WHITE PAPER microfluidics

Microfluidics documentation:

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PLUG & PLAY MICROFLUIDICS

Elveflow is a brand of the Elvesys microfluidics innovation center.

Droplet based microfluidics

Droplet-based microfluidics is an emerging technology based on hydrodynamics principles: fluids are handled in a precise and reliable manner providing essential tools to miniaturize and automatize assays.

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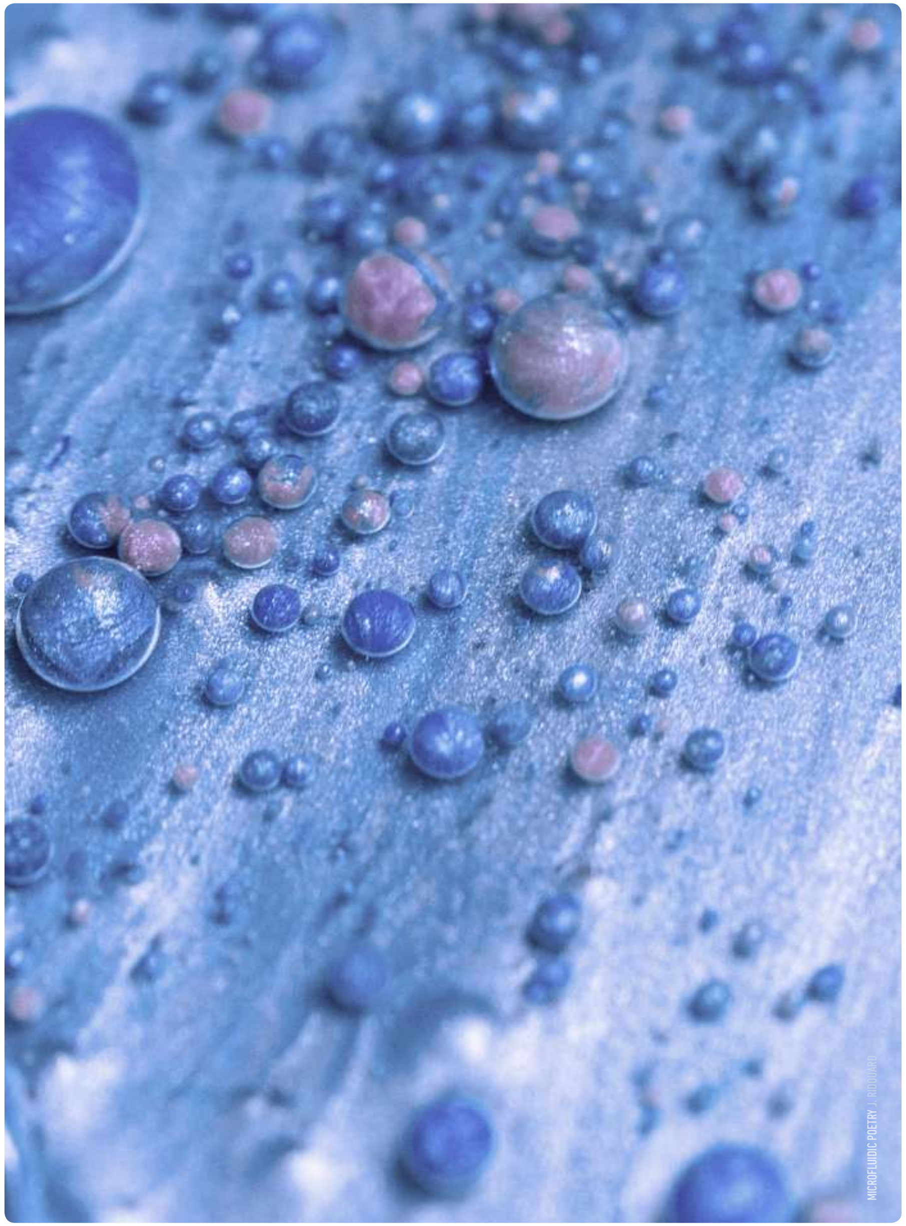
INTRODUCTION TO DROPLET BASED MICROFLUIDICS

Droplet-based microfluidics is an emerging technology based on hydrodynamics principles: fluids are handled in a precise and reliable manner providing essential tools to miniaturize and automatize assays[1].

“Droplet microfluidics” enables the manipulation of discrete fluid packets in the form of microdroplets that provide numerous benefits for conducting biological, chemical assays or particles synthesis. Among those benefits are a large reduction in the volume of reagent required for assays, the size of sample required, and the size of the equipment itself. Such technology also enhances the speed of biological and chemical assays by reducing the volumes over which processes such as heating, diffusion, and convective mixing occur. Once the droplets are generated, carefully designed droplet operations allow for the multiplexing of a large number of droplets to enable large-scale complex biological and chemical assays[2].

Droplets formed within microfluidic channels often serve as microreactors containing different chemical or biological compound, allowing massive numbers of independent reactions to be performed rapidly using a minimal amount of total reagent.

[1] [Joanicot and Ajdari, 2005] Joanicot, M. and Ajdari, A. (2005). Droplet Control for Microfluidics. Science, 309(5736):887–888.
[2] Microfluidic Droplet Manipulations and Their Applications ,Melinda G. Simon and Abraham P. Lee

