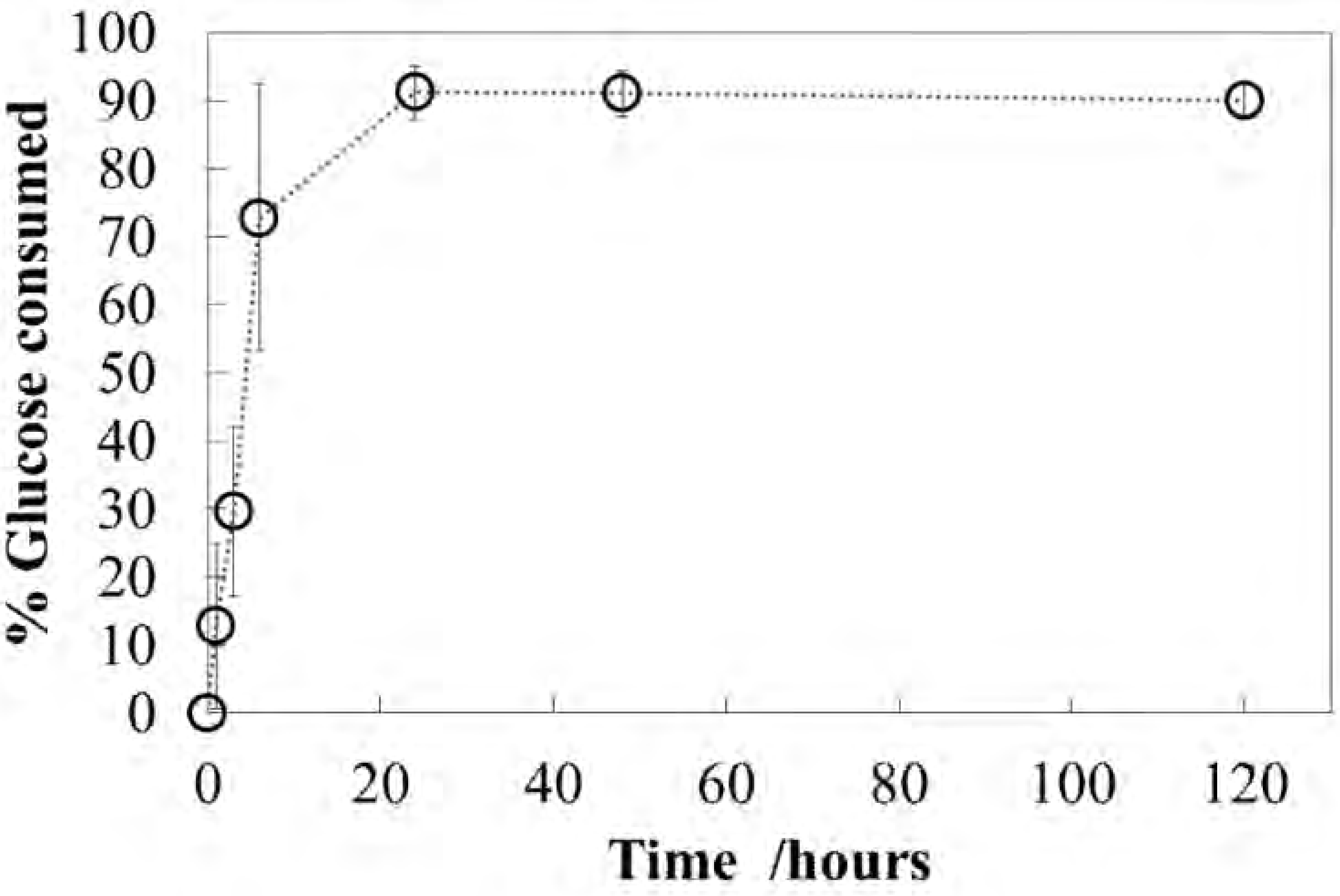


(a) Uncoated microparticle in water (b) O_1/O_2 emulsion during the coating process after 0 minutes and
(c) 4 hours, (d) microparticle re-suspended in water after washing in hexane and drying at room temperature.

