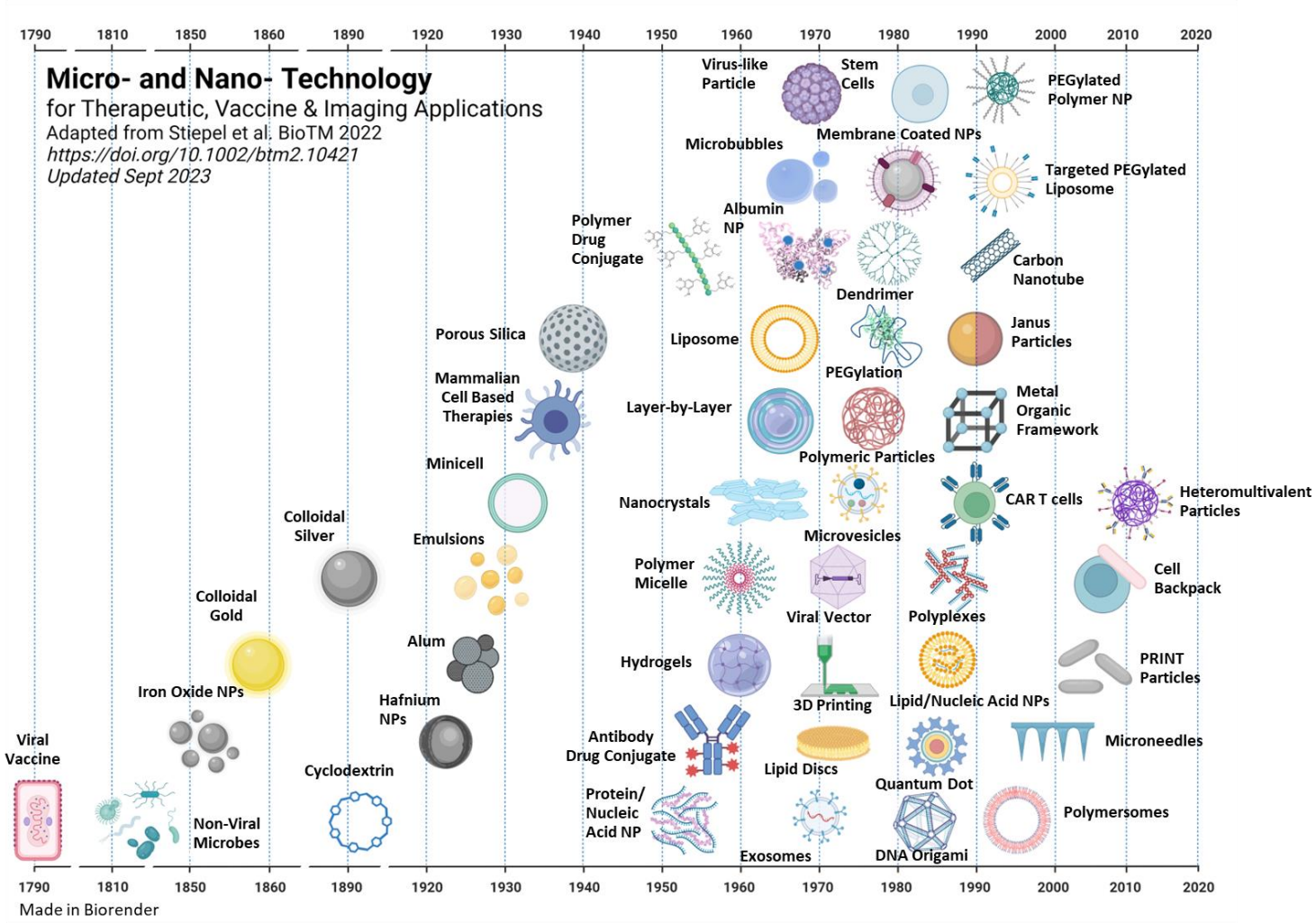
Master 2 Pharmacotechnie et Biopharmacie

Nano et microparticles: formulation strategies (UE 3)

Simona Mura | octobre 3, 2024 |

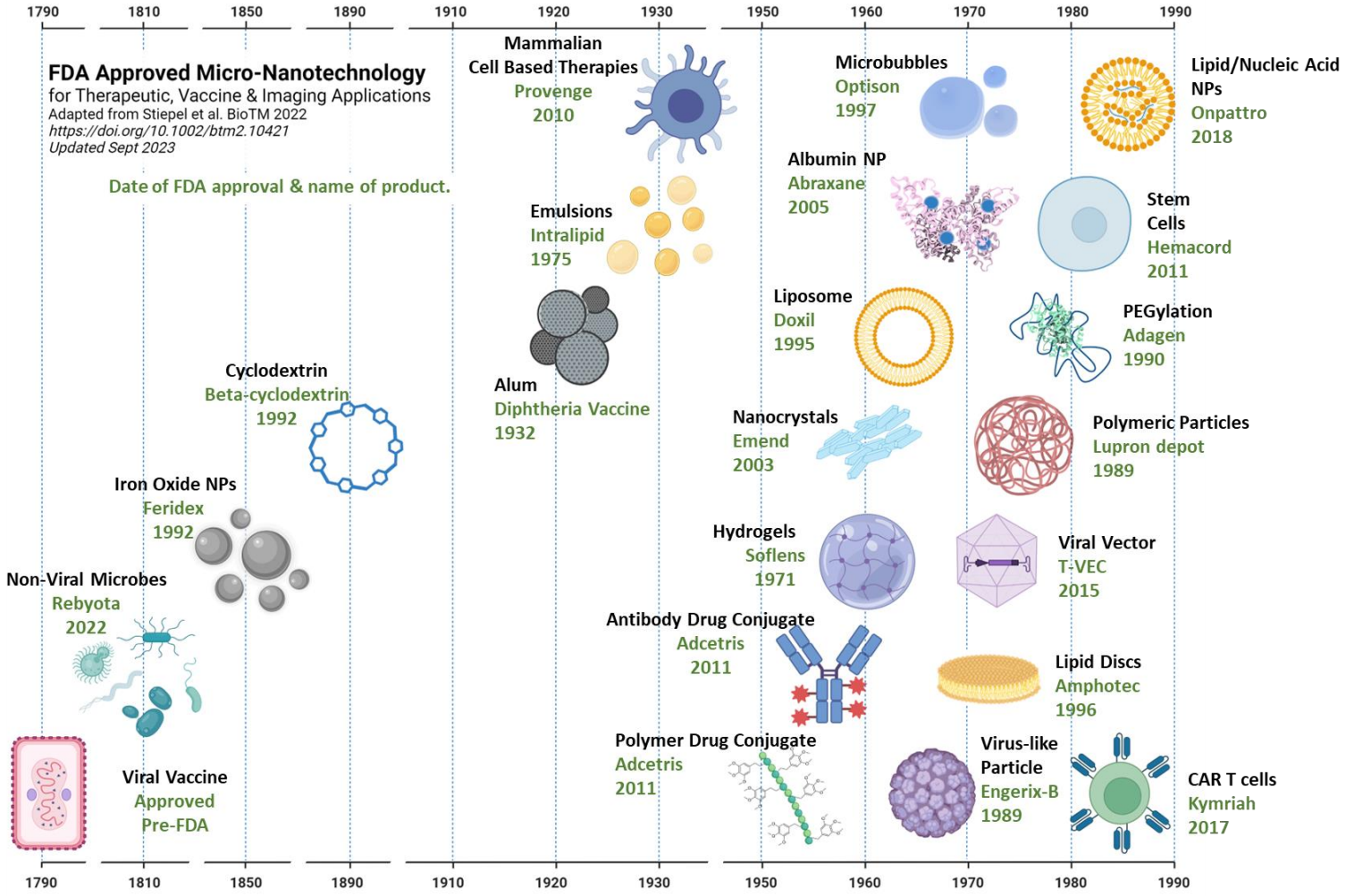
Micro and nanotechnologies

Timeline of first reports



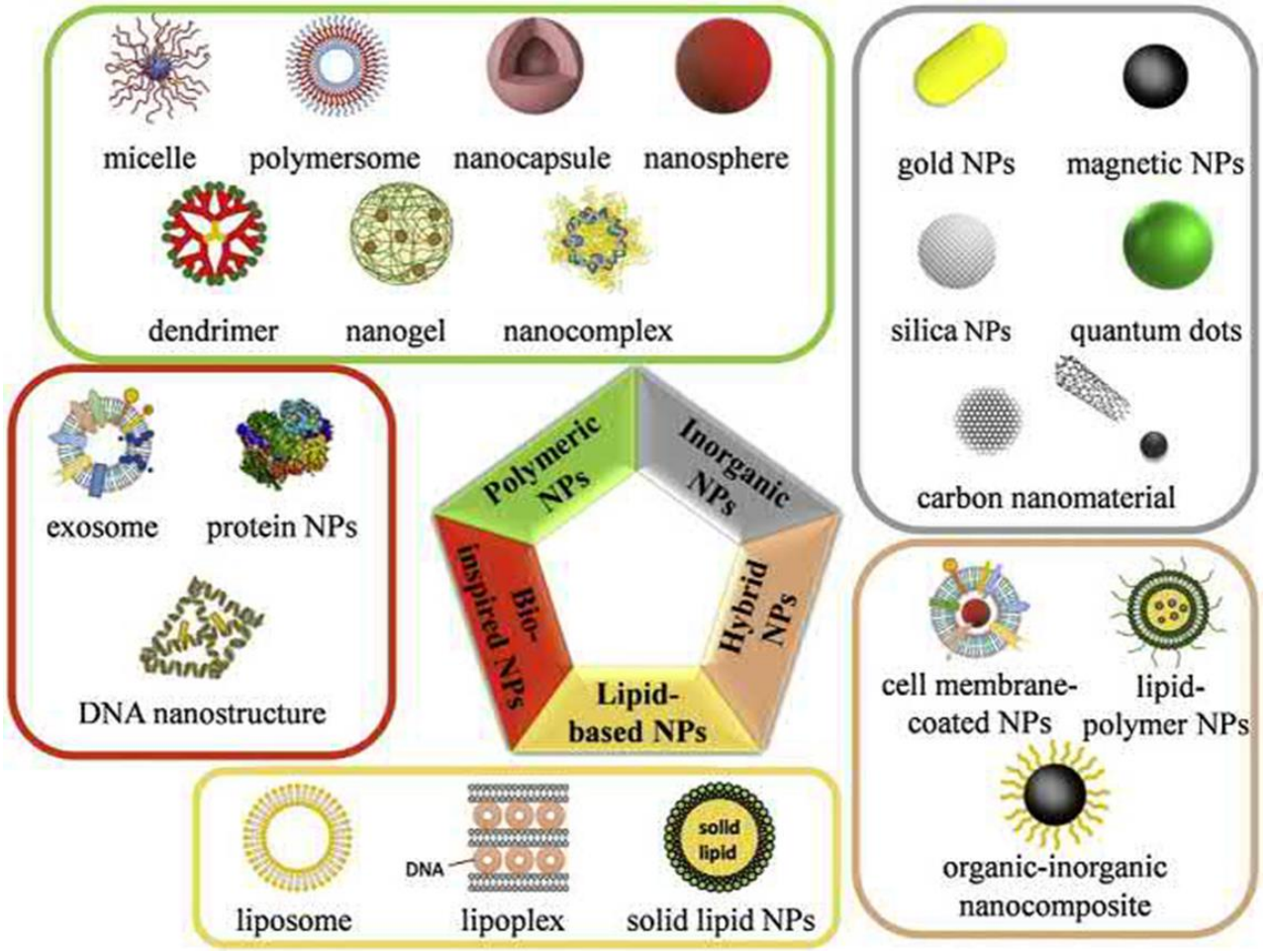
Micro and nanotechnologies

FDA-approved



Micro and nanotechnologies

Material-based classification



Polymer micro and nano carriers for drug delivery

Material selection

Biodegradable

Biocompatible

- They must have the capability to be eliminated by the body
- They should not induce toxic and/or inflammatory reaction