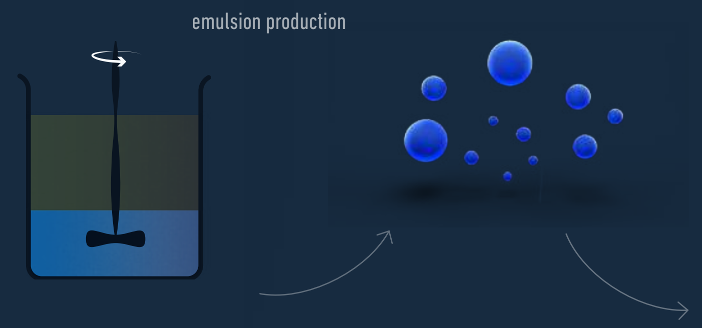


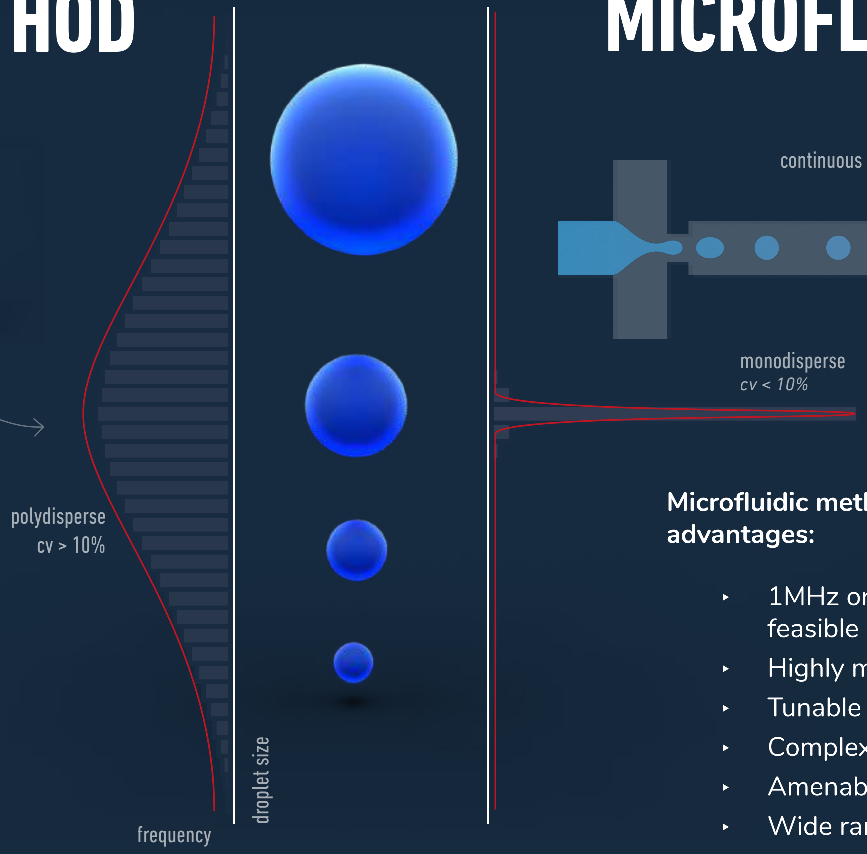
MICROFLUIDICS AND DROPLETS

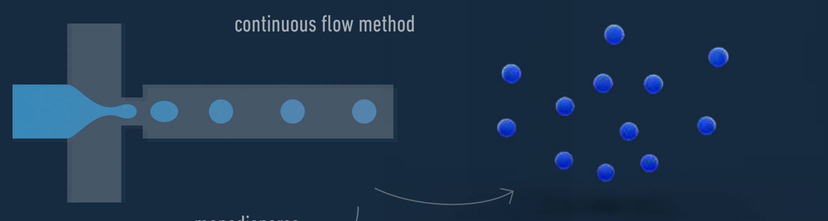
Why use microfluidics?

BATCH METHOD

MICROFLUIDICS







Traditionally, particles, nanoparticles and emulsions are formed by batch method: eg. using high shear methods such as sonication or homogenizers

These methods can produce large amounts of material, and can be quite simple to use. However, particles are (very) polydisperse, so filtering etc is often needed. High shear stress can also cause problems, eg. with encapsulated payload

Microfluidic methods offer a number of significant advantages:

- 1MHz or 10kg/day of droplets/ particles is feasible by a very compact system
- Highly monodisperse (typically 1 to 5%)
- Tunable to any particle size below 1mm
- Complex particles can also be produced
- Amenable to real time Quality Control
- Wide range of particle formation methods
- Consistent and reproducible

1. DROPLETS OVERVIEW

DROPLETS OVERVIEW

What are droplets?

The general terms “droplet” and “emulsion” are used as follows:

DROPLET

A droplet is a spherical volume of liquid or gel suspended in an immiscible fluid

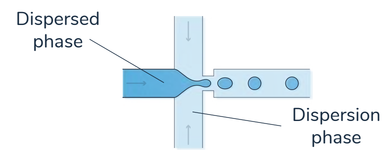
EMULSION

An emulsion is a fine dispersion of minute droplets in an immiscible fluid

When talking about droplets and emulsions, we use the following terms:

The dispersed phase is the phase constituting the droplets

The continuous phase (or dispersion phase) is the phase carrying the droplets

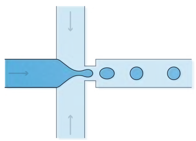


DROPLETS OVERVIEW

Droplet and particle types

One way to categorize the universe of droplets and particles is to consider:

- What are the droplets made from and how are they suspended?
- We can look at Solid, Liquid and Gas for each option
- This leads to a 3 x 3 matrix of possible droplet types: this whitepaper focuses on systems with a liquid dispersed phase



		DISPERSED PHASE		
		Gaz	Liquid	Solid
DISPERSION PHASE	Gaz	None all gases are miscible	**Liquid aerosol** eg. fog, sprays	**Solid aerosol** eg. smoke, ice cloud
	Liquid	**Foam** eg. whipped cream	**Emulsion** eg. milk, hand cream	**Sol** eg. pigmented ink, blood
	Solid	**Solid foam** eg. aerogels, pumice	**Gel** eg. agar, gelatine, jelly	**Solid sol** eg. cranberry glass

What is the purpose of the droplet?

- Option 1: Droplet and continuous phase are what matters
- Option 2: Identical droplets are what matters
- Option 3: Each droplet is a carrier for a unique entity

DROPLETS OVERVIEW

Types of liquid in liquid droplets

Type 1: Emulsions; both the particles and the continuous phase jointly form the product of interest (eg. foams, creams)

