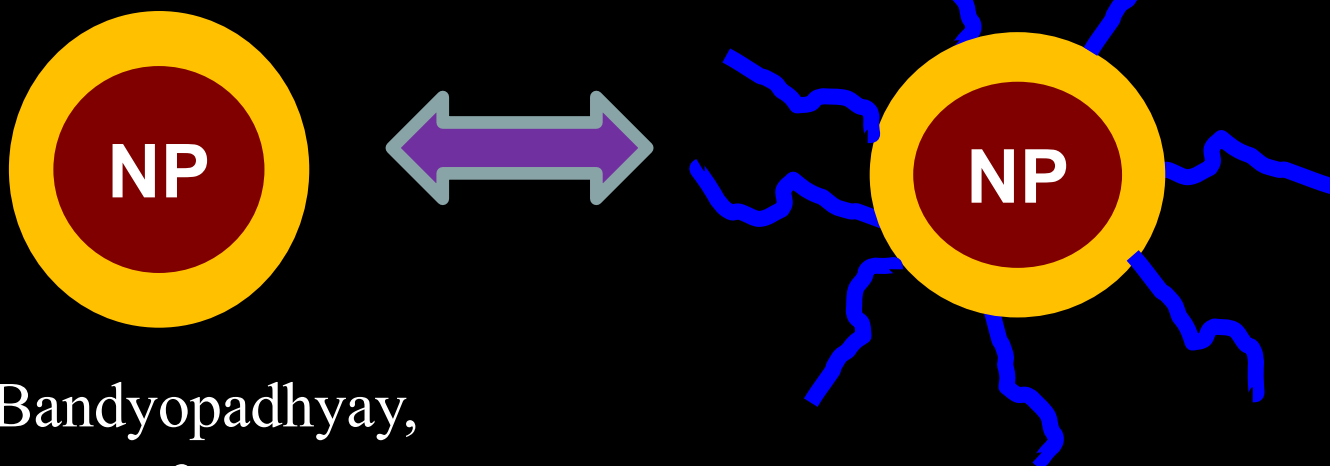


# Synthesis and Functionalisation of Polymer-based NPs



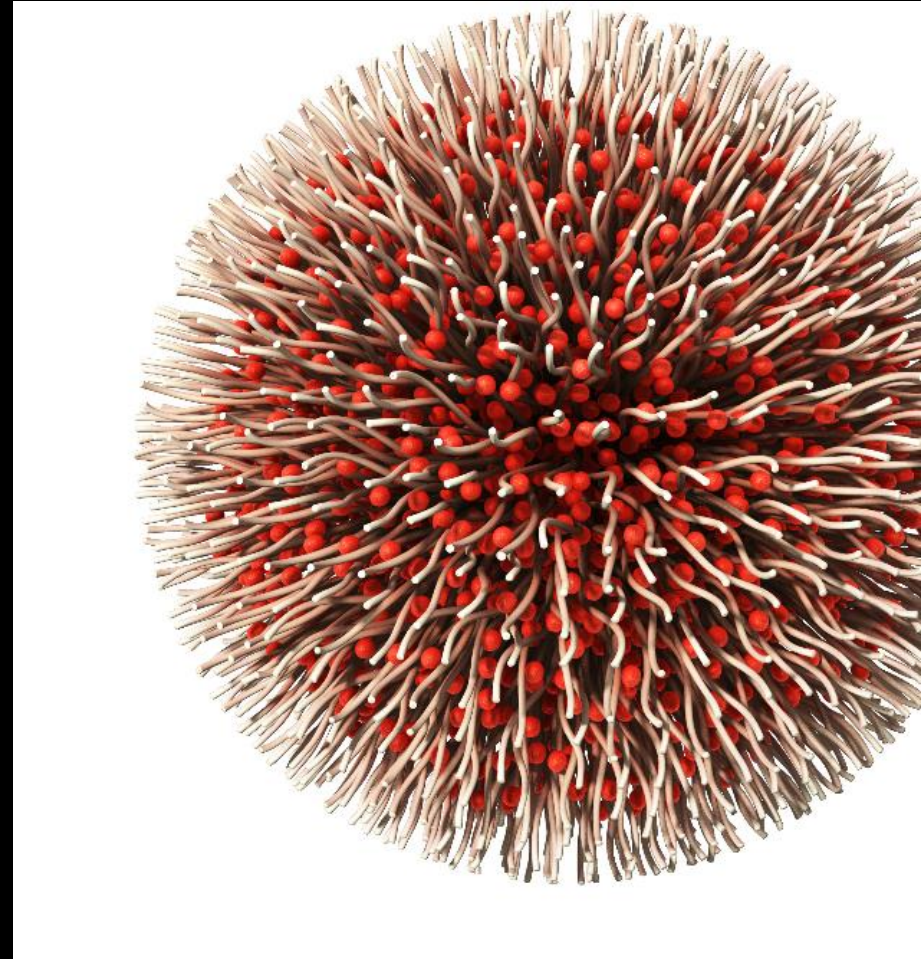
Sulalit Bandyopadhyay,  
Associate Professor,