Natural Polymers

Synthetic Polymers

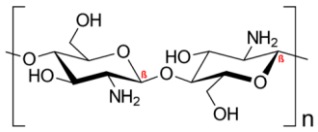
Only a limited number of materials satisfy these needs

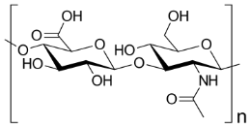
Polymer micro and nano carriers for drug delivery

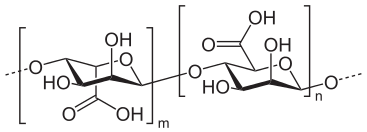
Material selection_natural polymers

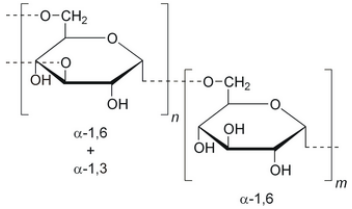
Polysaccharides

- Chitosan
- Hyaluronic acid
- Alginic acid
- Dextran



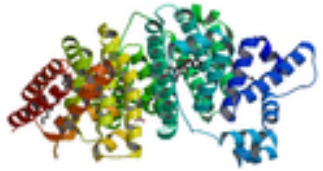


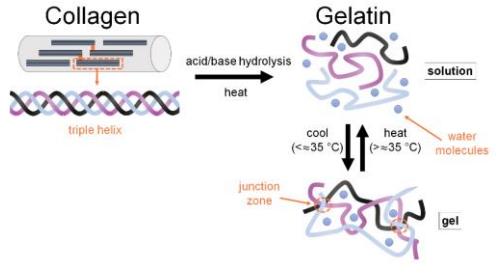




Proteins

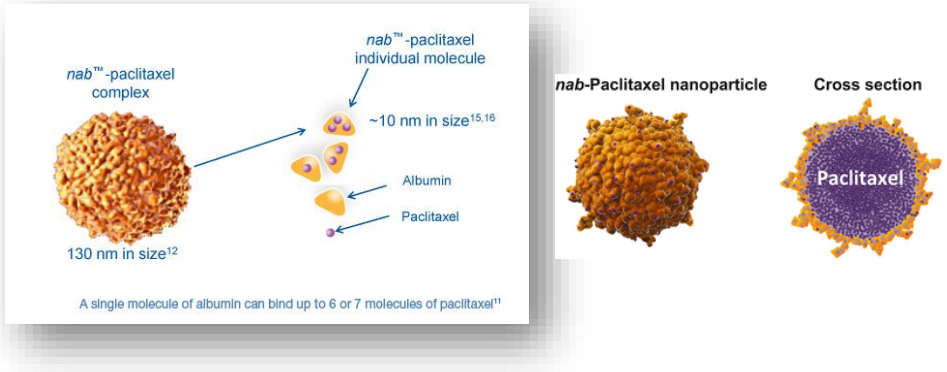
- Albumin
- Gelatin





Polymer micro and nano carriers for drug delivery

Nanoparticle albumin-bound (nab) technology



Taxol

- Ethanol/Cremophor-EL
- Allergic, and anaphylactic reactions
- Peripheral neuropathy
- Drug sequestration by cremophor micelles
- 3h infusion
- Non-linear, less-predictable PK

Human MTD 175 mg/m²

Abraxane

- No premedication
- Cremophor free
- Shorter infusion time (30 min)
- Linear, predictable PK

Human MTD 300 mg/m²

Polymer micro and nano carriers for drug delivery

Material selection_synthetic polymers

Polyesters

- Poly(lactic acid) (PLA)
- Poly(lactic-co-glycolic acid) (PLGA)
- Poly(caprolactone) (PCL)

Poly(aminoacid)s

- Poly(benzylglutamate) (PBLG)

Acrylates

- Poly(cyano acrylate d'alkyle) (PACA)

Poly(ether)

- Poly(ethylene glycol) (PEG)

☑ Ester hydrolysis, autocatalytic reaction

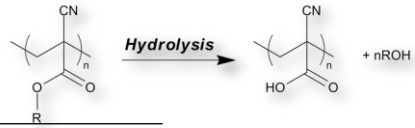
($t_{1/2}$ from several days to week or > 1year)

☑ Peptide bond hydrolysis

($t_{1/2}$ not determined)

☑ Hydrolysis of lateral ester bonds

($t_{1/2}$ a few hours)



☐ Non degraded in vivo

Renal excretion

Polymer micro and nano carriers for drug delivery

Material selection_chose the role

Structural

- Carrier formulation
- Carrier morphology
- Drug loading
- Controlled release

Functional

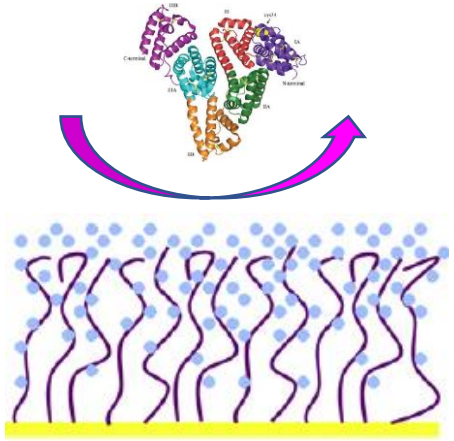
- Coating
  - *Stabilization/adhesion*
- Functionalization
  - *Target recognition*
- Control interactions with biological medium
  - *Stealth features*

Polymer micro and nano carriers for drug delivery

Material selection_functional role

Control interactions with biological medium

- Stealth features

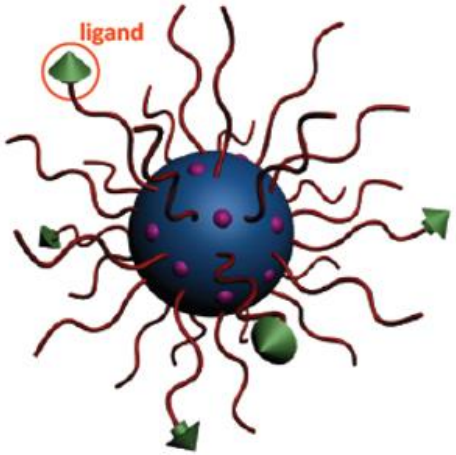


Hydration Layer

Hydrophilic polymer

Functionalization

- Target recognition

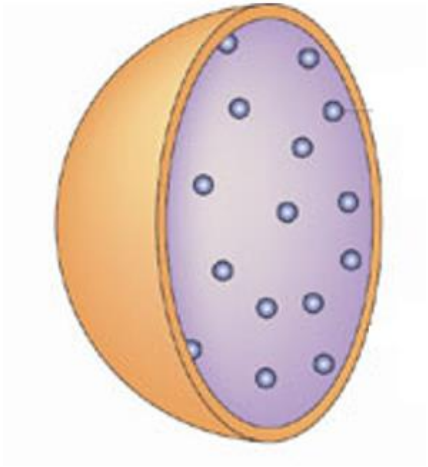


Polymer nanoparticles

Structure

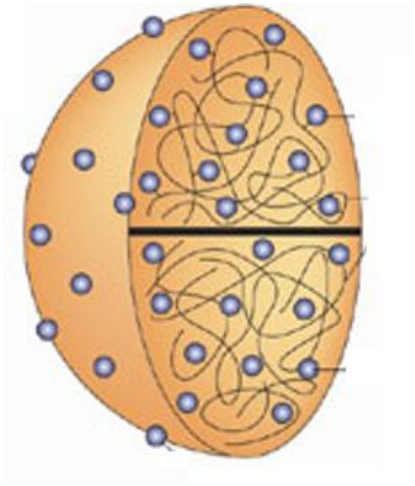
Nanocapsules

- Polymer shell
- Liqui core (oil / water)



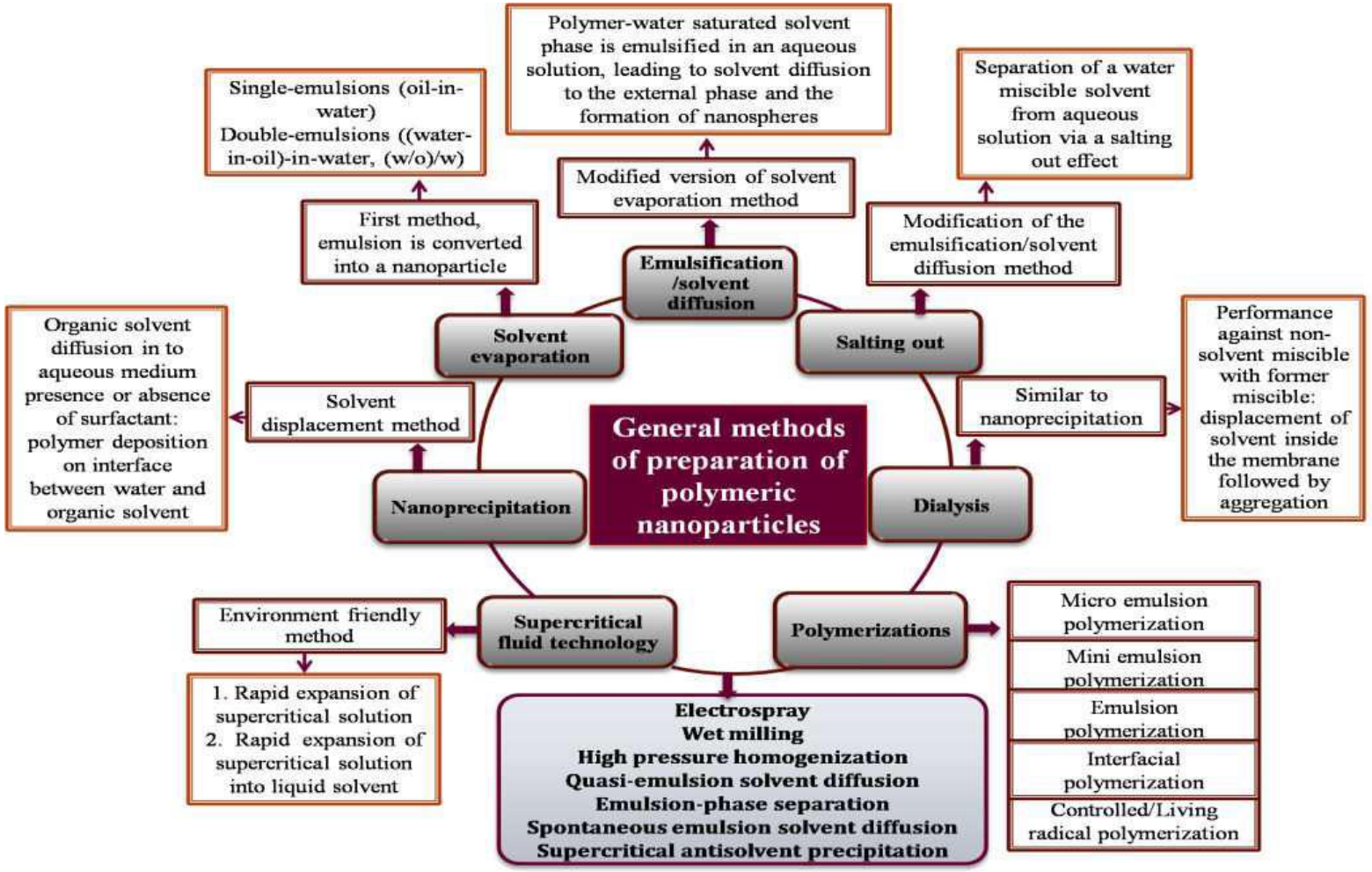
Nanosphere

- Solid polymer matrix



Polymer nanoparticles

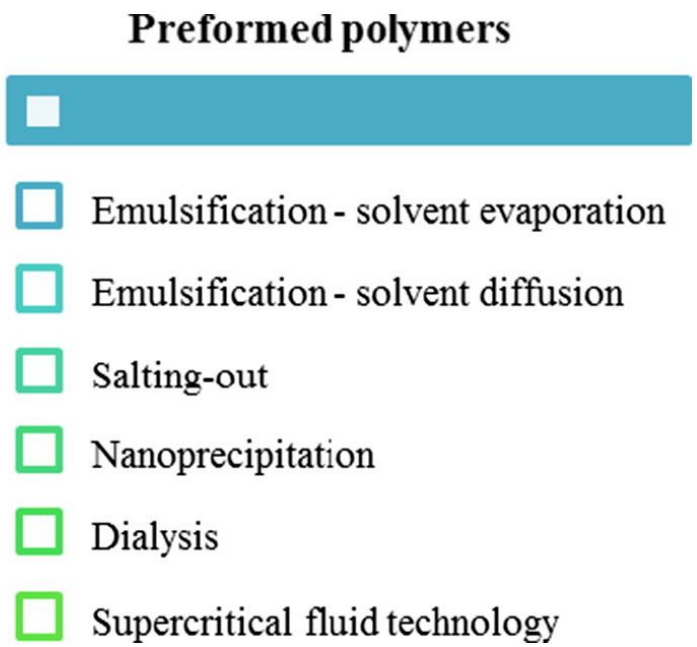
Formulation approaches



Bioengineering & Transla Med, Volume: 8, Issue: 2, First published: 18 October 2022, DOI: (10.1002/btm2.10421)