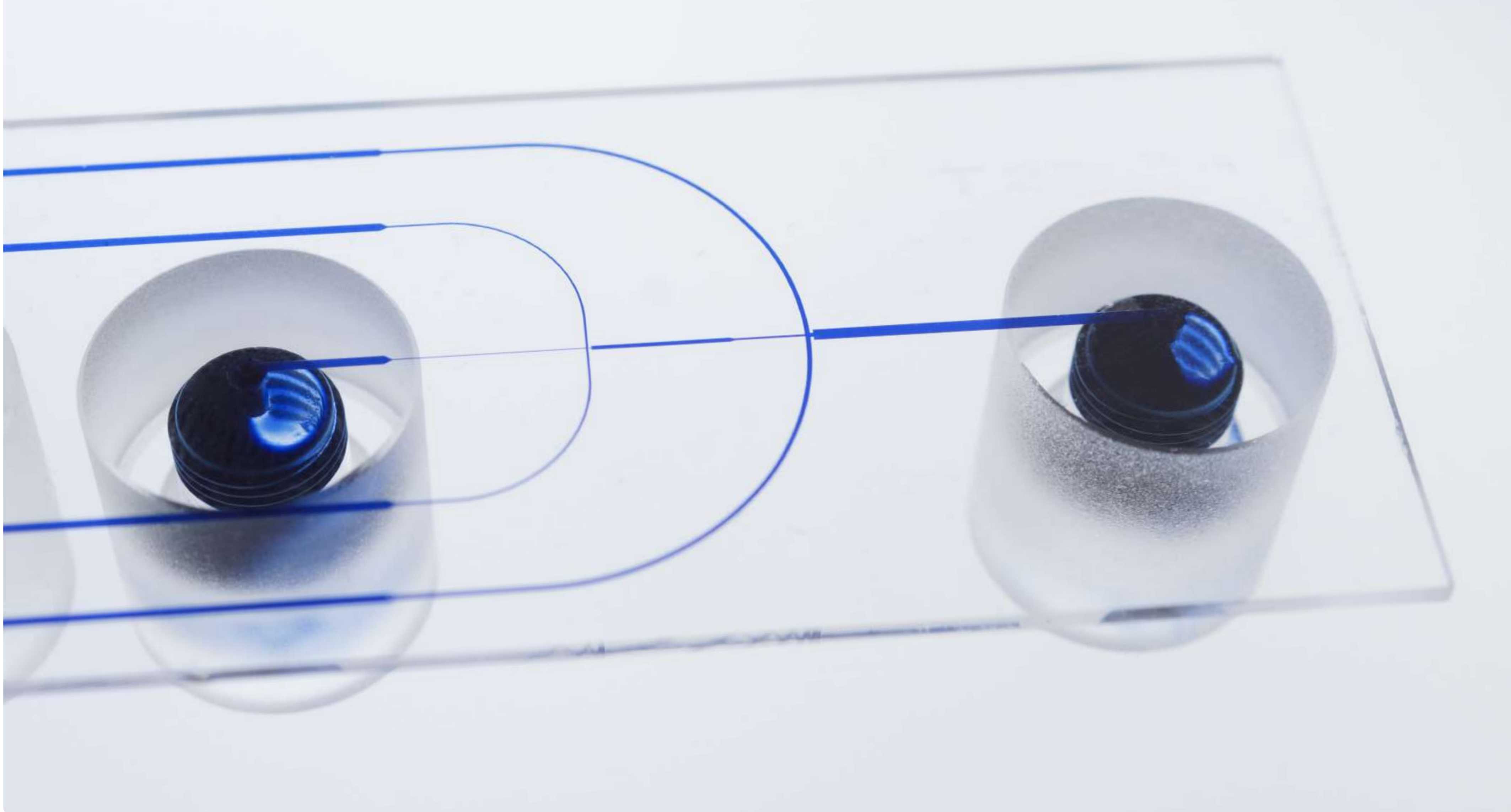
Type 2: Droplets; Only the droplet is of interest, and the continuous phase fluid is of secondary interest as a carrier for the droplets

- **Type 2A: Simple droplets** where the droplet is composed of a single fluid, such an alginate gel or a polymer particle.
- **Type 2B: Complex droplets**, where the droplet is formed from two or more fluids, such as core/shell particles or Janus Particles.

Type 3: Encapsulations; the contents of the droplet are the key factor

- **Type 3A: Homogeneous payload droplets**, where each droplet carries the same payload in the same quantity (eg. drug delivery particles).
- **Type 3B: Heterogeneous payload droplets**, where each droplet contains a unique payload (eg. cell suspensions for analysis)

2. A BIT OF THEORY



A BIT OF THEORY

Key formulas

Re is the Reynold number
ρ is the density of the fluid (SI units: kg/m^3)
u is the velocity of the fluid with respect to the object (m/s)
L is a characteristic linear dimension (m)
μ is the dynamic viscosity of the fluid (Pa·s or $N·s/m^2$ or kg/m·s)
ν is the kinematic viscosity of the fluid (m^2/s).

γ Surface tension (N/m)
F is the force required to stop the side from starting to slide (N)
L is a characteristic linear dimension (m)

Ca Capillary number
V is a characteristic velocity

$$\mathrm{Re} = \frac{\rho u L}{\mu} = \frac{uL}{\nu}$$

Reynolds number
The Reynolds number, Re is an important dimensionless number in fluid mechanics used for the prediction of flow patterns by correlating the inertia forces to the viscous forces. It allows identifying the laminar or turbulent flow regime. Droplets can only be obtained in laminar mode Re<2300

$$\gamma = \frac{1}{2}\frac{F}{L}$$

Surface tension
Elastic tendency of a fluid surface which makes it acquire the least surface area possible
High surface tension results in droplets

$$\mathrm{Ca} = \frac{\mu V}{\gamma}$$

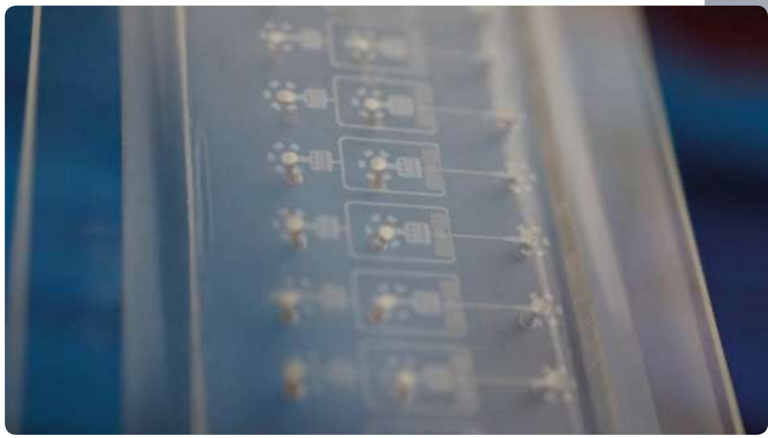
Capillary number
Relative effect of viscous drag forces versus surface tension forces acting across an interface between two immiscible liquids

The generation of droplets is a complex dynamical process depending on shear stress tending to draw the fluids along the channel and surface forces acting towards the droplet formation to minimize the surface tension. For further theory and an introduction to drop formation regime map: [Utada et al., 2007] Utada, A. S., Fernandez-Nieves, A., Stone, H. A., and Weitz, D. A. (2007). Dripping to jetting transitions in coflowing liquid streams. Physical Review Letters, 99(9):1–4.

A BIT OF THEORY

What do you need to make droplets in microfluidics?