Department of Chemical Engineering, NTNU

# Topics

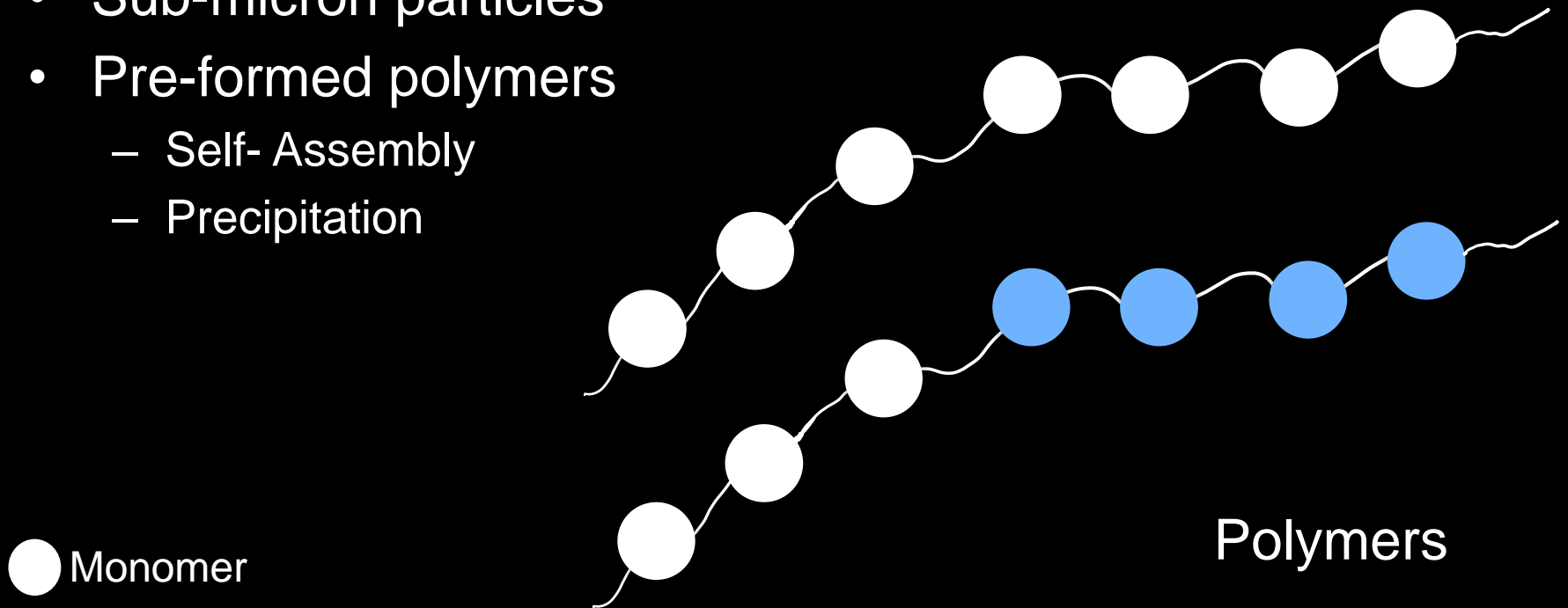
- **Metallic NPs**
  - Synthesis Methods
    - Reduction of Metallic Precursors
    - Thermal Decomposition
    - Colloidal Templating
    - One pot methods
  - Anisotropic NPs
- **Functionalization of NPs**
- **Polymer-based NPs**
  - Nanoprecipitation
  - Flash Nanoprecipitation
  - Precipitation polymerization

# Polymer-based NPs

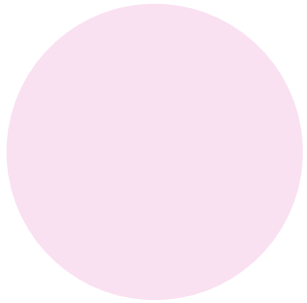


# Polymer-based NPs

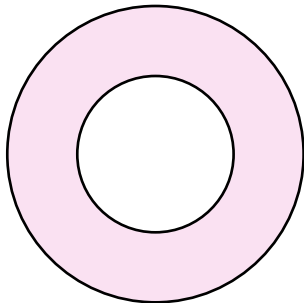
- Sub-micron particles
- Pre-formed polymers
  - Self-Assembly
  - Precipitation