Polymer nanoparticles

Formulation approaches_a simplified version

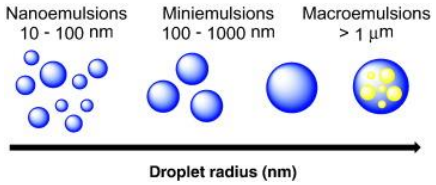


Two-step procedures based on emulsification

One-step procedures

Polymer nanoparticles

Two-step procedures



Emulsion

- External phase = dispersing phase = continuous phase
- Internal phase = dispersed phase = discontinuous phase

Oil-in-water emulsion

- oil is the dispersed phase/ water is the continuous phase

Water-in-oil emulsion

- water is the dispersed phase/oil is the continuous phase

Multiple emulsions

- water-in-oil-in-water emulsion

Microemulsions

- size < µm
- thermodynamically stable
- high amounts of TA

Nanoemulsions

- nanometric size
- thermodynamically unstable
- low amounts of TA

Polymer nanoparticles

Two-step procedures_preformed polymers

1 Emulsification

Polymer organic solutions in an aqueous phase

Drug is introduced in the polymer solution

2 Nanodroplets

Use of low- and high-energy emulsification techniques

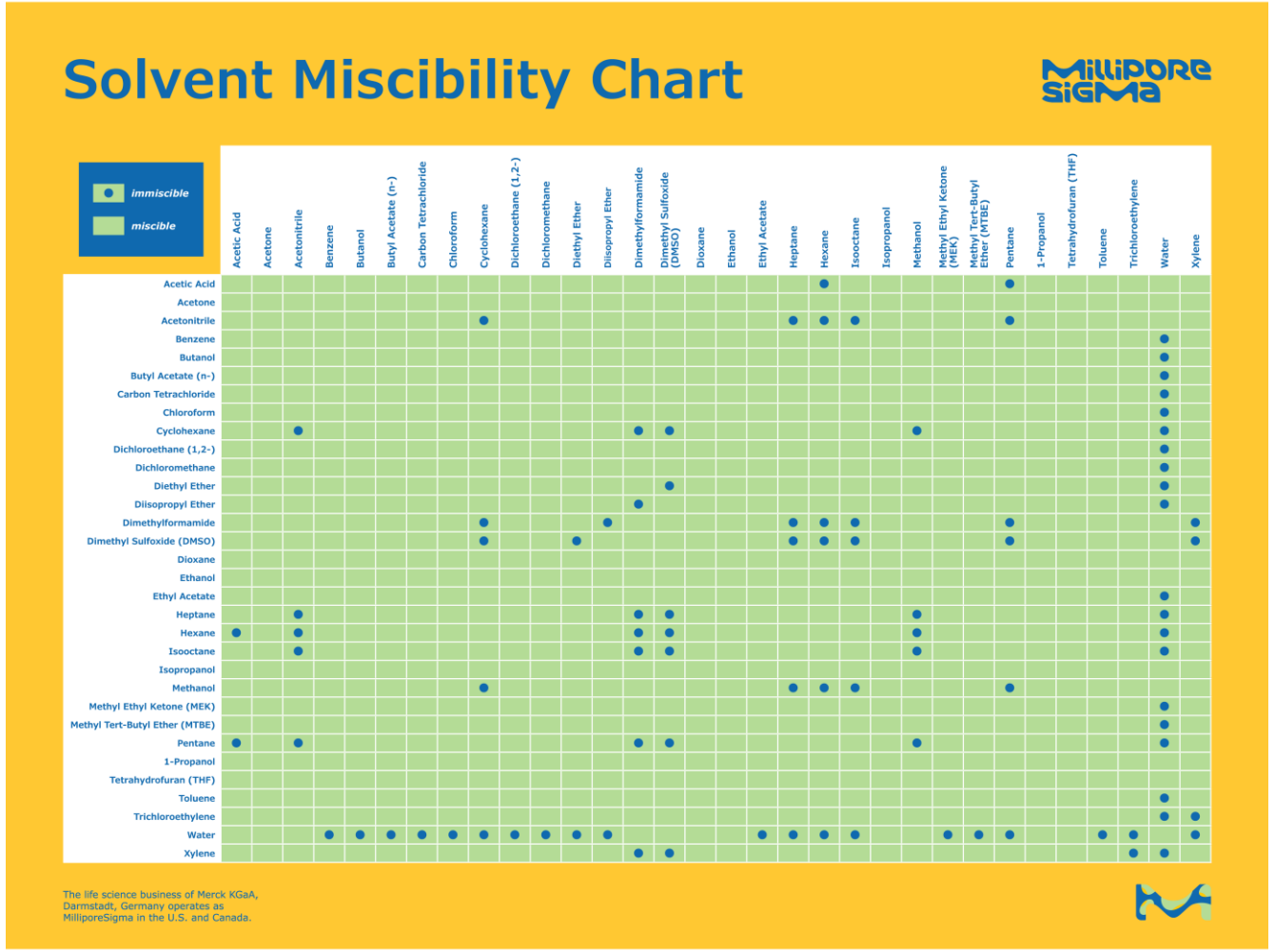
Critical step

3 Precipitation

Polymer onto preformed nanodroplets

Polymer nanoparticles

Formulation approaches_ solvent miscibility



https://www.sigmaaldrich.com/FR/fr/technical-documents/technical-article/analytical-chemistry/purification/solvent-miscibility-table

Polymer nanoparticles

Two-step procedures_Emulsification-solvent evaporation

Polymer solution

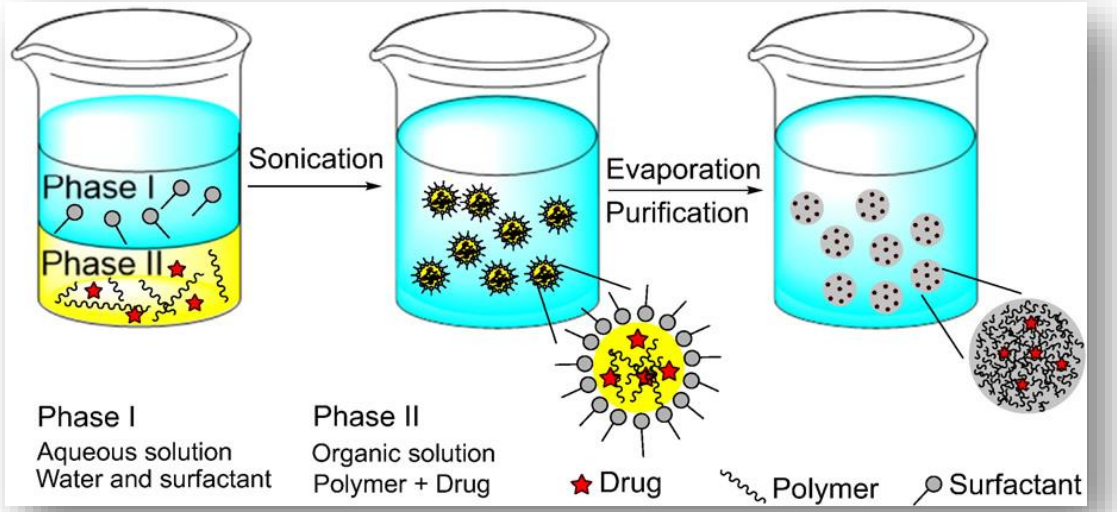
- Volatile organic solvent
- Water immiscible

Emulsification

- aqueous phase containing a surfactant
- high-speed homogenization and/or ultrasonication
- Nanodroplets formation

Solvent removal

- Magnetic stirring
- Under vacuum



Polymer nanoparticles

Two-step procedures_Emulsification-solvent diffusion

Polymer solution

- Volatile organic solvent partially water miscible
- Saturation with water

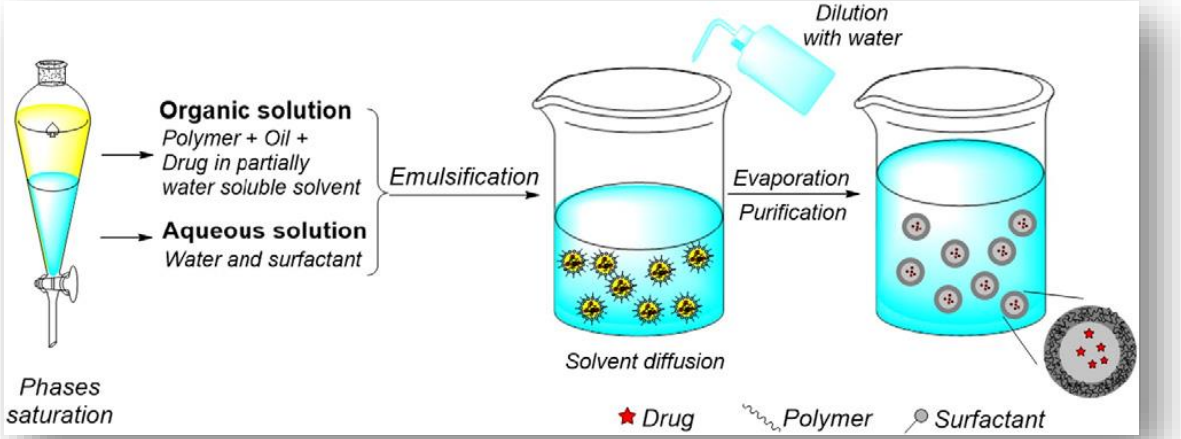
Emulsification

Dilution with water

- Gentle solvent diffusion from dispersed droplets into external phase
- Formation of particles

Solvent removal

- Evaporation
- Filtration



Mainly nanospheres

Small amount of oil in the organic phase: nanocapsules

Polymer nanoparticles

Two-step procedures_Emulsification-solvent diffusion

Pros

- **Particle Size**
  - Controlled
  - Reproducible
- **Solvent**
  - Reduced volume
  - Ease removal

Overall process

- Mild
- Versatile
- Ease Scaling-Up

Critical

- **Aqueous phase**
- High volume to remove
- Leakage of water soluble drugs during emulsification