- Immiscible fluids
- A chip with micro-size features
- Surfactants
- Flow control system



A BIT OF THEORY

Immiscible fluids

Immiscible fluids

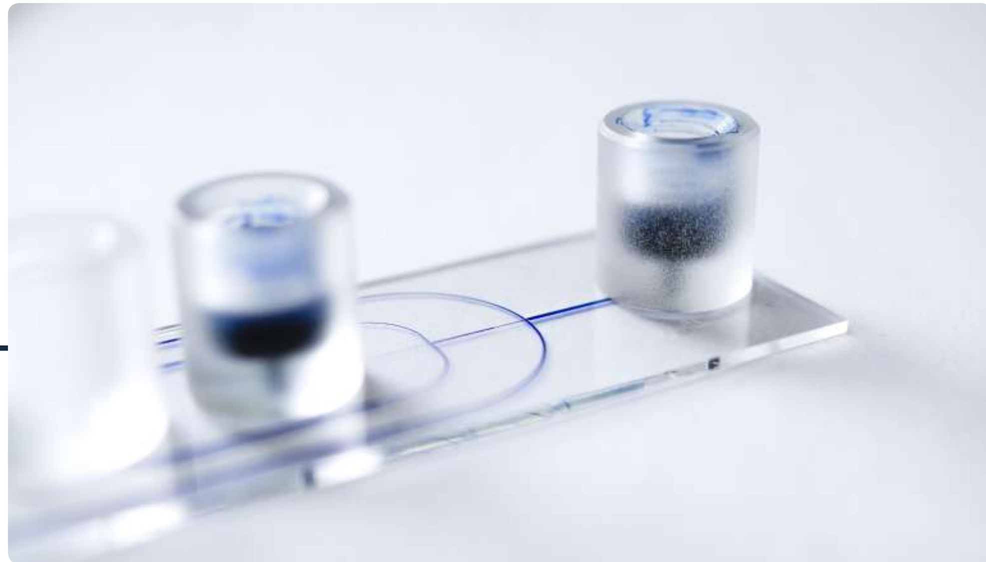
- By definition, droplets can only be formed by one fluid in suspension in another one
- Those conditions only appear when the fluids are immiscible

Most common droplets in microfluidics: water-in-oil or oil-in-water

- Oil: FC40, HFE-7500 (Novec) made by 3M

A BIT OF THEORY

Chip



Chip channel size

- Need micro-size features for maintaining laminar flow and high surface tension
- Will determine the size of the droplets

Chip material

- Glass, quartz, polymer (PDMS, COC...)
- Determines nature of walls: hydrophobic or hydrophilic
  - Water iDroplet type Water in Oil: needs hydrophobic walls to get high surface tension for water
  - Oil in water: needs hydrophilic walls to get high surface tension for oil

Chip geometry

- Determines the application
- Coflow for mixed droplets, double junction for double emulsions, etc...

A BIT OF THEORY

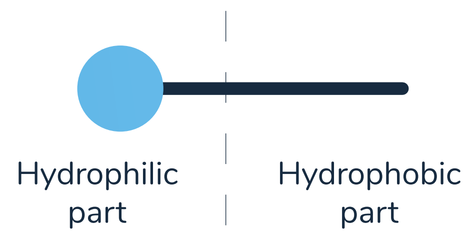
Surfactants

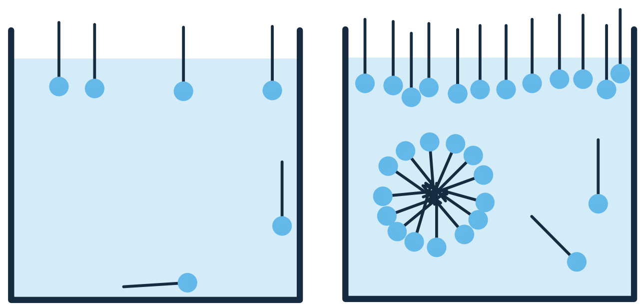
Surfactants are chemicals that are added to either the continuous or the dispersed phase

- They have a hydrophobic head and a hydrophile tail
- Common surfactants: SPAN80, SDS

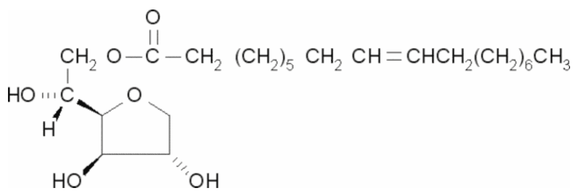
They decrease a fluid's surface tension

- A little surfactant assists droplet formation and stability (2%, 5%...)
- Too much prevents the droplet formation