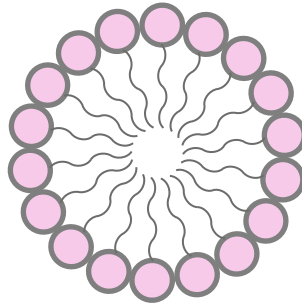
# Classification



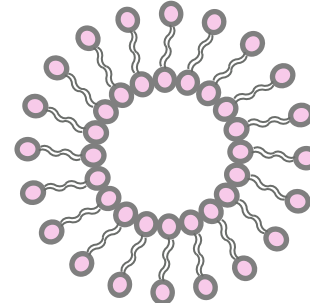
**Nanospheres/ NPs**



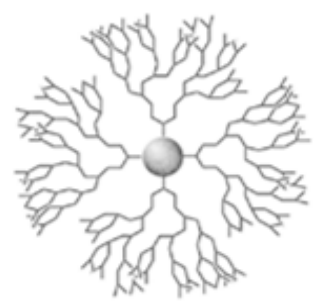
**Nanocapsules**



**Polymeric Micelles**

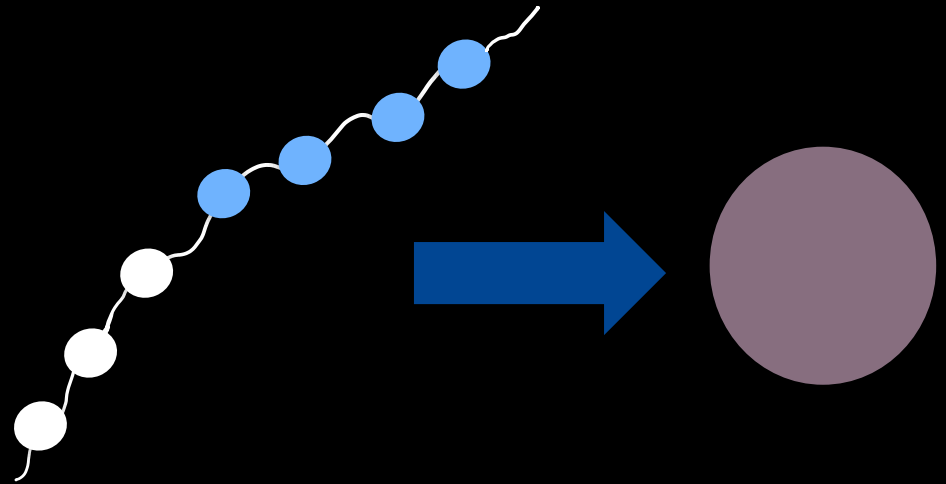


**Polymerosomes**



**Dendrimer**

# Synthesis Methods



# Categories

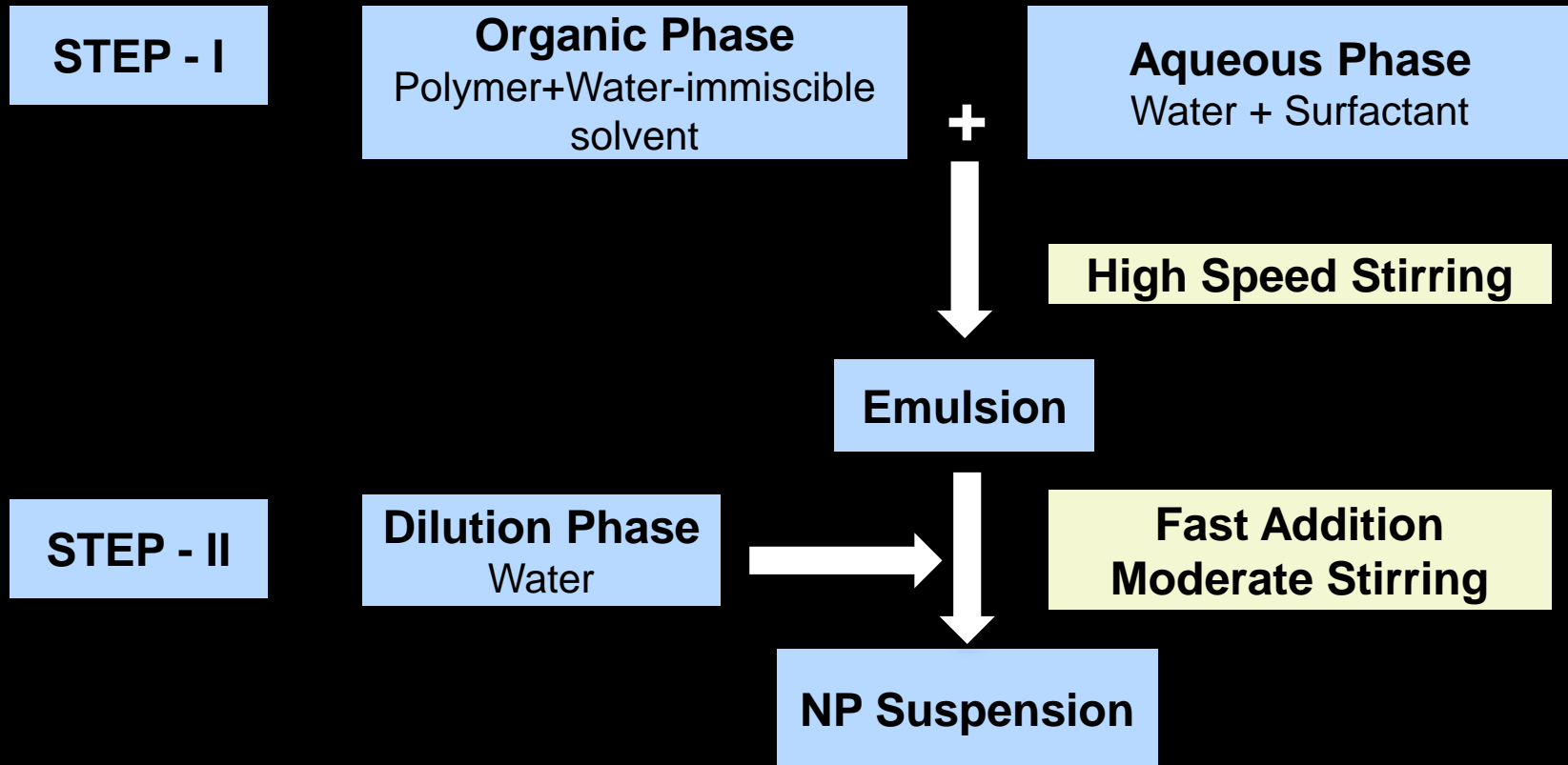
## Emulsion based processes

- 2 Step Process
- Preparation of an emulsion
- Particle formation by precipitation or cross-linking
  
- Eg: Emulsification – Diffusion, Emulsification - Evaporation

## Solvent - Displacement

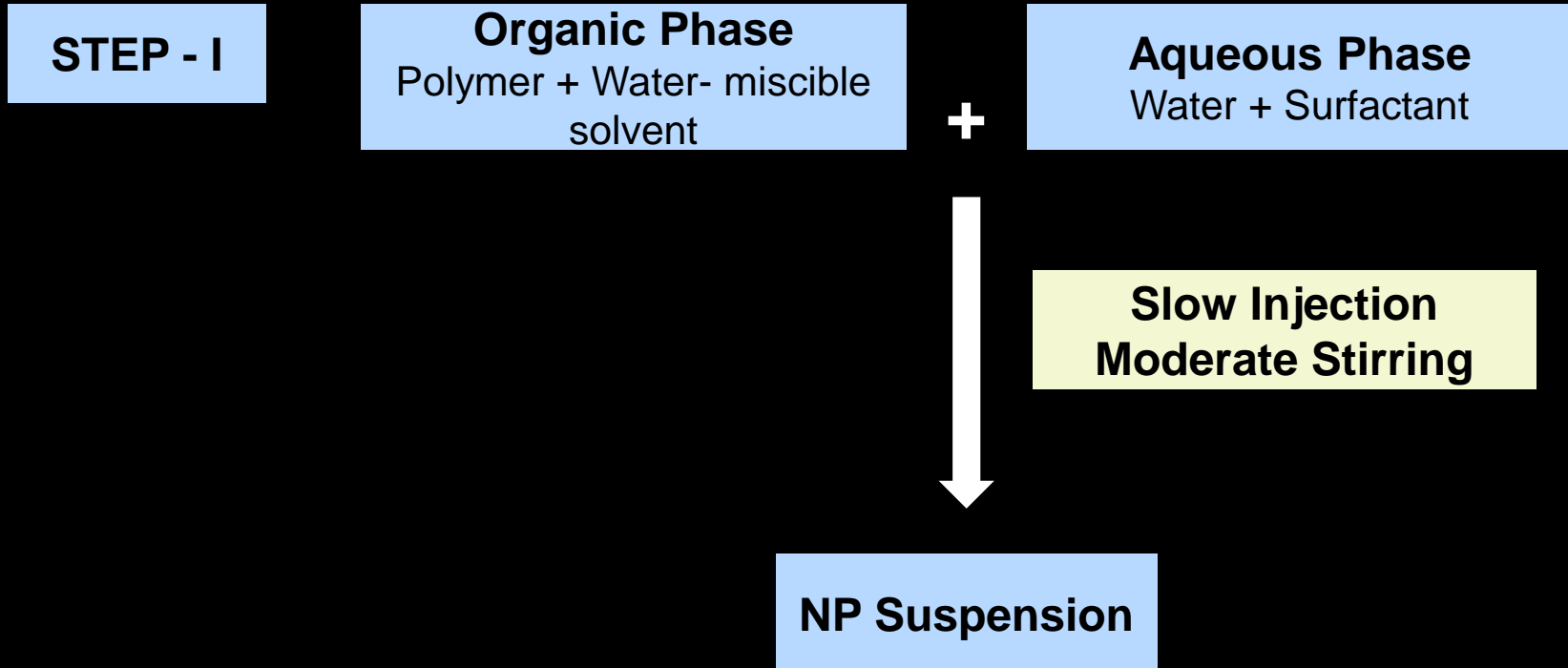
- Single Step Process
- Polymer precipitation or self-assembly or poly-electrolyte complexes
  