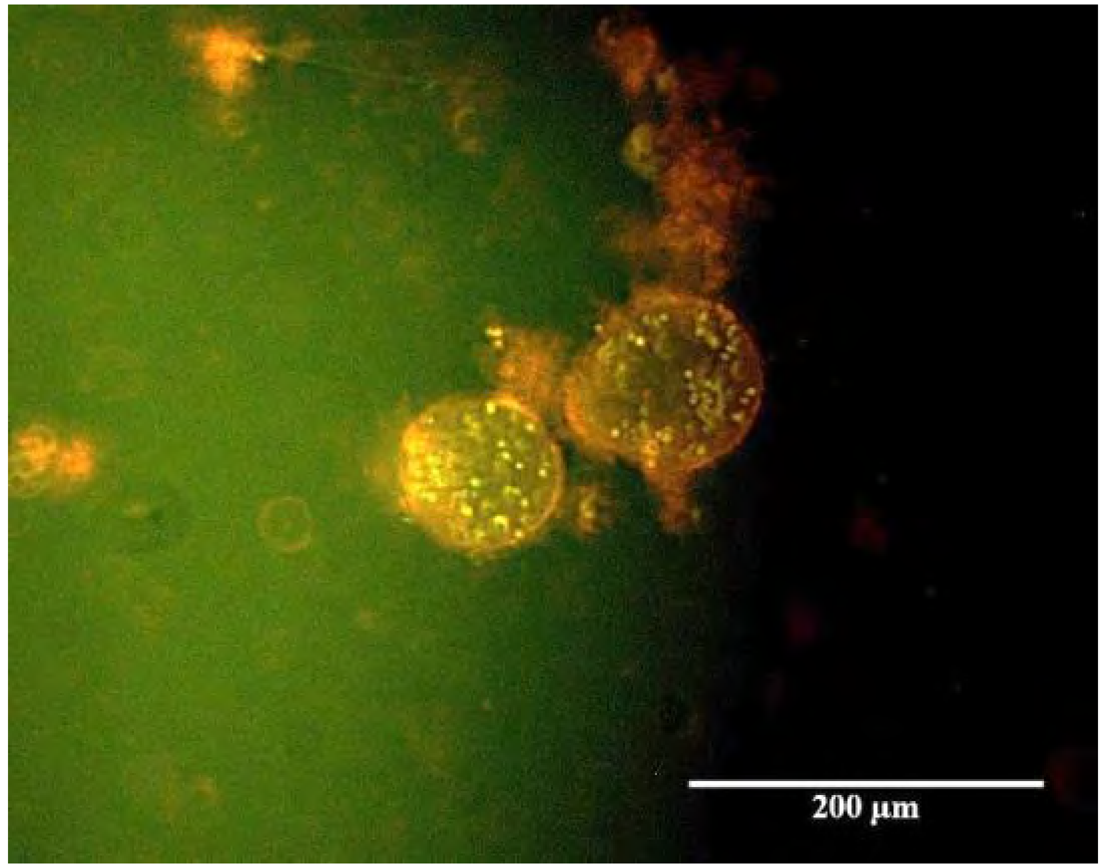
Eudragit coated particles survived the acidic environment and released the content at pH 7-8