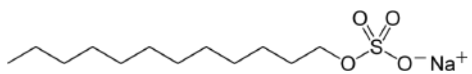




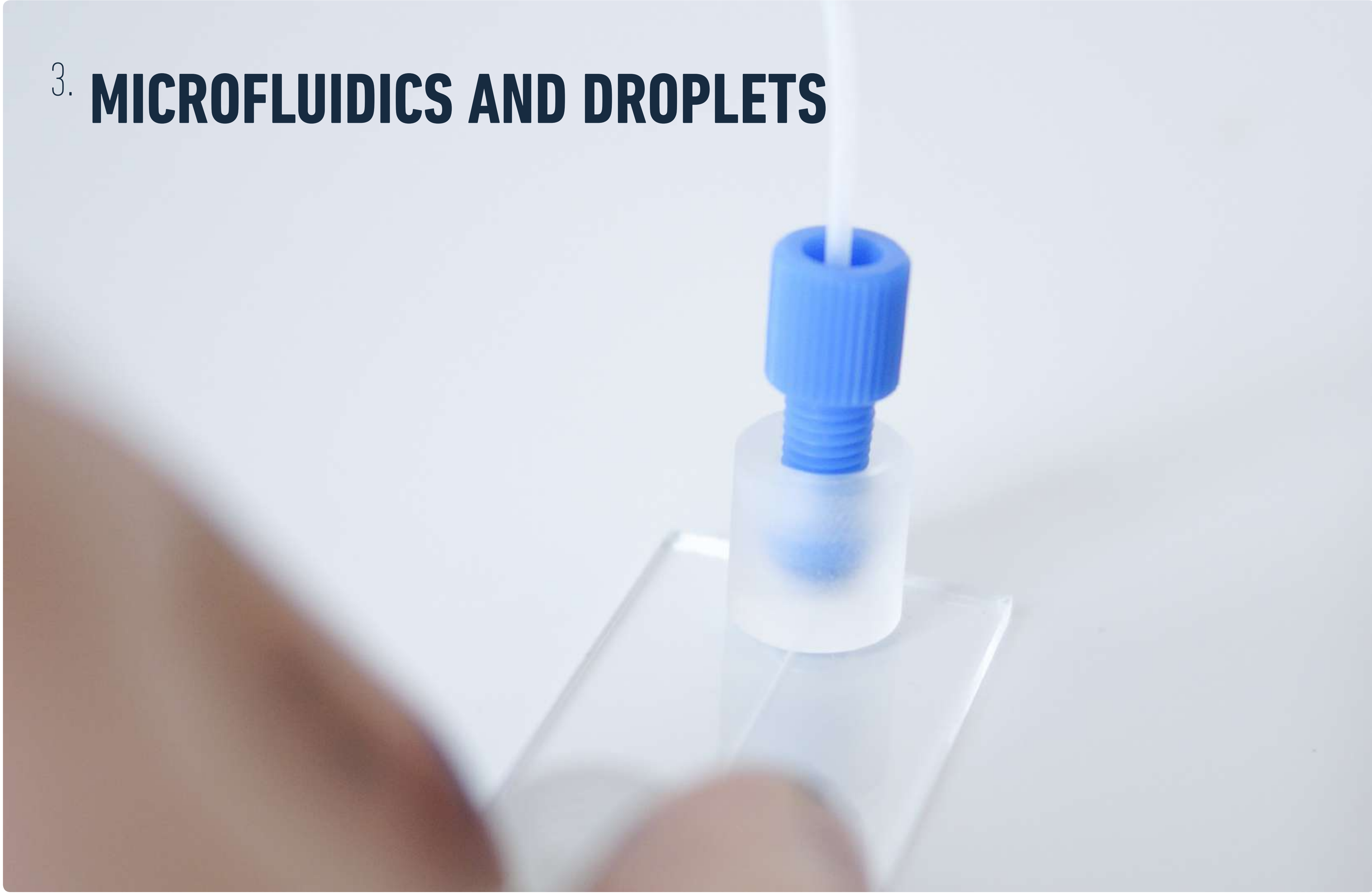
SPAN80



SDS



3. MICROFLUIDICS AND DROPLETS



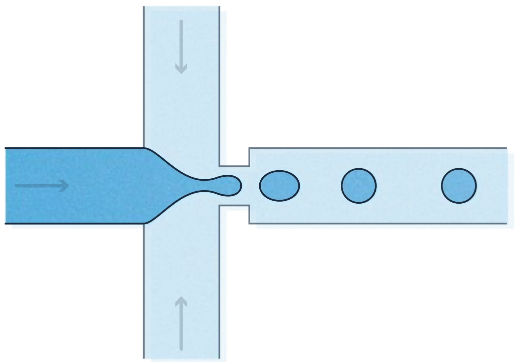
MICROFLUIDICS AND DROPLETS

Methods

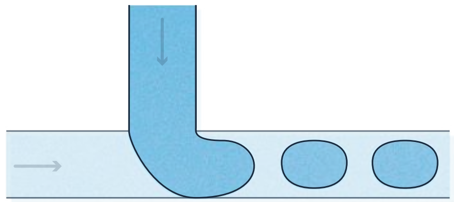
There are three methods commonly used for forming droplets and particles using microfluidics

In order of importance (papers, number of users):

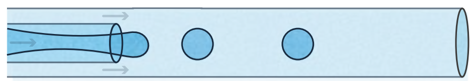
Flow focusing junctions



T-junctions

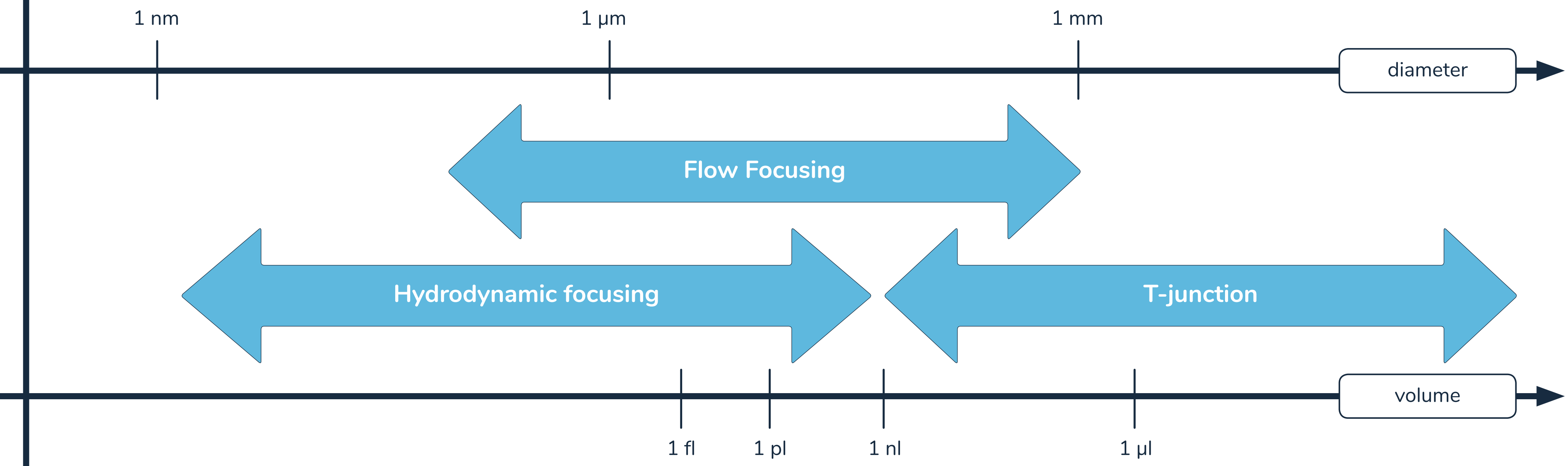


Hydrodynamic focusing



MICROFLUIDICS AND DROPLETS

Droplet sizes



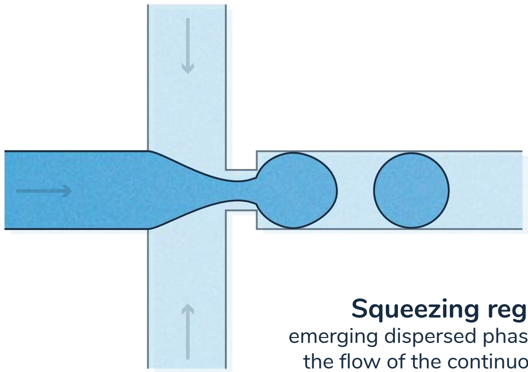
Monodispersity: 1 to 5%

Diameter: nm to 250 µm+

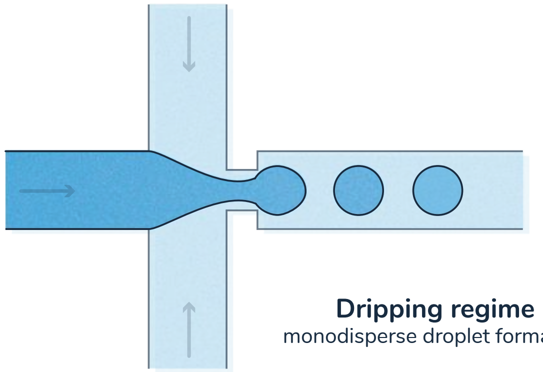
Throughput: 1 Hz to 1 MHz
(nl/min to ml/min)