- Eg: Nanoprecipitation, layer-by-layer technique

# Emulsification-Diffusion

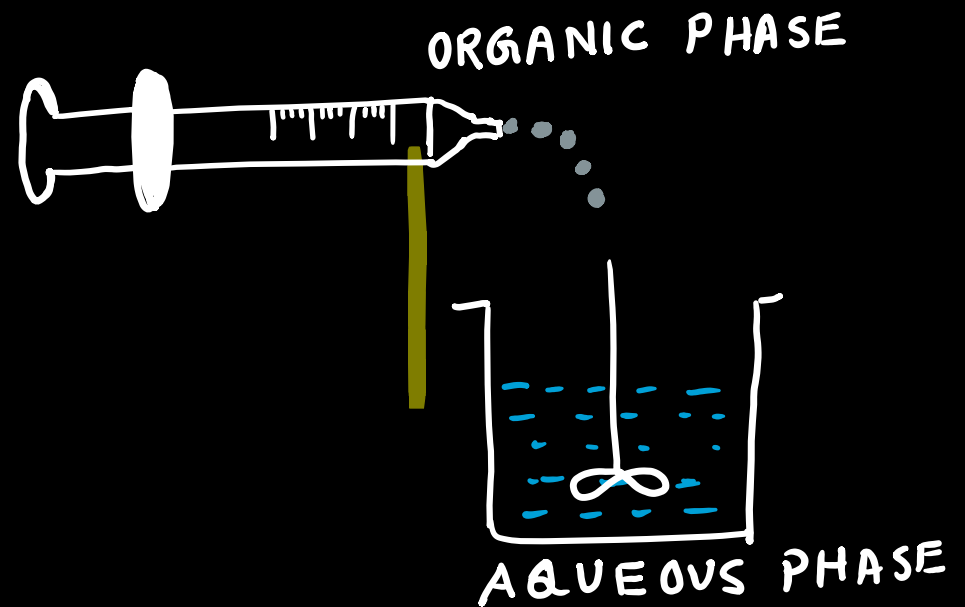




# Solvent Displacement



# Nanoprecipitation



# Process Overview

- Method to synthesize polymeric NPs.
- Components:
  - Solvent; containing polymer
  - Non solvent; containing surfactant
- Organic solvent can be removed by evaporation at ambient temperature or a rotavapour.
- Aqueous phase can be removed using ultracentrifugation or freeze-drying.
- Patented by Fessi *et al.* in 1989.
- Was originally designed to encapsulate hydrophobic drugs, however research has been conducted with hydrophilic drugs.

# Mechanism

## Mechanical Mechanisms

- Gibb's Marangoni Effect
- Interfacial tension driven
  - Variations in interfacial tension at the solvent/non-solvent interface
  - Disturbances in mechanical equilibrium
- Factors:
  - Physico-chemical properties of organic phase
  - Interaction with aqueous medium