Polymer nanoparticles

Two-step procedures_Emulsification-reverse salting-out

Polymer solution

- Volatile organic solvent water miscible
- Saturation with water

Emulsification

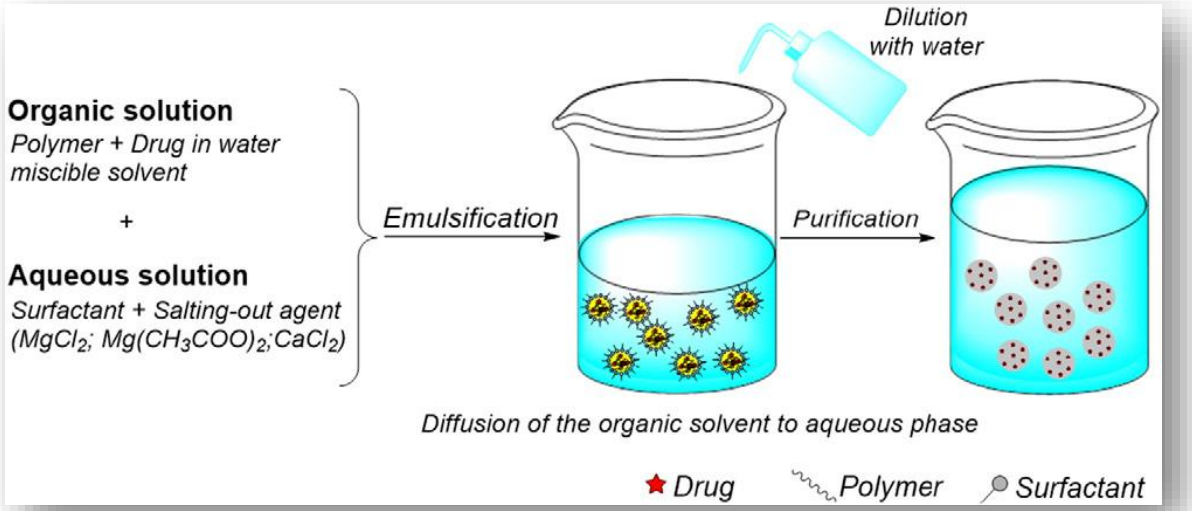
- aqueous phase containing a surfactant & a salting out agent
- Exploits the Ouzo effect

Dilution with water

- Solvent diffusion in the aqueous phase
- Polymer precipitation

Solvent & salting out agent removal

- Cross-flow filtration



Polymer nanoparticles

Two-step procedures_Emulsification-reverse salting-out

Pros

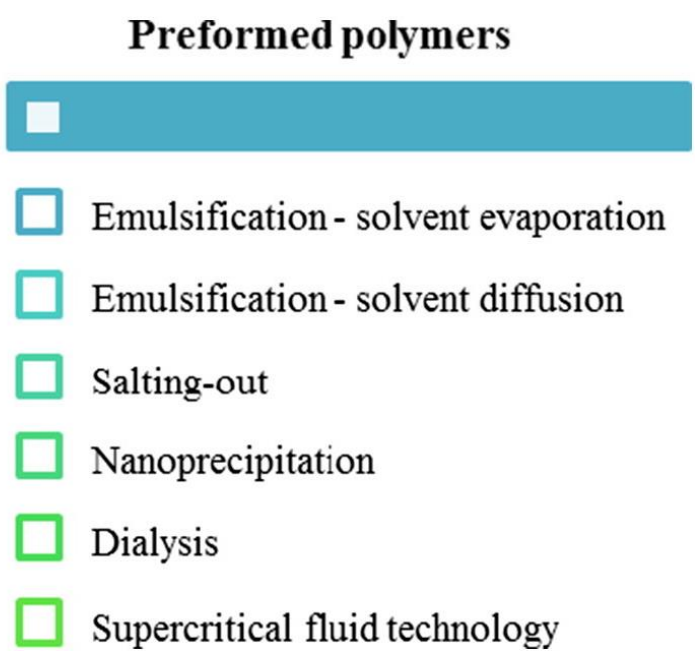
- **Safety**
  - No chlorinated solvents
- **Drug**
  - Suitable for lipophilic moieties

Critical

- **Drug**
  - Only lipophilic moieties
- **Purification**
  - Extensive
  - Challenging

Polymer nanoparticles

Formulation approaches_a simplified version



Two-step procedures based on emulsification

One-step procedures

Polymer nanoparticles

One step procedures_Nanoprecipitation (solvent displacement)

Polymer solution

- Volatile organic solvent water miscible

Addition to the aqueous phase

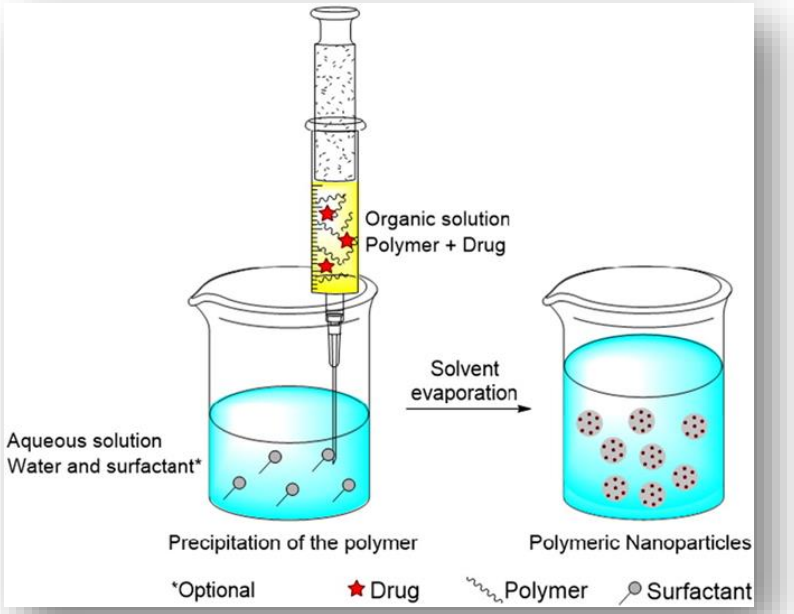
- Under stirring
  - in one shot
  - Stepwise
  - Dropwise
  - by controlled addition rate

Nanoparticle formation

- Solvent diffusion in the aqueous phase
- Polymer precipitation

Solvent removal

- Under vacuum



Well defined size and narrow distribution

Surfactants are not essential

Polymer nanoparticles

One step procedures_dialysis

Polymer solution

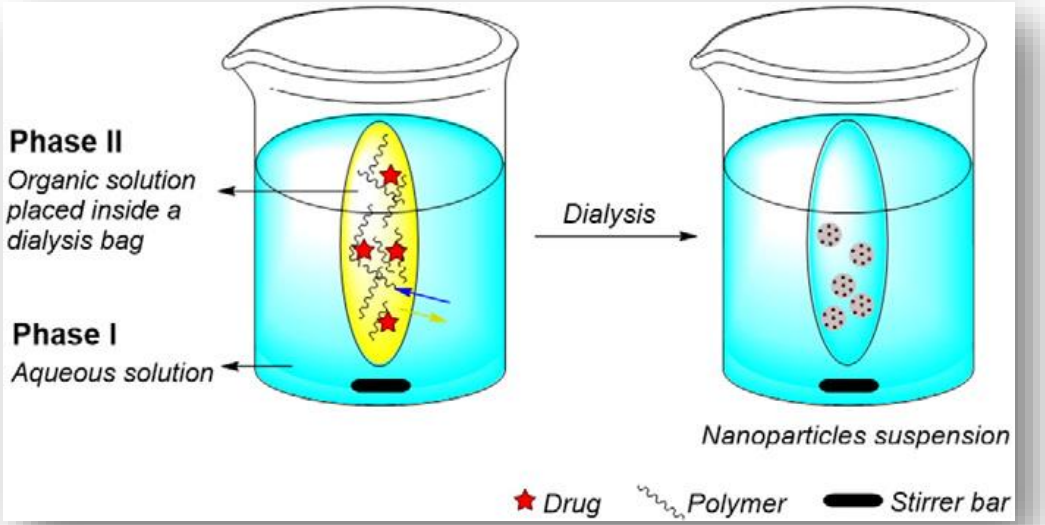
- organic solvent water miscible

Addition to the aqueous phase

- Organic solution inside the dialysis membrane
- Outside: polymer non solvent

Nanoparticle formation

- Displacement of the solvent inside the membrane
- Polymer precipitation



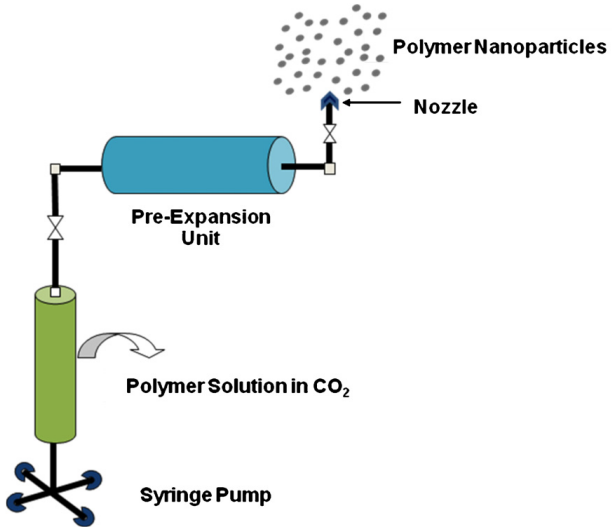
Narrow size distribution

Risk of premature drug release during the process

Polymer nanoparticles

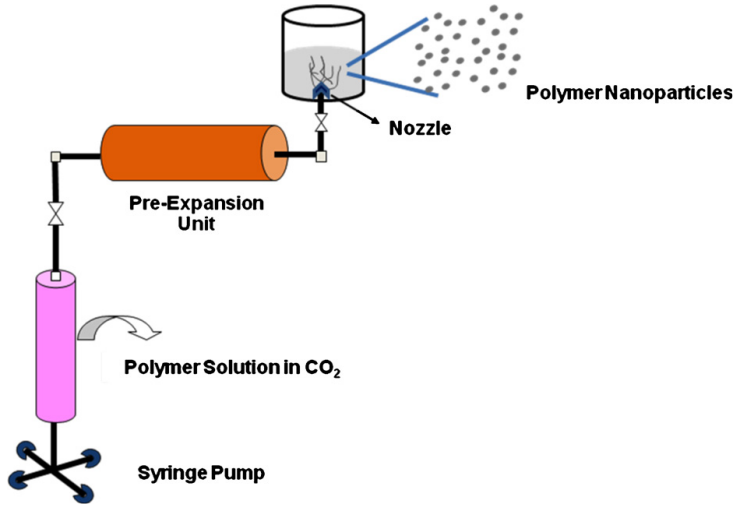
One-step procedures_Supercritical fluid technology

Rapid expansion of supercritical solution (RESS)



Mainly microparticles

Rapid expansion of supercritical solution into liquid solvent (RESOLV)



Mainly nanoparticles

High pressure equipment
Supercritical fluid soluble polymers

Polymer nanoparticles

One-step procedures_Ionic Gelation

Polymer solution (polysaccharides)

- Aqueous solution

Addition to the aqueous phase

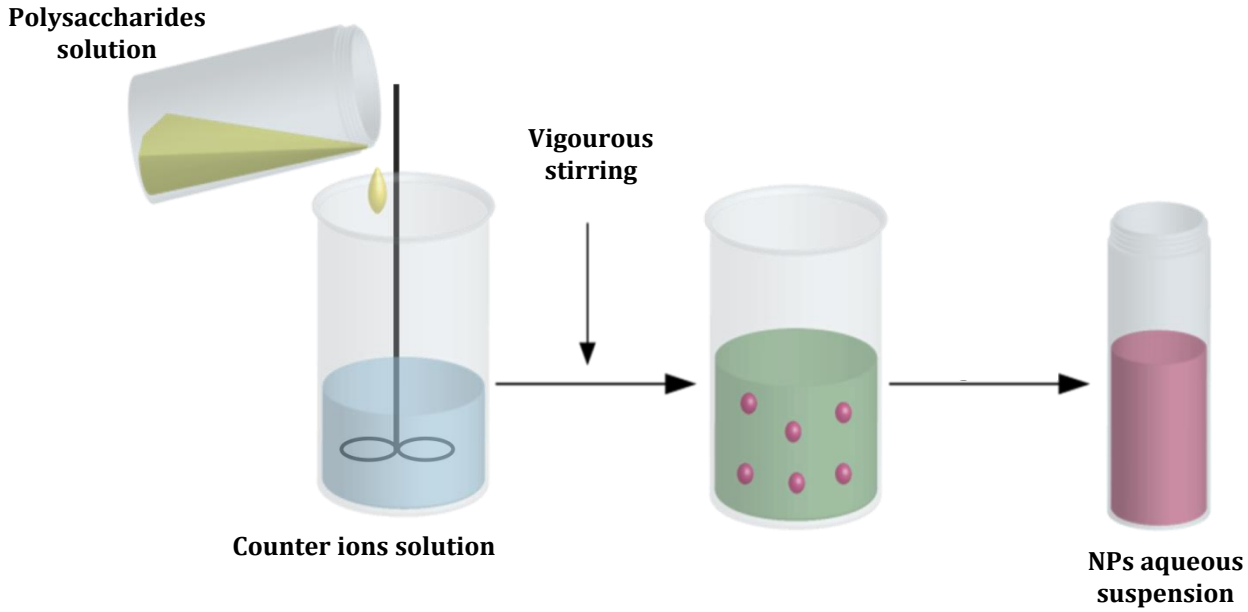
- Solution of oppositely charged species