MICROFLUIDICS AND DROPLETS

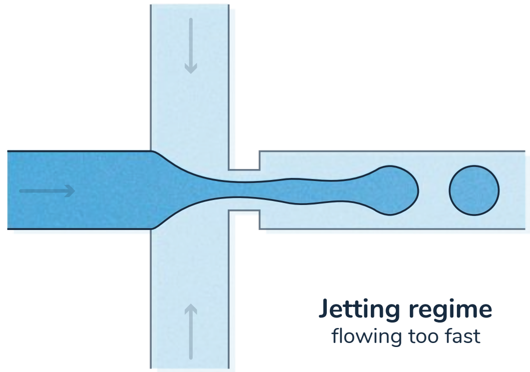
Regimes



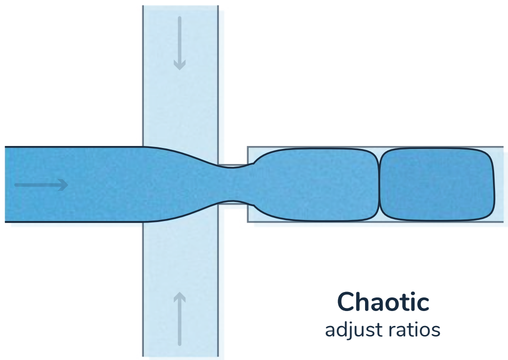
Squeezing regime
emerging dispersed phase obstructs the flow of the continuous phase, causing its pressure to rise



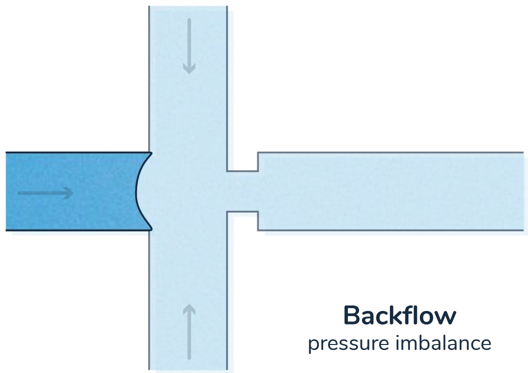
Dripping regime
monodisperse droplet formation



Jetting regime
flowing too fast



Chaotic
adjust ratios



Backflow
pressure imbalance

4. APPLICATIONS

APPLICATIONS

What droplets are used for?

- Emulsions
- Double Emulsions
- Diagnostics
- Cell Encapsulation
- Polymer Beads Synthesis
- Hydrogels Synthesis
- Nanoparticle Synthesis
- Drug Delivery

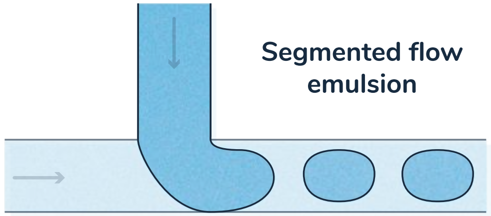
APPLICATIONS

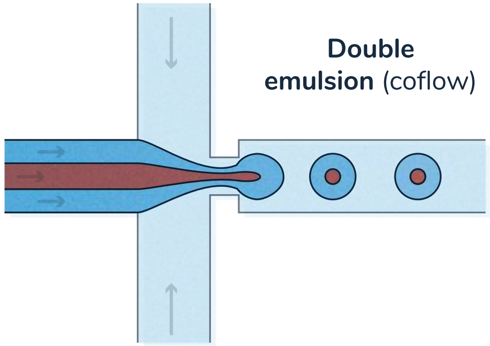
Emulsions

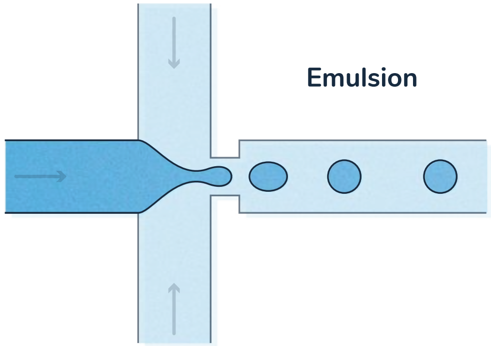
Continuous production of oil-in-water or water-in-oil emulsions or droplet-in-droplet (water-in-oil-in-water (w/o/w) or oil-in-water-in-oil) emulsions containing highly monodisperse droplets from 2 µm to 250 µm.

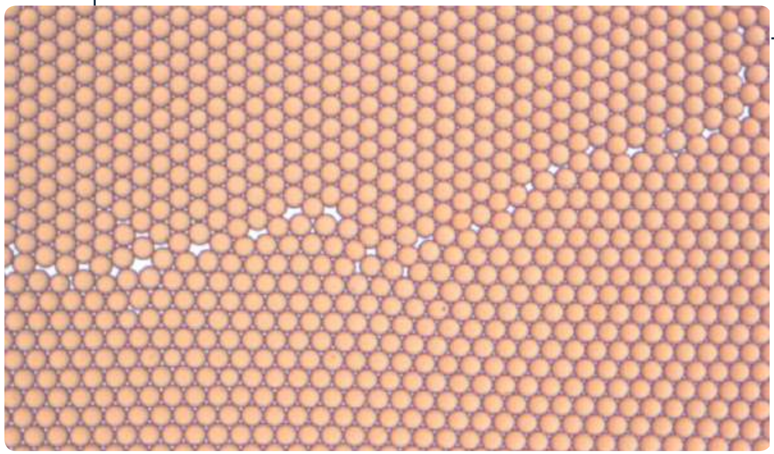
Industrial applications

- Food: mayonnaise, salad creams, beverage
- Cosmetics: creams, lotions, hair sprays
- Pharmaceuticals: anaesthetics, lipid emulsions, encapsulated drugs
- Agrochemicals: encapsulated pesticides
- Oil Industry: crude analysis for recovery strategy making
- Paints: alkyd resins, latex emulsions