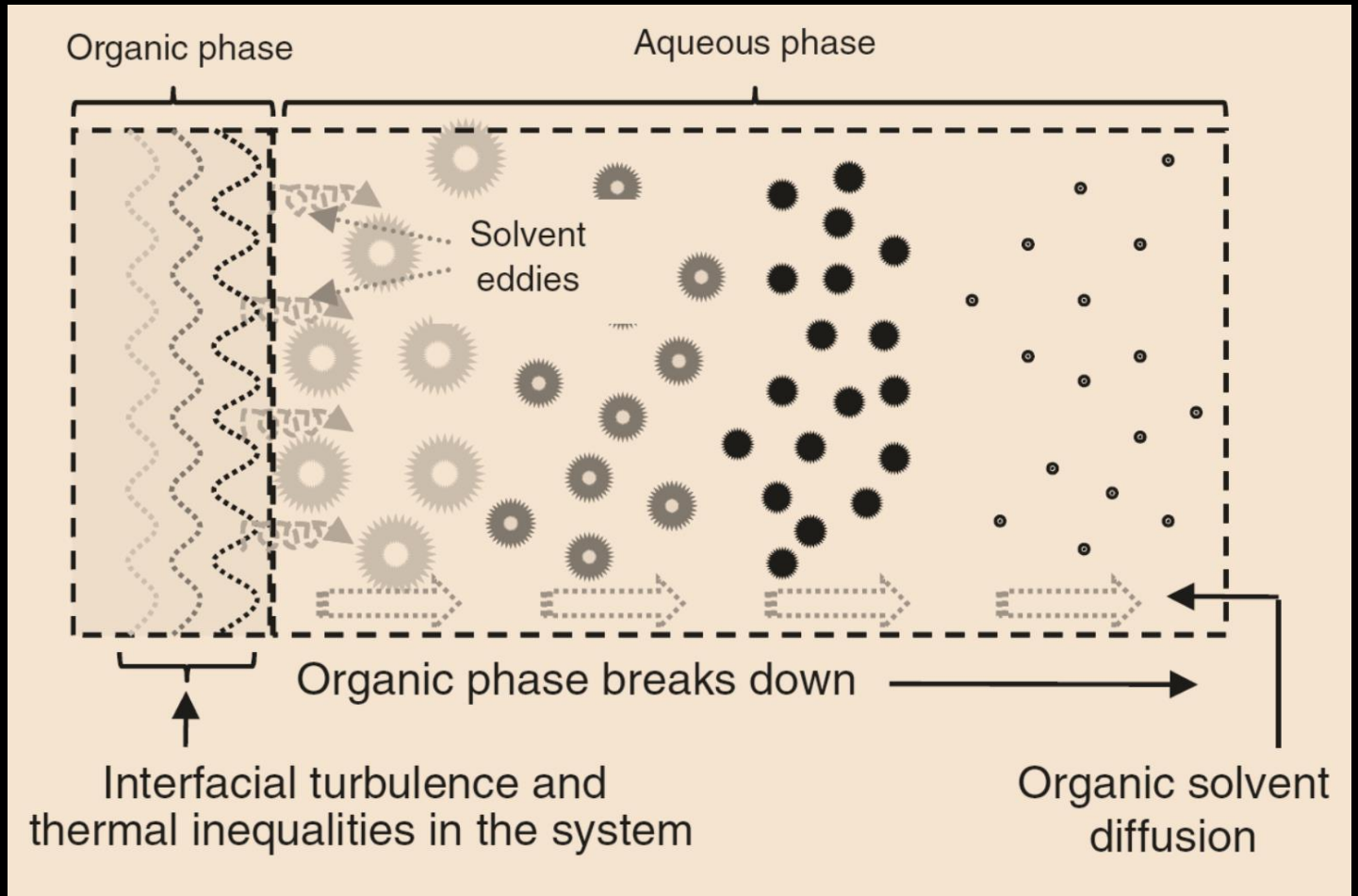
## Chemical Instability

- Supersaturation driven
  - Nucleation and growth
  - Size enlargement
- Factors:
  - Composition of polymer/solvent/non-solvent system
  - Interaction between particles formed
  - Physico-chemical properties of dispersive medium

# Gibb's Marangoni Effect

$$\gamma_{ORG} < \gamma_{AQU}$$

- Interfacial turbulence, thermal inequalities
- Solvent Eddy formation - Interfacial convective flows
- Increasing mass-exchange rate between phases
- Violent spreading (miscible system)
- Organic phase breaks into smaller droplets
- Solvent flows away from low interfacial tension region
- Polymer precipitates



# Gibb's Marangoni Effect

$$Ma = \frac{\Delta\gamma\Delta C}{\eta D_{AB}}$$

$\Delta\gamma$  = rate of change of interfacial tension

$\Delta C$  = concentration gradient

$\eta$  = viscosity of the organic phase

$D_{AB}$  = diffusion coefficient of the organic phase into aqueous phase

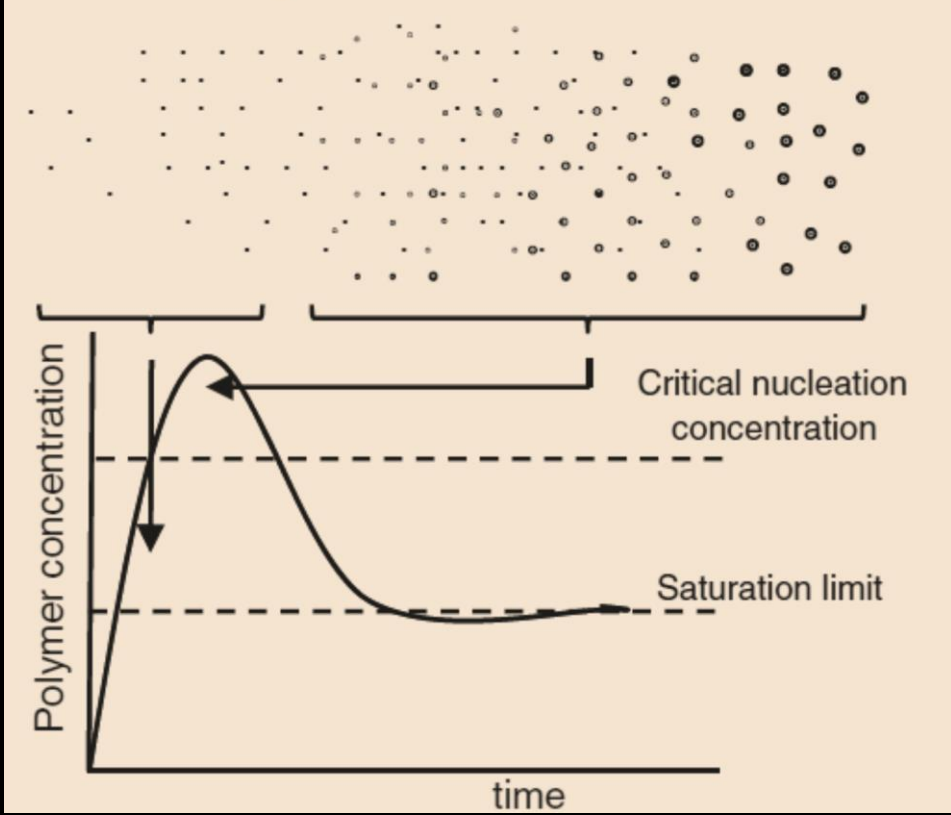
$Ma$  = Marangoni number

# Chemical Instability

- Polymer solution in contact with water
- Solvent diffuses into aqueous phase
- Local S 
$$S = \frac{C_{POLYMER}}{C_{POLYMER}^*}$$
- Nucleation & Growth – further size enlargement
- Blending rate and molecular diffusion are extremely rapid, in comparison to the nucleation rate