Nanoparticle formation

- Complexation
- Physical crosslinking

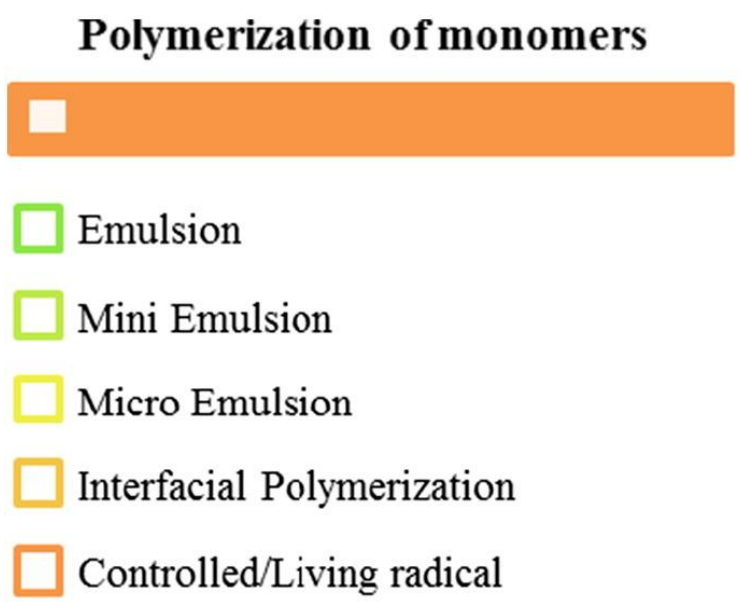
Nanoparticle collection

- Filtration
- Washing step



Polymer nanoparticles

Formulation approaches_a simplified version_Starting from monomers

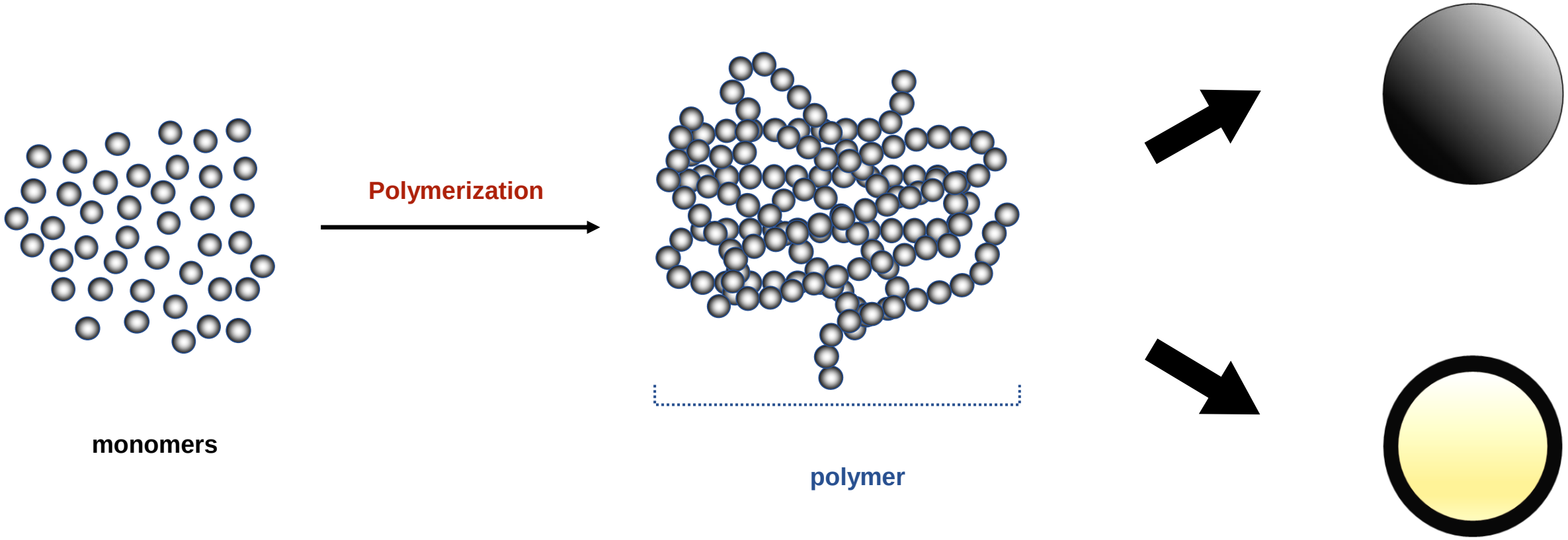


Two-step procedures based on emulsification

One-step procedures

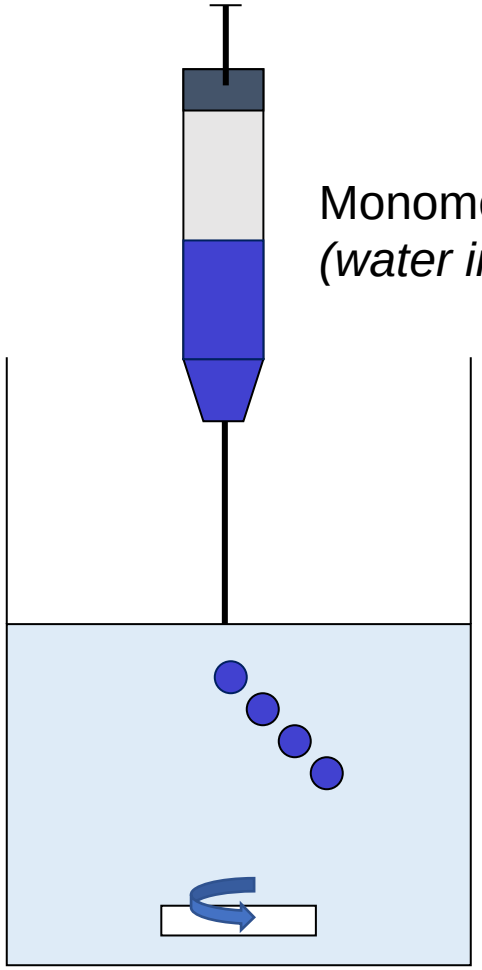
Polymer nanoparticles

Formulation approaches_Starting from monomers



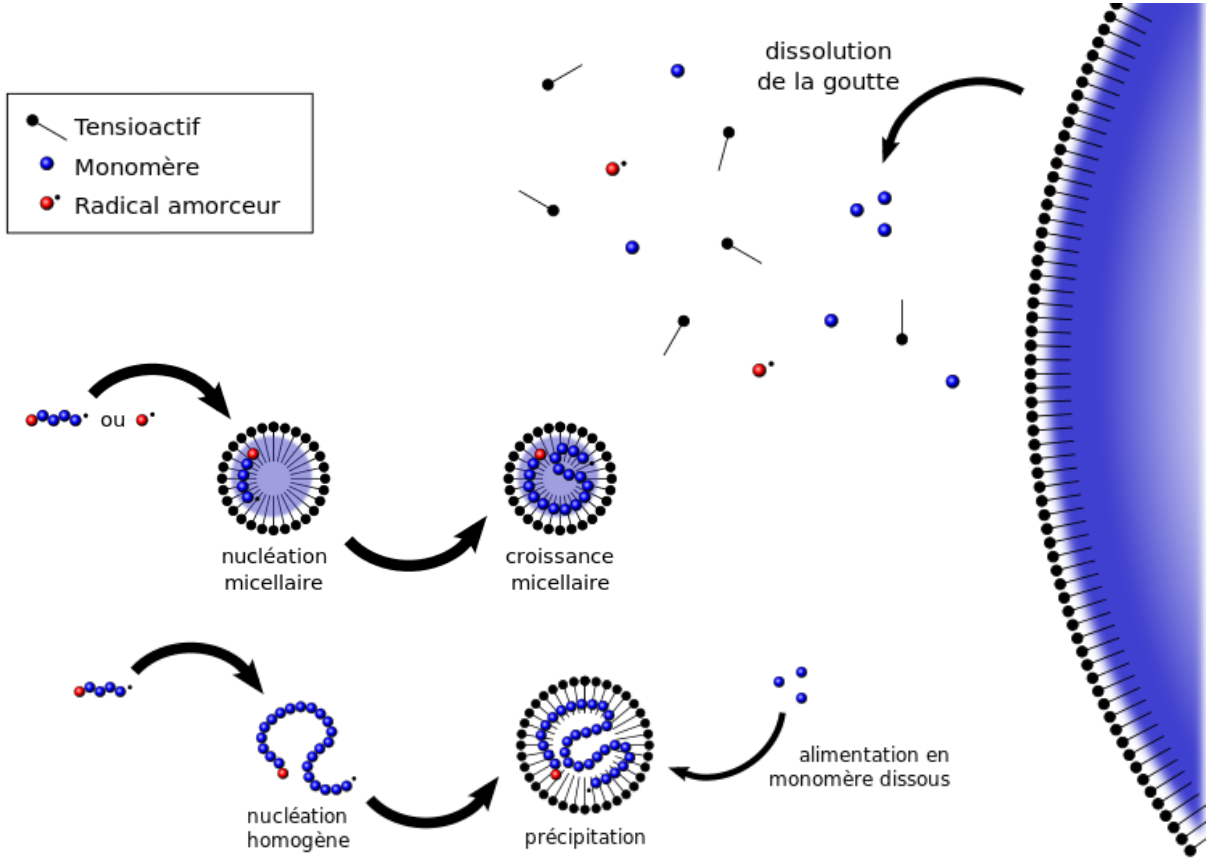
Polymer nanoparticles

Formulation approaches_Conventional Emulsion Polymerization



Monomer
(water insoluble)

Polymerization medium
- Water
- Surfactant
- Water-soluble initiator



Polymerization **does not** occur in the droplets of a monomer emulsion

Polymer nanoparticles

Formulation approaches_Conventional vs Surfactant free Emulsion Polymerization

Monomers

- Methyl Methacrylate
- Butyl acrylate
- Styrene

Surfactants

- SDS (Sodium Dodecyl Sulfate)
- CTAB (cetyltrimethylammonium bromide)
- AMA-80 (sodium dihexyl sulfosuccinate)
- DMMA-PS3-(N,N-dimethylmyristylammonio)
- Propanosulfonate (zwitterionic salt)

Polymer nanoparticles

Formulation approaches_Conventional vs Surfactant free Emulsion Polymerization

Monomers

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- Propanosulfonate (zwitterionic salt)