Cell viability determination

Glucose consumption with time



Confocal analysis using fluorescent dyes

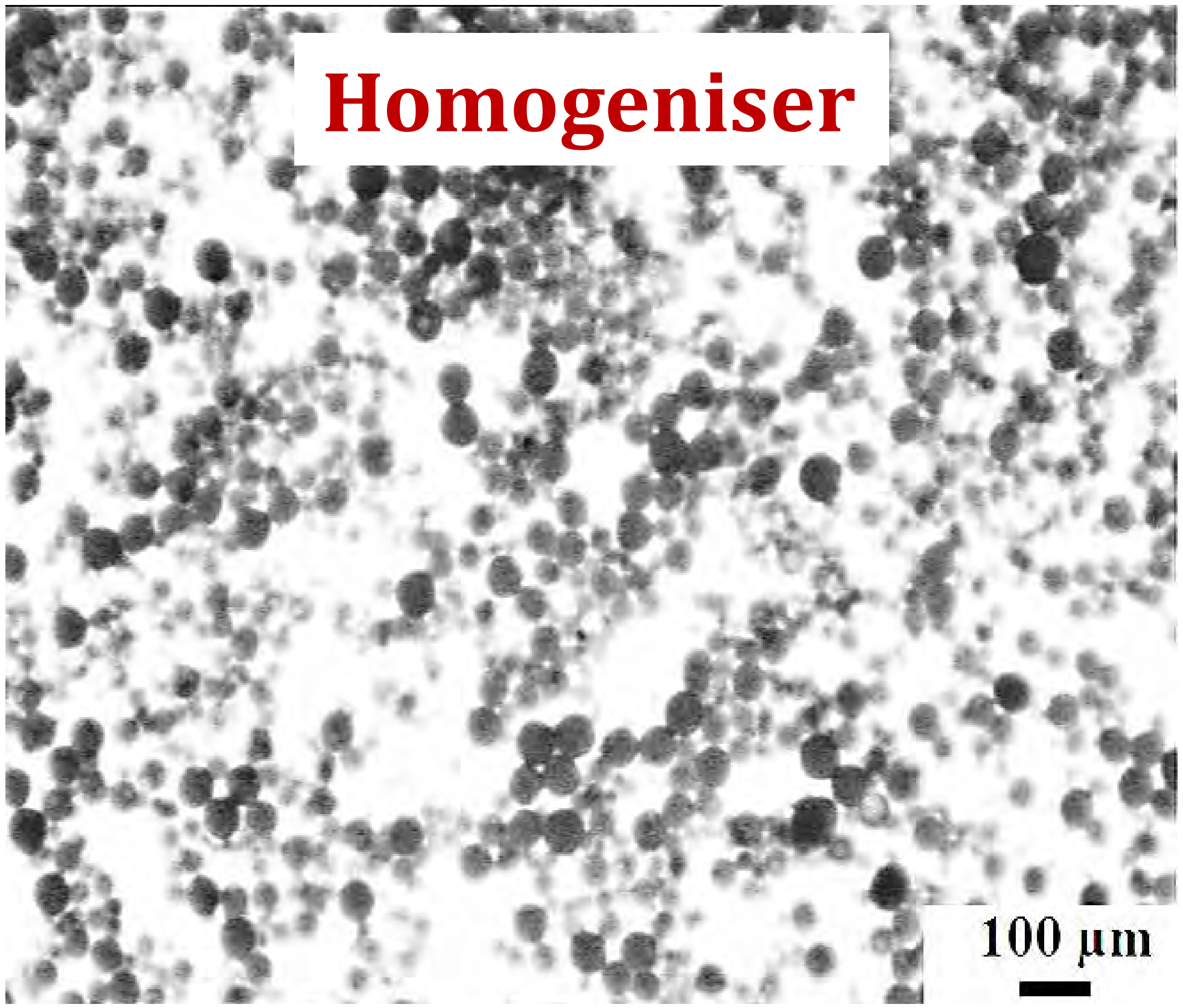


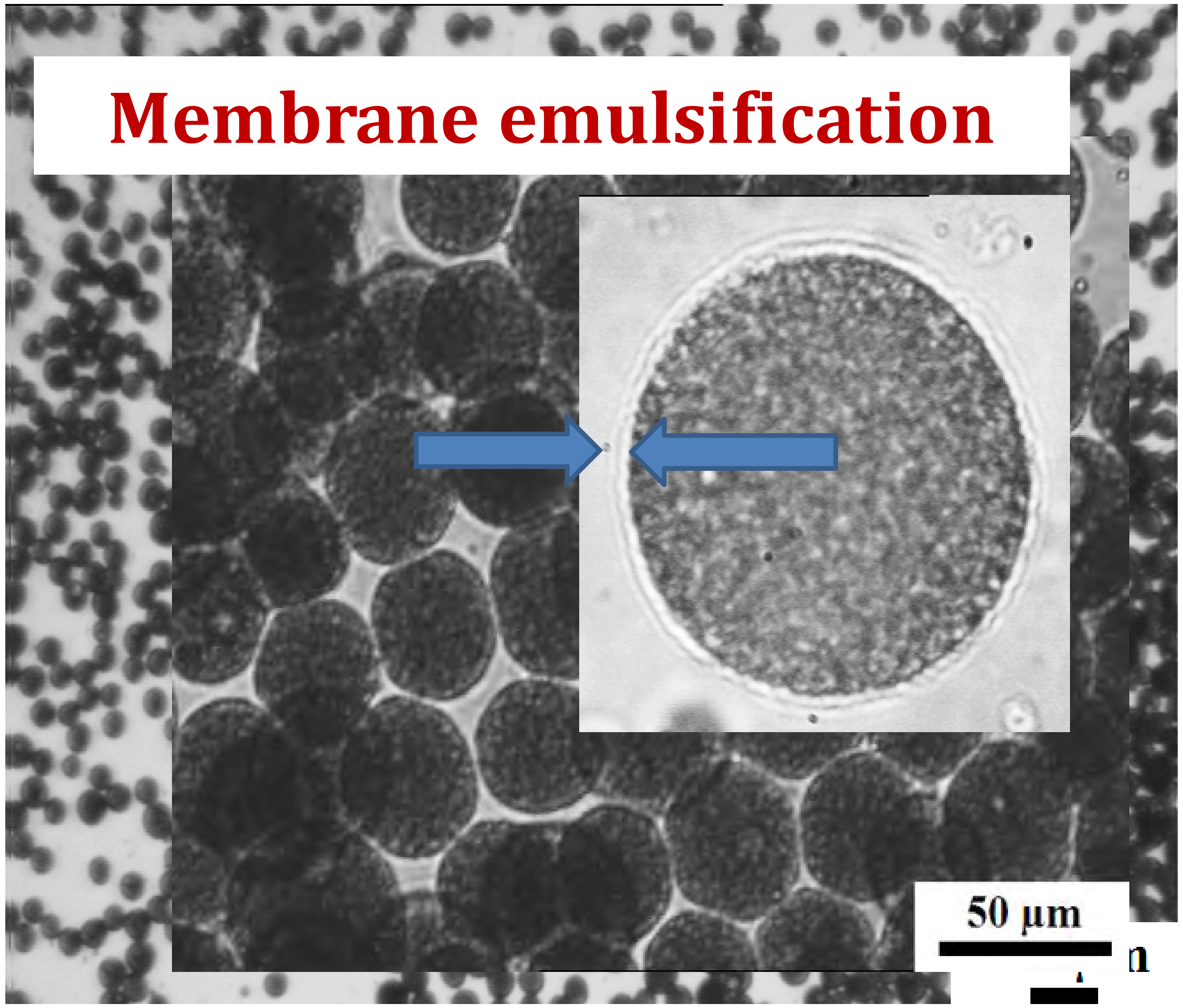
$$\%\ Glucose\ consumed = \frac{(Glu_i - Glu_n) * 100}{Glu_i}$$

The yeast released from the particles survived to the encapsulation process and stomach pH

CONCLUSION

- Metal membranes and single pass system provide high throughput up to 10 L h^{-1}
- Process can be scaled up
- Uniform particles 10 – 250 µm





• Conventional formulation needs to be adjusted to work

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Emma Piaccentini, CNR Italy,
Alessandra Imbrognio, CNR Italy
Miguel Angel Suarez Valdes, UNIDAV, Spain

Students:
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Serena Morelli,
Seyitan Odunola, Ryan Barnfield,
Alix Barton,

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