# Polymer/solvent/nonsolvent



# Chemical Instability

Nucleation:

$$J = \frac{2D}{d^5} \exp\left(-\frac{16\pi\gamma^3 v^2}{3k_B^3 T^3 [\ln(S)]^2}\right)$$

$J$  = nucleation rate

$D$  = molecular diffusion of the polymer molecule

$d$  = molecular diameter

$k_B$  = Boltzmann constant

$T$  = temperature

$\gamma$  = interfacial tension between already formed particles and the solution

$v$  = polymer molecular volume

$S$  = supersaturation

# Chemical Instability

Growth:

$$G = \frac{2k_m M_w C}{\rho} (S - 1)$$

$G$  = growth rate

$M_w$  = molecular weight of the polymer

$C$  = concentration of the polymer

$k_m$  = mass transfer coefficient

$\rho$  = density of the polymer

Aggregation:

- Size of the particles
- Probability of encounters due to Brownian motion (perikinetic aggregation)
- Probability of encounters due to fluid motion (orthokinetic aggregation).

# Chemical Instability

Aggregation:

**Perikinetic :**

- dynamic viscosity of the dispersive medium
- $T$
- Particle size

**Orthokinetic :**

- Particle size
- Shear rate

# Controlling Size - Steps

- Growing process
- Aggregation phenomena
- Stabilizing agent

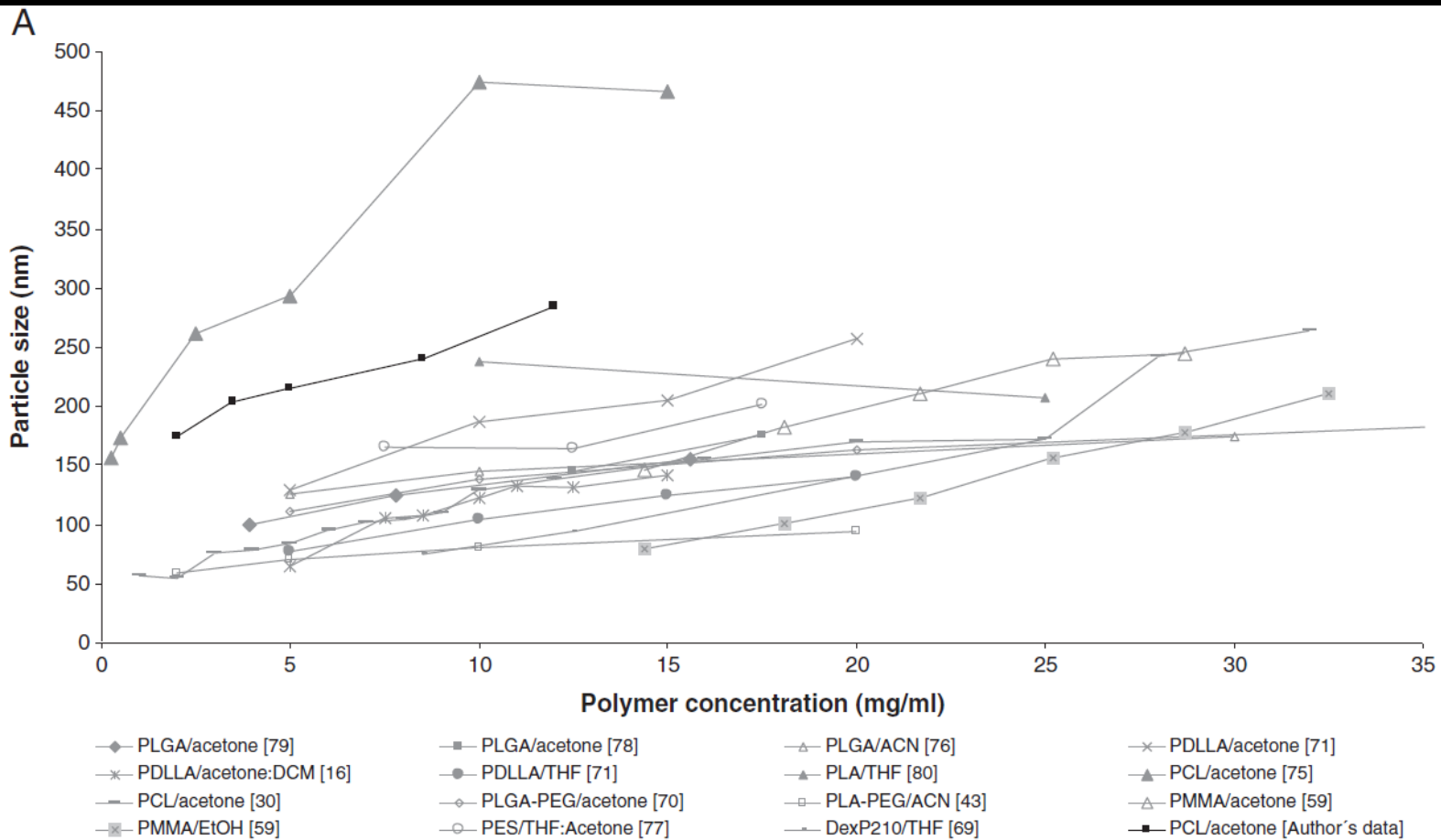
# Controlling Size - Factors

## Operating Variables

- Organic/aqueous phase ratio
- Organic phase addition method
- Stirring system
- Temperature
- Final stirring time

## System Components

- Nature of the polymer
- Polymer concentration
- Nature of the stabilizing agent
- Stabilizing agent concentration
- Nature of the solvent
- Stabilizing agent concentration
- Nature of the solvent