Monomers

- Methyl Methacrylate
- Hydroxylethyl methacrylate
- Styrene

Surfactants

- **Not Applicable**

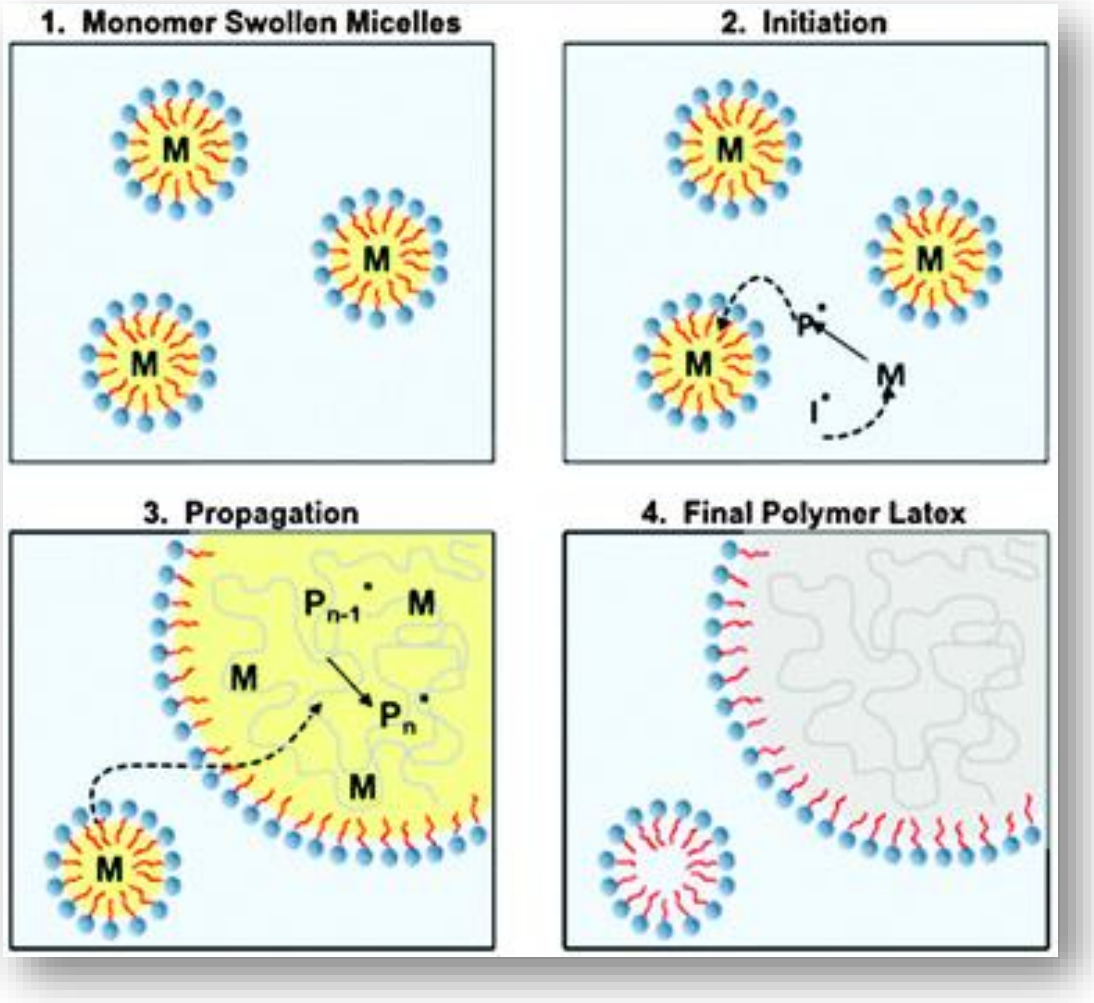
Stabilizers

- Laponite
- Poly vinyl alcohol
- 4-styrenesulfonic acid sodium salt hydrate

Wide size distribution

Polymer nanoparticles

Formulation approaches_micro emulsion Polymerization



Radical polymerization in very highly concentrated surfactant/co-surfactant solution

Formation of ultrasmall nanoparticles

Chem. Soc. Rev., 2012, 41, 3061–3076

Polymer nanoparticles

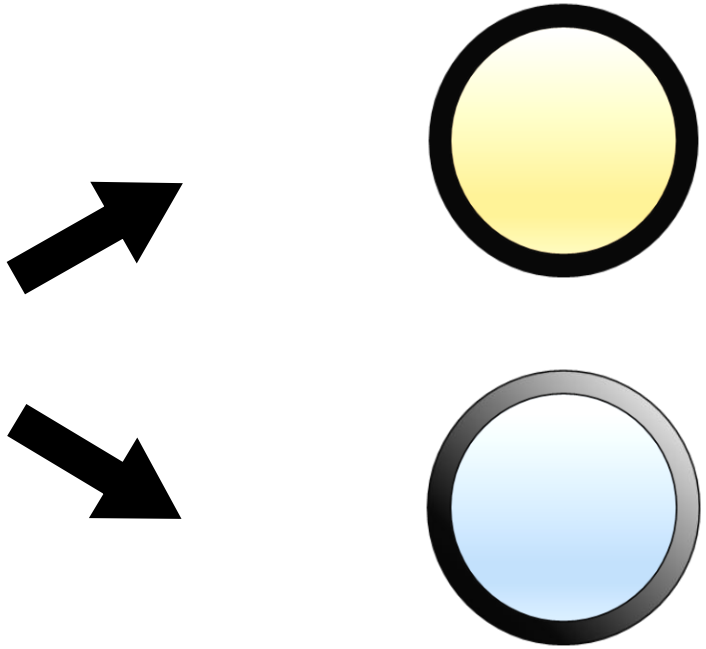
Formulation approaches_interfacial Polymerization

Polymerization

- Reactive monomers in two phases (continuous and dispersed)
- At the liquid/liquid interface

Hollow Polymer Particles

- Oily core
- Aqueous core



Oil-containing Nanocapsules

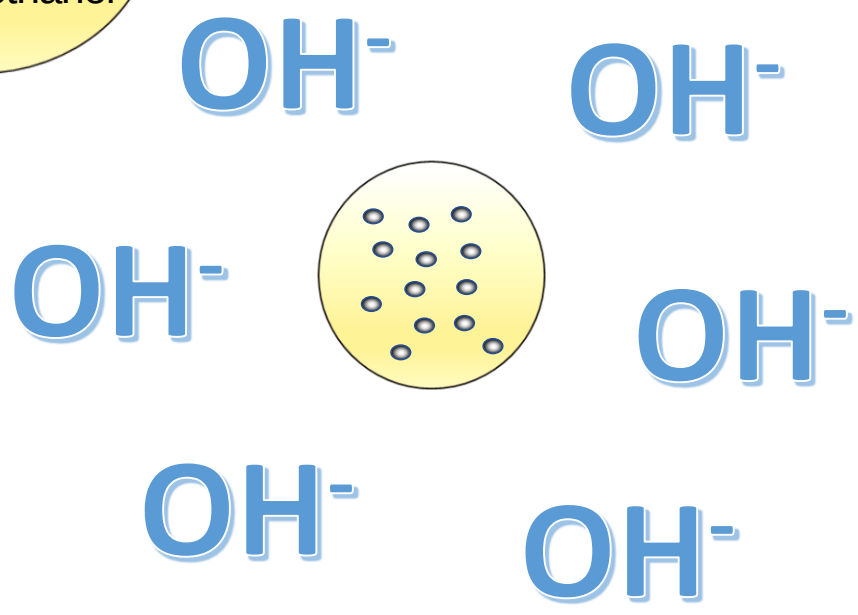
water-containing Nanocapsules

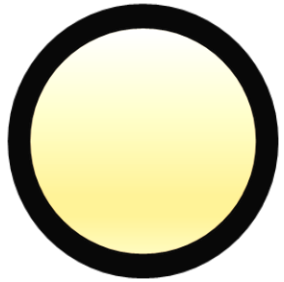
Polymer nanoparticles

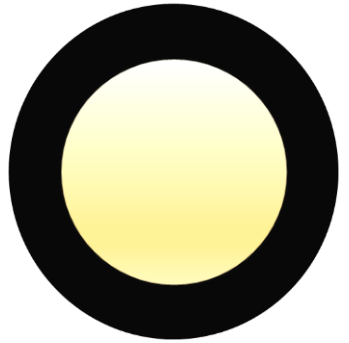
Formulation approaches_interfacial Polymerization_oil in water emulsion

droplet

- Monomers
- oil/ethanol







Liquid oily core

Polymer shell

Polymer microparticles

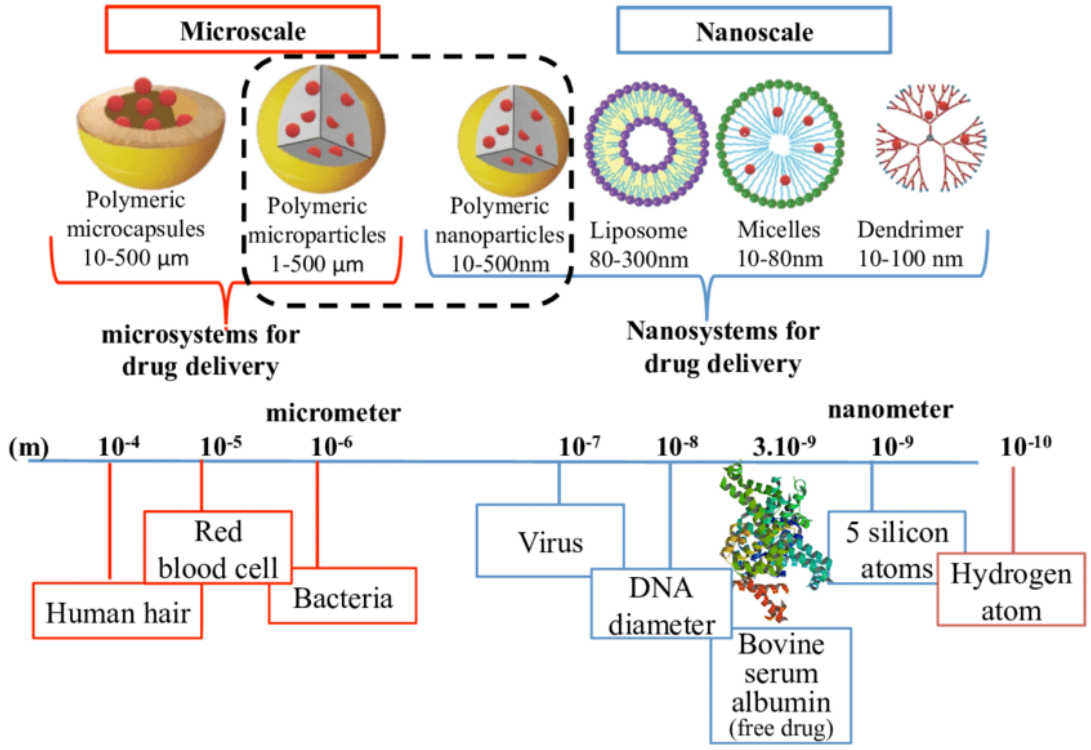
Why Size Matters

Route of administration

- oral; pulmonar; tissular
- Depot formulation

Biological barriers

- injected into tissues tend to stay in place
- resist clearance by the kidney
- Less important cellular penetration
- Taken up by phagocytic cells