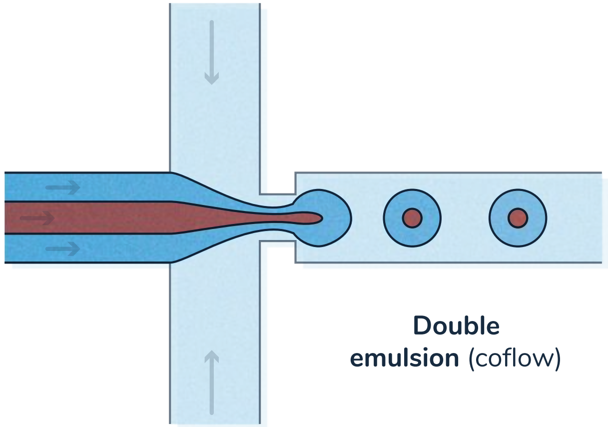
APPLICATIONS

Double-emulsions

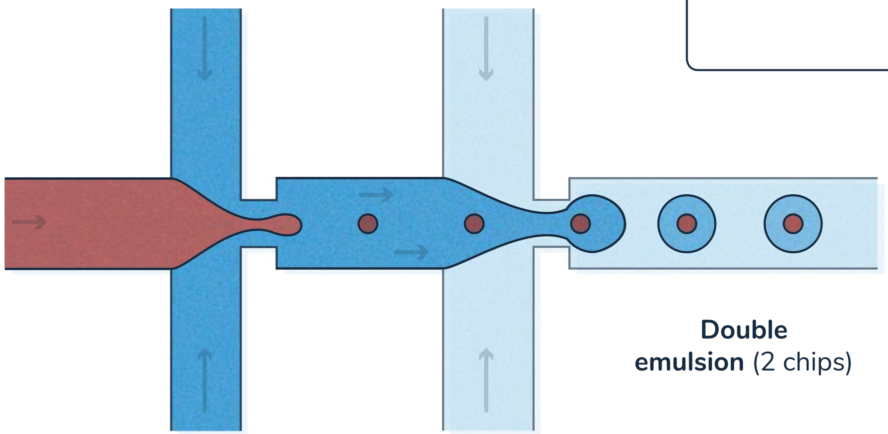
Monodisperse water-in-oil-in-water (w/o/w) or oil-in-water-in-oil (o/w/o) droplet production in a single step.

Industrial applications

- Drug delivery
- Industrial applications in cosmetics: used as a carrier of the active ingredient
- Food processing: low fat content (by the use of air filled fat particles), as is low sodium (using tastemaker)
- Flow cytometry FACS machines for in-vitro compartmentalization and directed evolution studies



Double emulsion (coflow)



Double emulsion (2 chips)

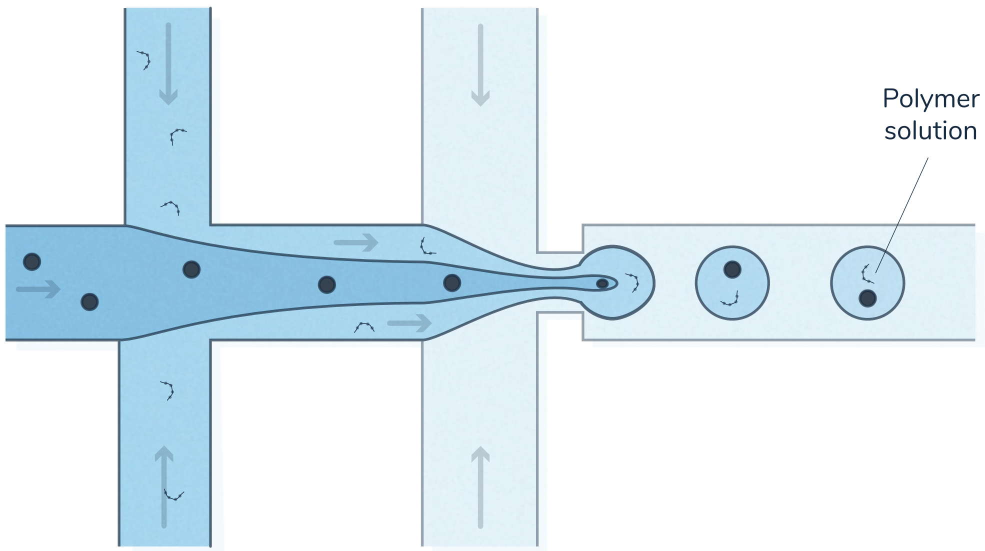
APPLICATIONS

Polymer beads

Automated production of 1,000 s of droplets, microparticles or multiphase droplets (e.g. gas filled polymer spheres, Janus particles, and ternary polymer particles)
High control over size (from 20 nm to 250 μm), shape (spherical, disks or oblate) and morphology (beads, plugs and disks)

Industrial applications

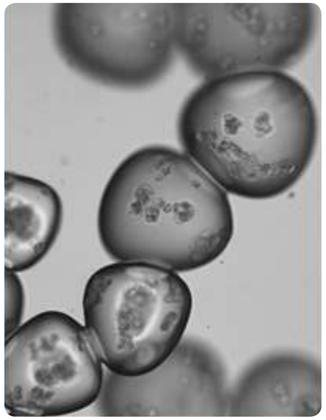
- Diagnostic tests and assays
- Controlled drug release/targeted drug delivery.
- μ-PIV (Particle Image Velocimetry)

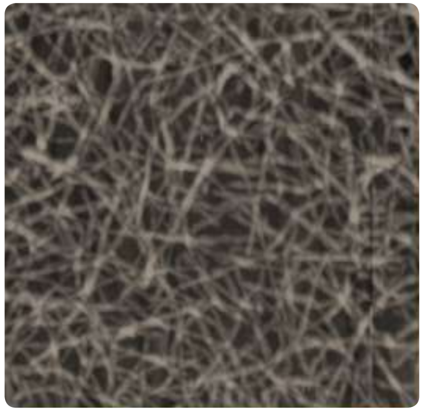


APPLICATIONS

Hydrogels

Production of hydrogel particles in the range 5µ to 500µm diameter (+/- 10%) with exceptional control over size, shape and morphology