# Size of Polymeric NPs

## Polymer Concentration

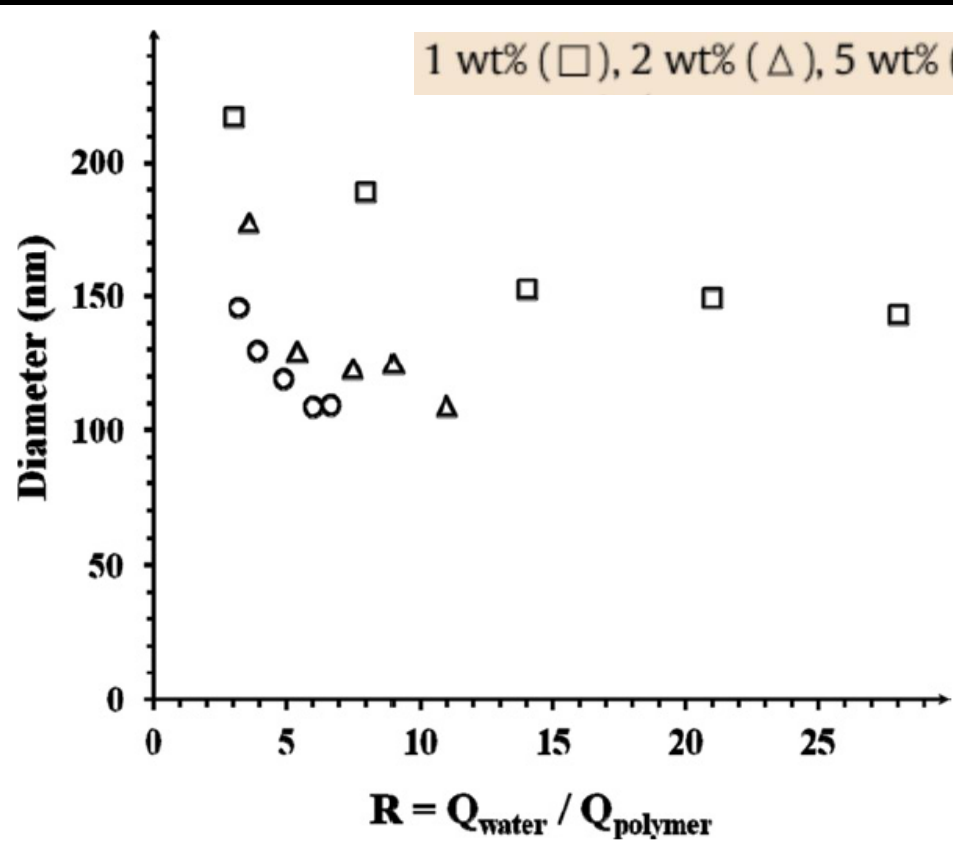
- Size increases with increase in the polymer concentration

## Why?

- No. of polymer chains increase per volume, increases  $J$  – more no. of nuclei
- Higher polymer-polymer interaction/ association
- Increase in viscosity of organic phase
  - Resistance to mass transfer
  - Decrease in diffusion rate of organic phase into aqueous phase

$$J = \frac{2D}{d^5} \exp\left(-\frac{16\pi\gamma^3 v^2}{3k_B^3 T^3 [\ln(S)]^2}\right)$$





R: Proportion of non-solvent to solvent

# Size of Polymeric NPs

## Polymer Concentration and R

- Increasing R, decreases particle size
- At a certain R, size decreases with increasing polymer concn.

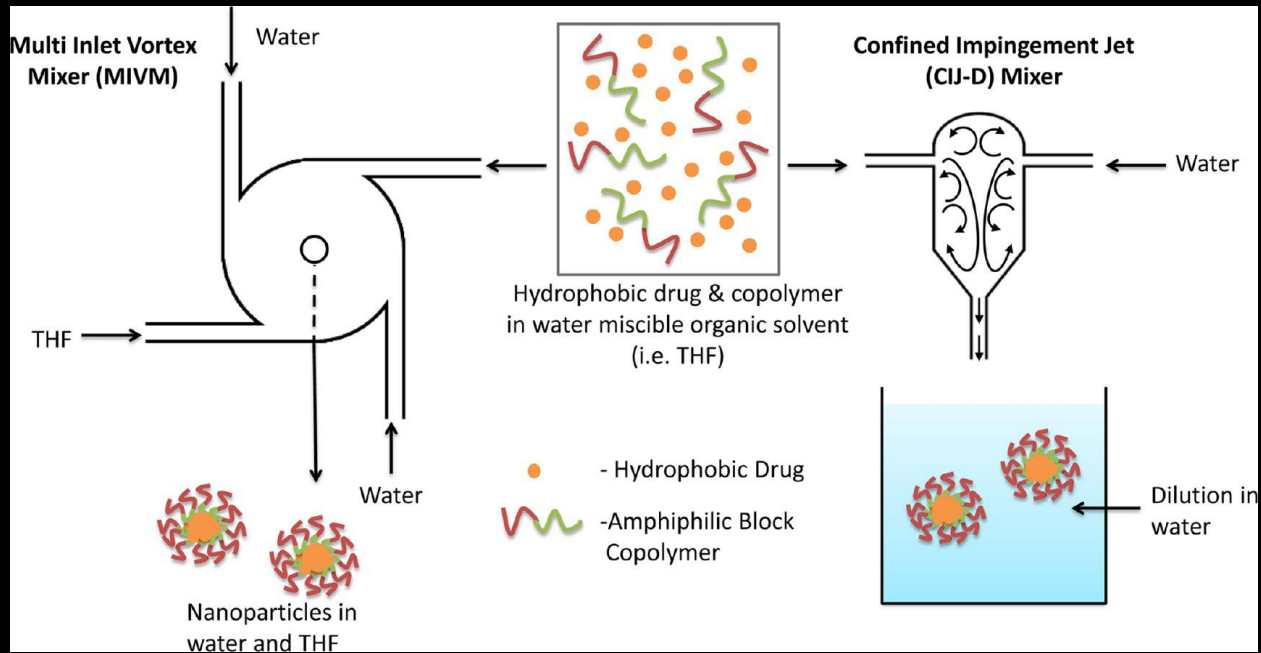
## Why?