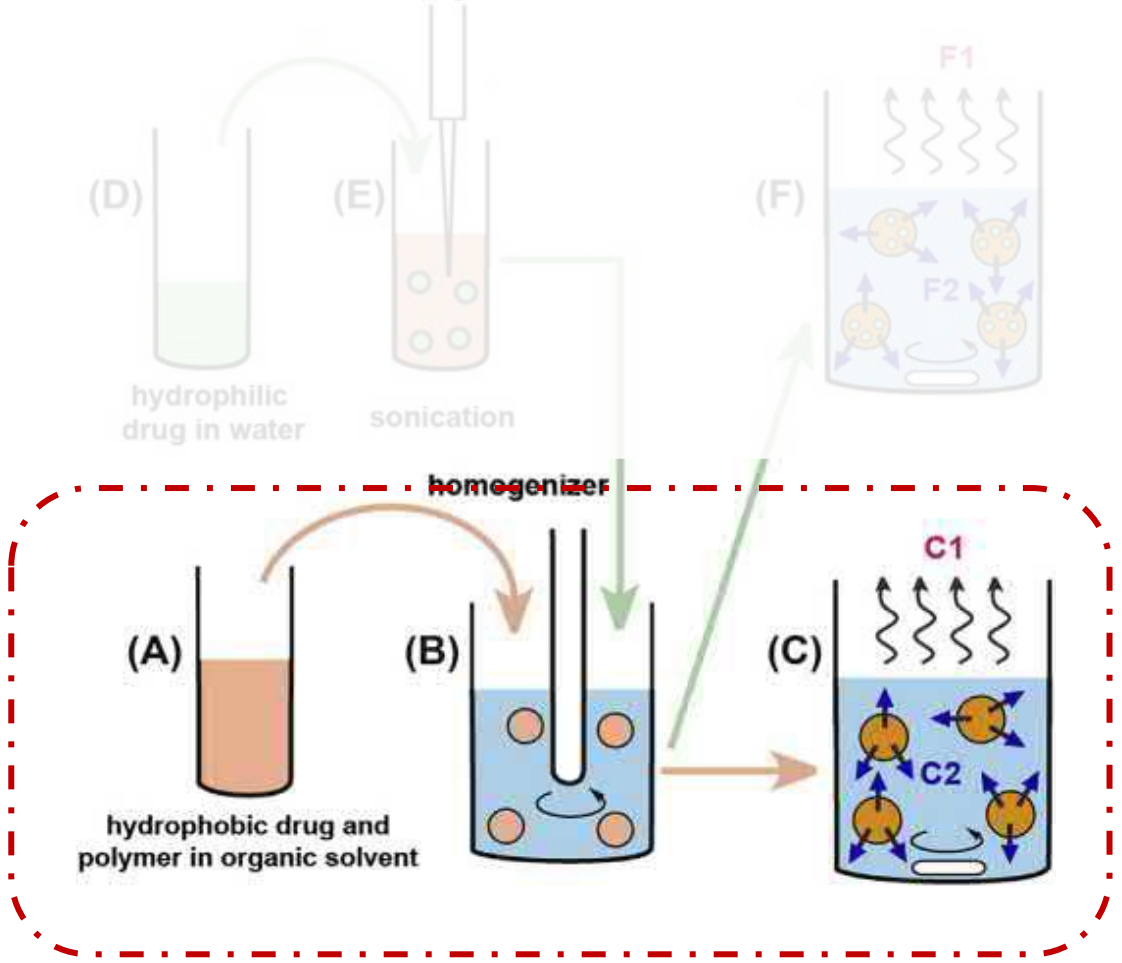


Polymer microparticles

Single and double emulsion

single emulsion system

- encapsulating hydrophobic drugs



Polymer microparticles

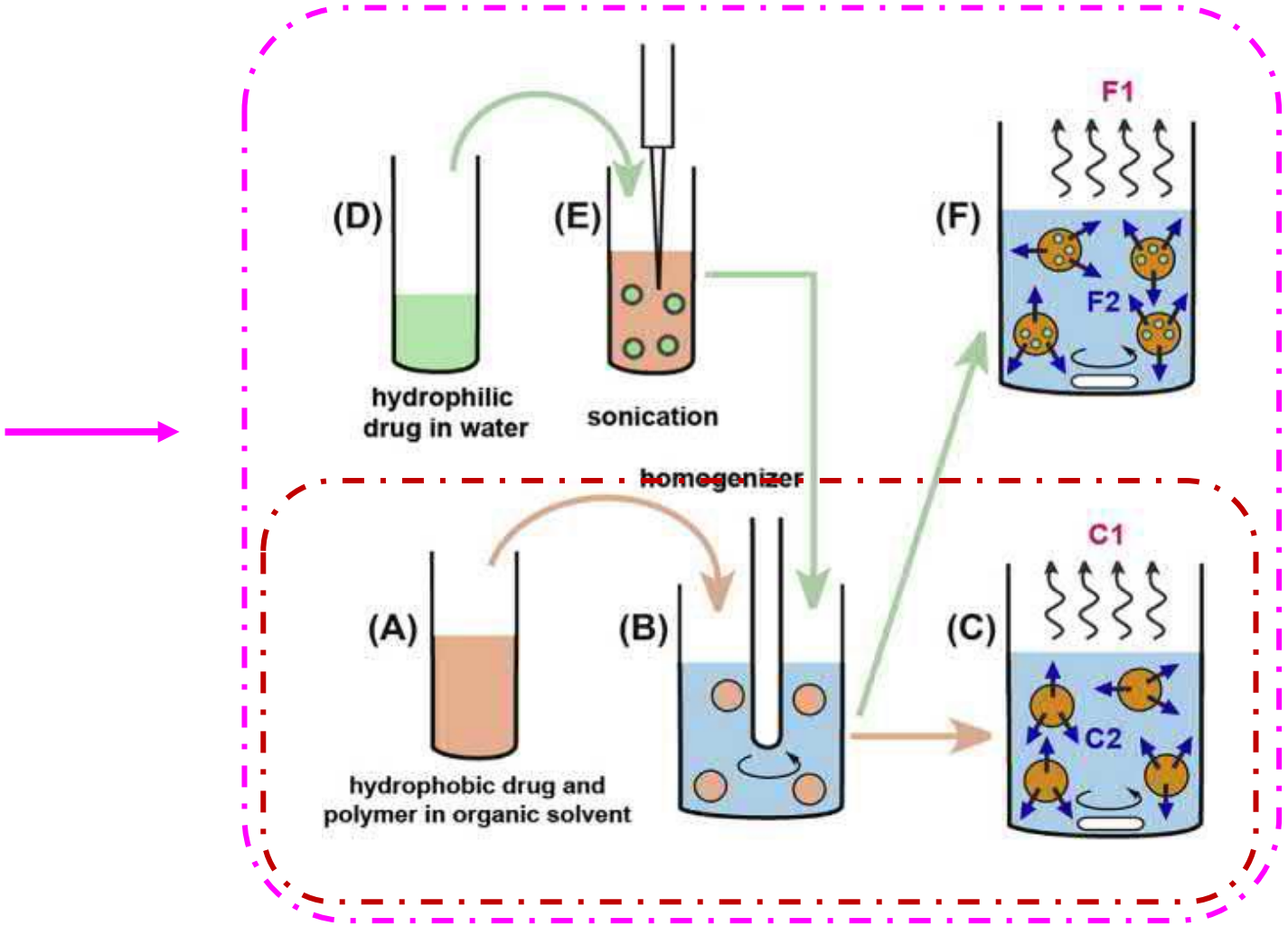
Single and double emulsion

single emulsion system

- encapsulating hydrophobic drugs

Double emulsion system

- encapsulating hydrophilic drugs



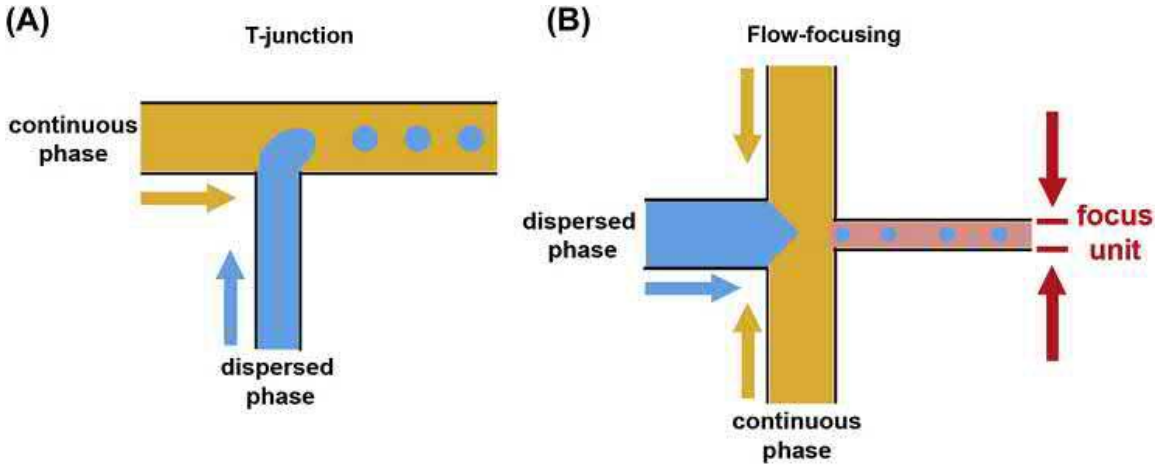
Polymer microparticles

Microfluidic

T-junction devices

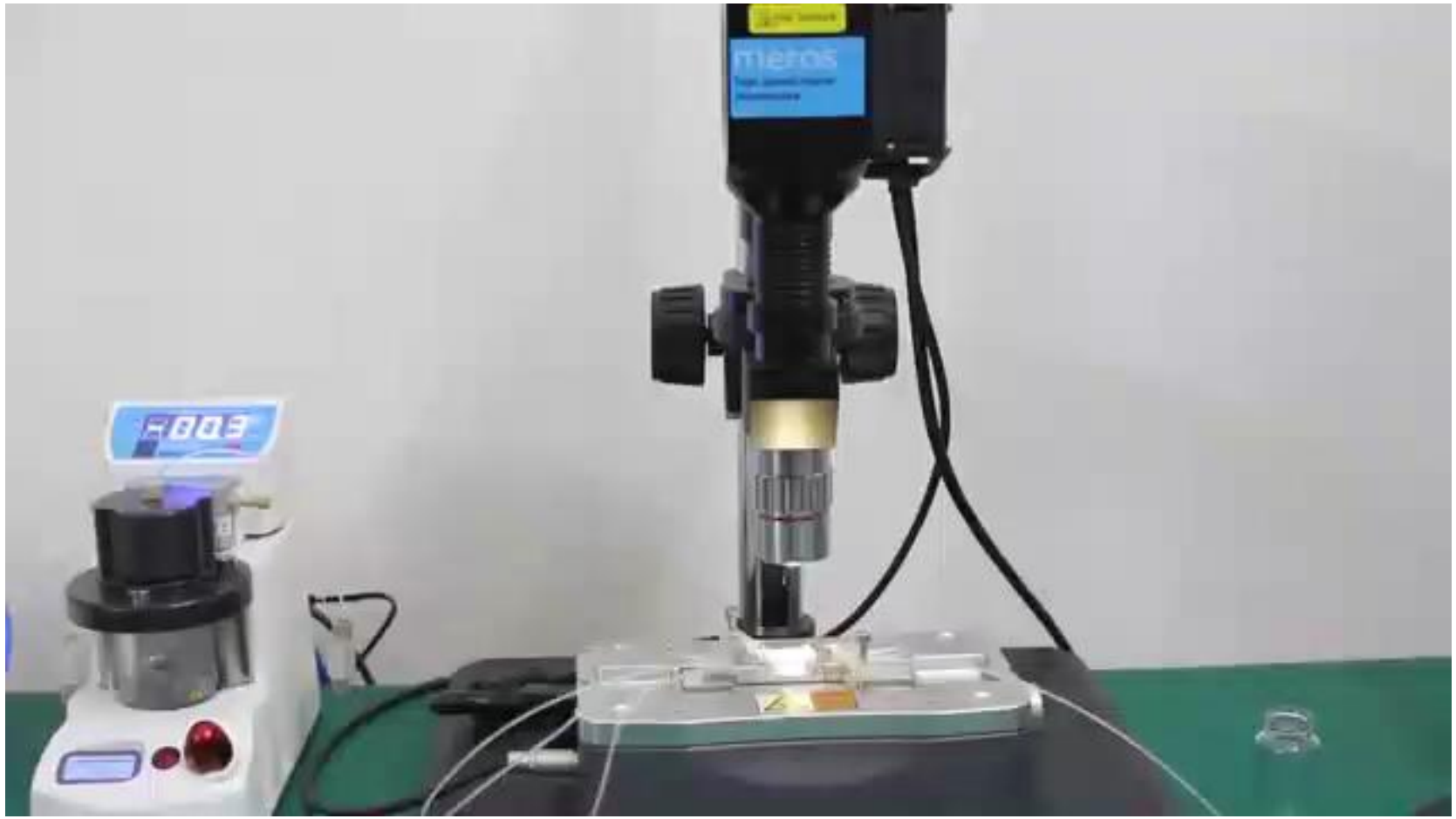
flow-focusing nozzle devices

- Precise control over fluid flow rates
- Continuous, reproducible, and scalable
- Precise compositions, structures, and polydispersities