Industrial applications

- Biomedical – separation of biomolecules for analysis, scaffolds for tissue engineering,
- Drug delivery – vehicle for drug delivery (in microparticle form)
- Optics and fluidics – actuators for optics and fluidics
- Biological studies – a model extracellular matrices

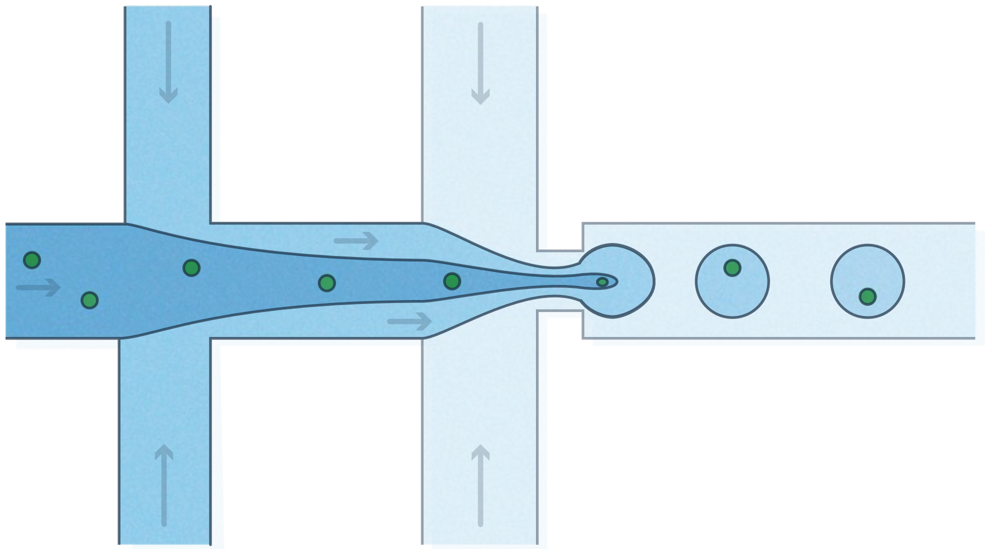
APPLICATIONS

Targeted drug delivery

Production of highly monodisperse microparticles (PLGA), nanoparticles (PLGA, PEG-PLA), and double emulsions (gas in PLGA in water) for carrying active pharmaceutical ingredients, enabling highly controlled predictable drug release. Easy scale up to tonnes/month.
Polymer degrades predictably within the body resulting in slow, steady release of the drug

Industrial applications

- Controlled drug release/targeted drug delivery – novel application – generation of biodegradable microparticles



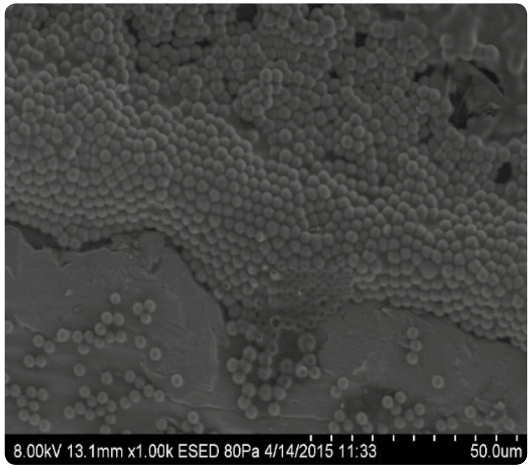
APPLICATIONS

Nanoparticles

Highly reproducible production of solid, semi-solid or soft nanoparticles from 20nm to 250μm with high control over particle size, shape (spherical, disks or oblate), crystal structure and composition consistency.

Industrial applications

- Optics – quantum dots for high resolution cameras and screens
- Chemistry – metal particles for catalysis
- Biology – supra magnetic nanoparticles



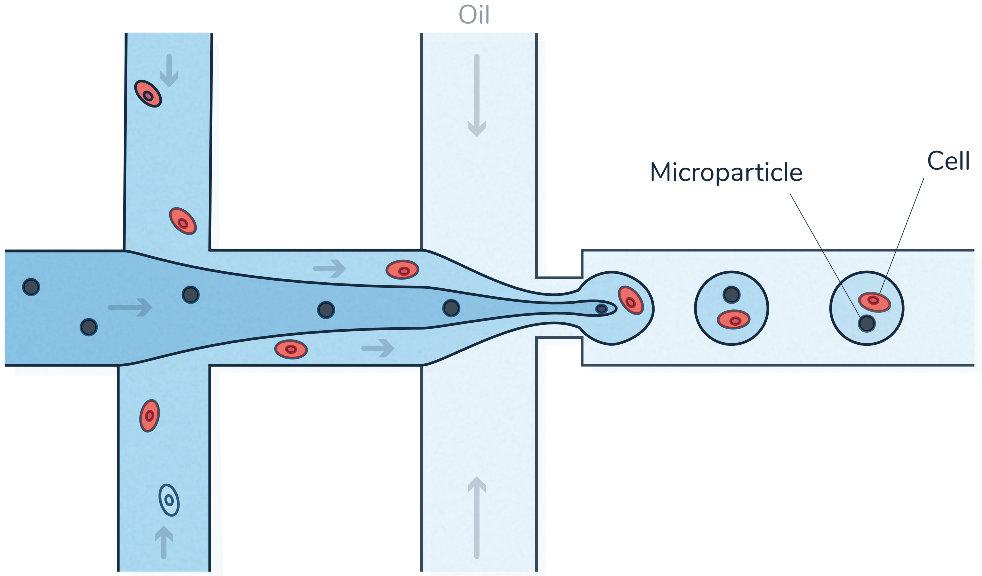
APPLICATIONS

Cell encapsulation

The aim of these experiments is to isolate a single cell, with a reaction mix, or mRNA capture beads, and encapsulate them in an oil shell

Industrial applications

- Biology – sample preparation for RT-PCR, mRNA capture, polymerisation of droplet



DO YOU WANT TO BENEFIT FROM DROPLET MICROFLUIDICS?

Ask yourself the following:

- Are you already using microfluidics?
- What kind of droplet do you want to make?
- What are your dispersed and continuous phases?
- What is the size of the droplets you would like to achieve?
- Do you have any scientific publication describing your goals?

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ELVEFLOW
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Elveflow focuses on the development of high performance and plug and play flow control systems perfect for microfluidic research. We provide the only microfluidic flow control systems using Piezo technology and blazing fast flow changes in your microdevice.

Multidisciplinary experts here to help you
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