Polymer microparticles

Microfluidic



Polymer microparticles

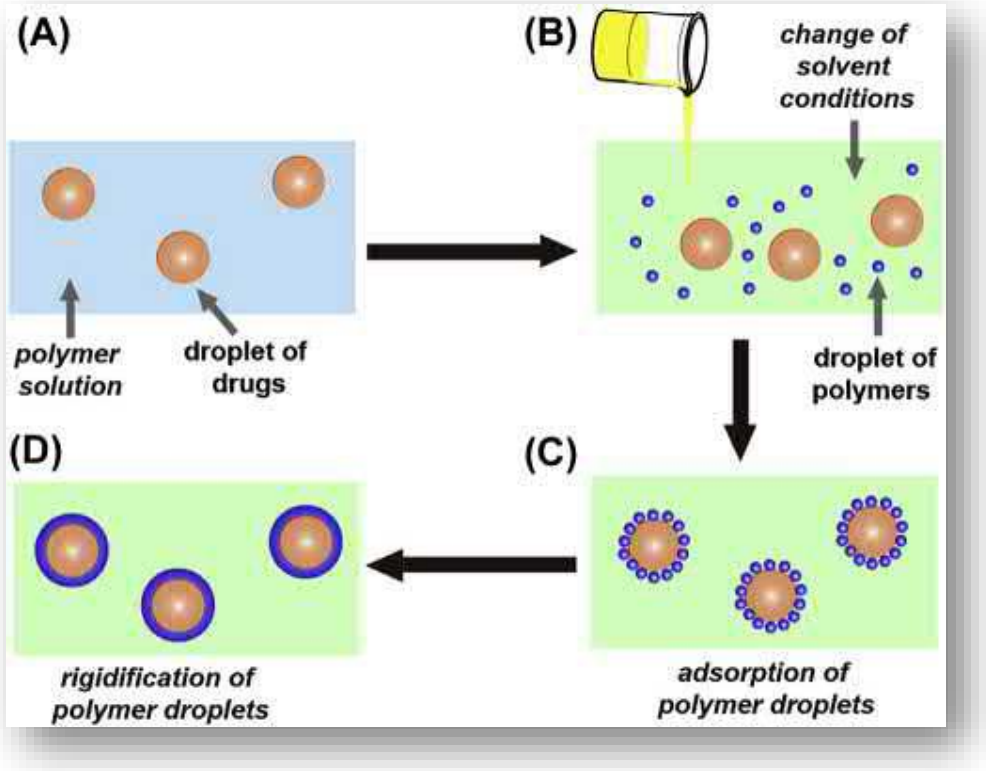
Coacervation phase separation

Exploits changes in polymer solubility

- homogeneous polymer solution that separates into
  - polymer rich phase (coacervate)
  - polymer poor phase (coacervation medium)
- Separation of a liquid phase of coating material
- Coating of the suspended particles

Suitable for temperature sensitive drugs

high loading efficiency



Polymer microparticles

Spray drying

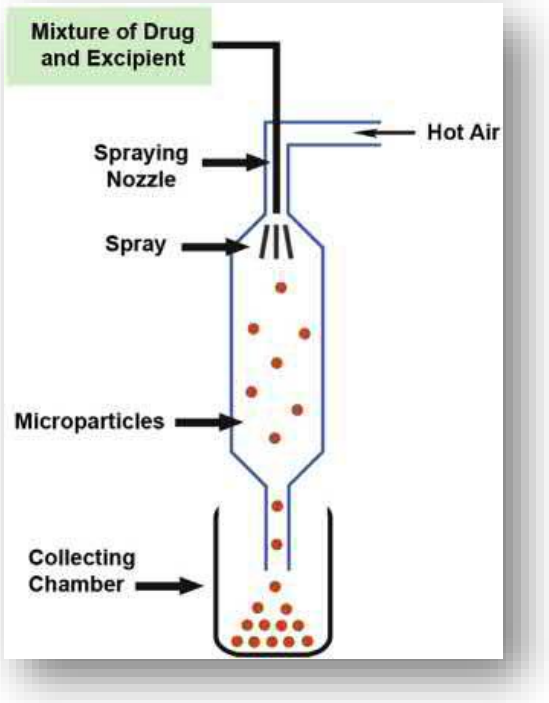
Dispersion in a solvent system

Spraying through a fine nozzle into a chamber

- Temperature control

Solvent evaporation in the chamber

Microparticle formation (1 -100 μm)



High drug loading, no external phase for drug leakage

Mass loss due to aggregation and chamber wall adhesion

Process parameters

- solution viscosity
- nozzle characteristics
- air/solvent flow rate
- pressure.

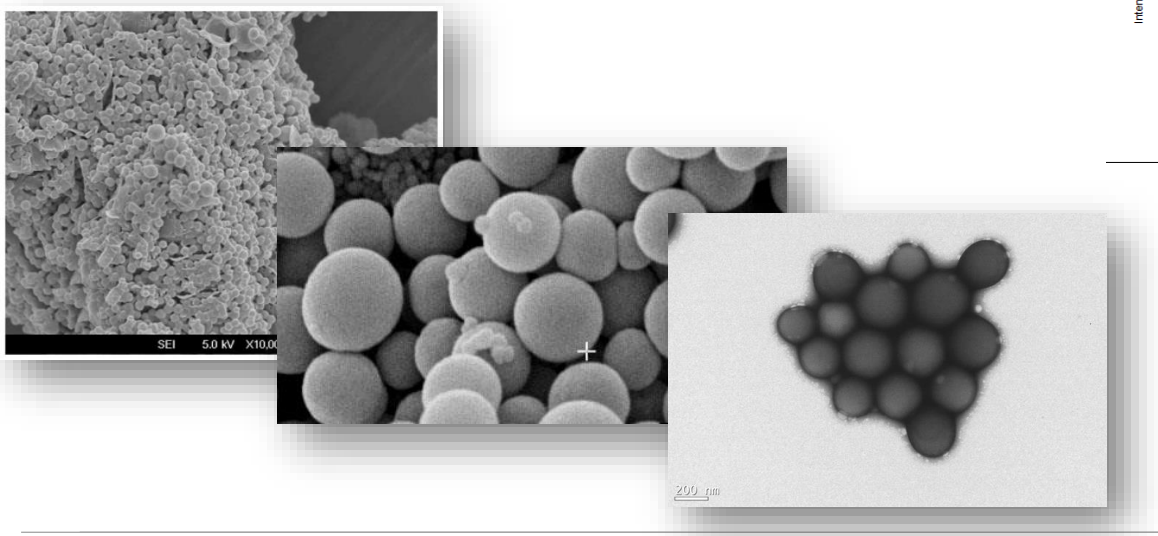
Polymer micro and nanoparticles

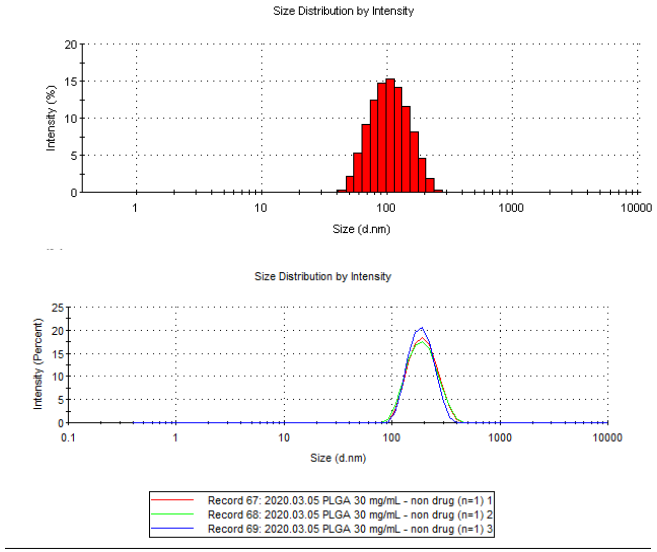
Characterization

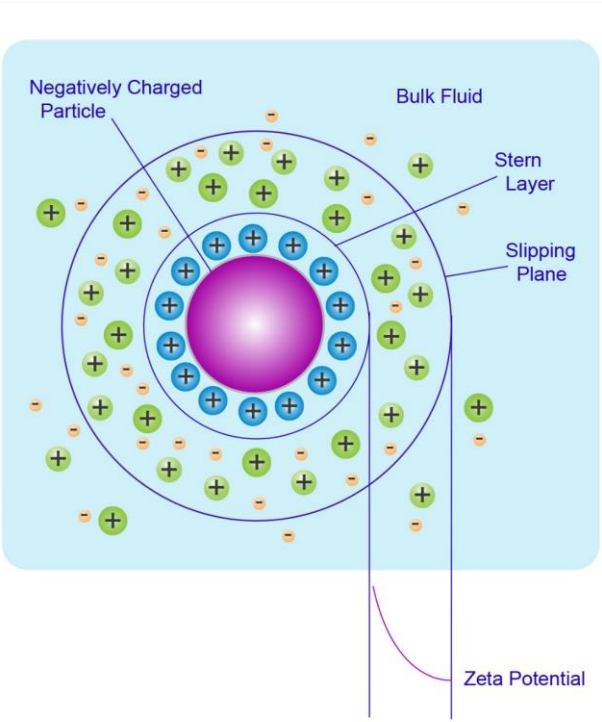
Morphology

Size and polydispersity

Surface charge







MBiomaterials Science, An Introduction to Materials in Medicine, pp 431-451

Polymer micro and nanoparticles

Formulation & Characterization

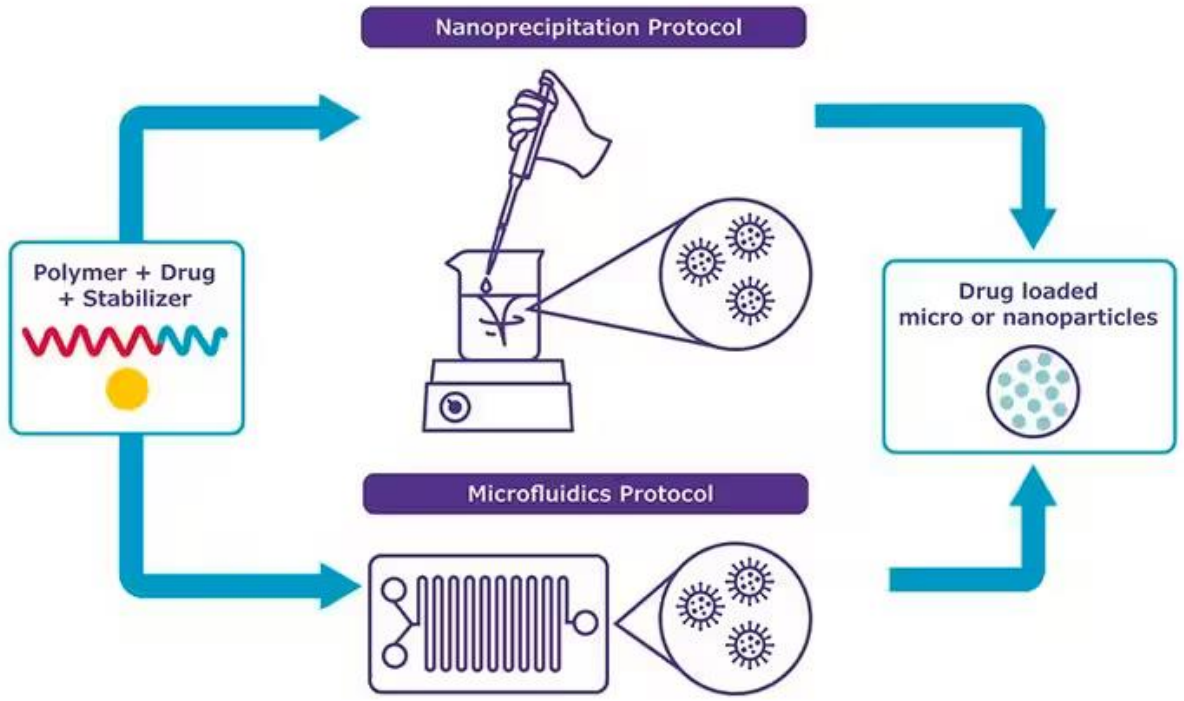
Polymer micro and nanoparticles

Formulation Kit NanoFabTx

https://www.sigmaaldrich.com/FR/fr/products/materials-science/biomedical-materials/drug-delivery-formulation-kits

Polymer micro and nanoparticles

Formulation Kit NanoFabTx



https://www.sigmaaldrich.com/FR/fr/products/materials-science/biomedical-materials/drug-delivery-formulation-kits

Polymer micro and nanoparticles

MERCK

NanoFabTx™

Materials

Materials supplied

Each *NanoFabTx™* PLGA-Nano kit is supplied as follows:

Catalog Number	Quantity
907782	PLGA-Nano (500mg)
907766	Stabilizer-Nano (5g)

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Q&A