- High R, high S – smaller particle size (Chemical Instability)
- High R, potential interface increases, more droplets formed during phase separation. Local concentration of the polymer decreases, smaller NPs (Mechanical Mechanisms)

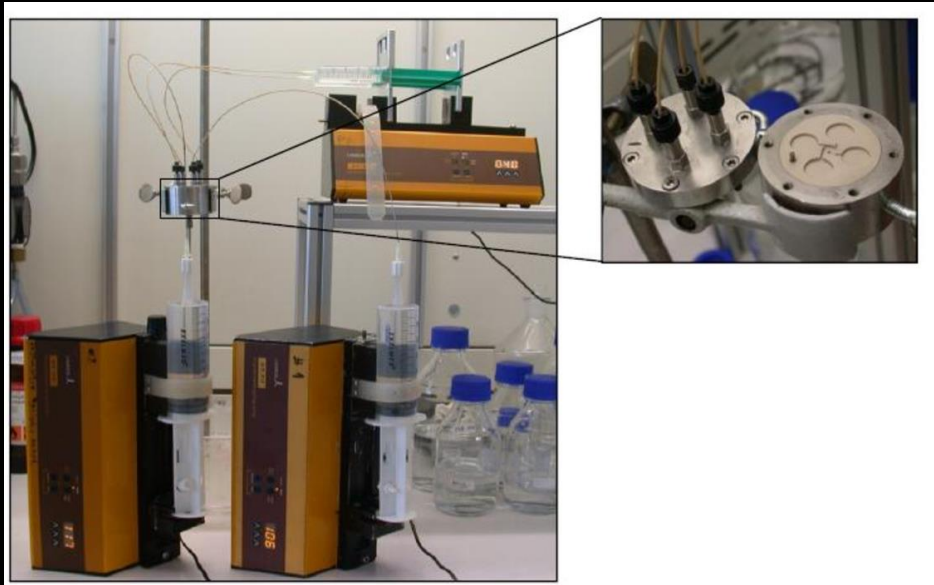
# Flash Nanoprecipitation

- Rapid micromixing
  - Solvent , anti-solvent mix at a time scale shorter than formation of NPs
- Creation of high supersaturation
- Leads to precipitation of dissolved hydrophobic components
- Mixing time must be less than induction time for polymer aggregation and induction time for nucleation & growth.
- Kinetically controlled process
- Narrow particle size distribution

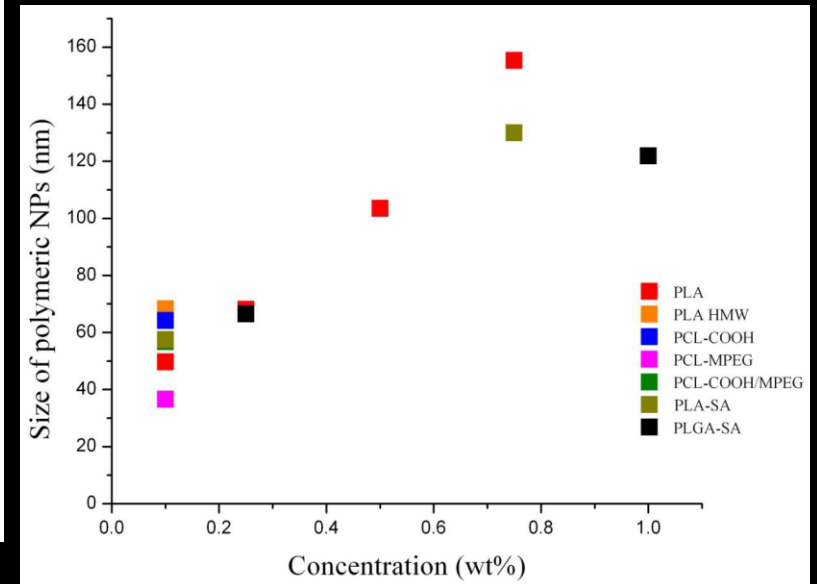
## MIVM Setup



## MIVM Setup



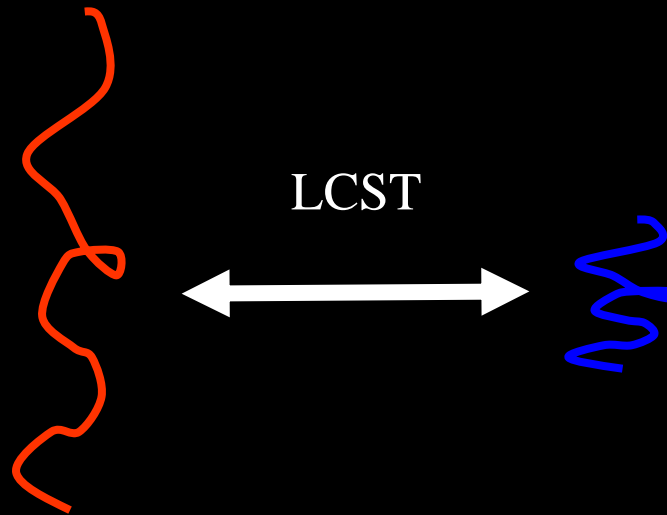
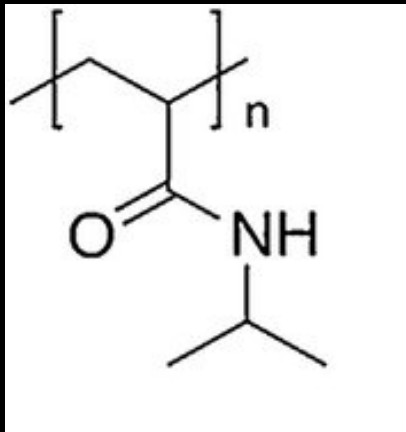
Multi Inlet Vortex Mixer (MIVM) setup for Flash Nanoprecipitation.



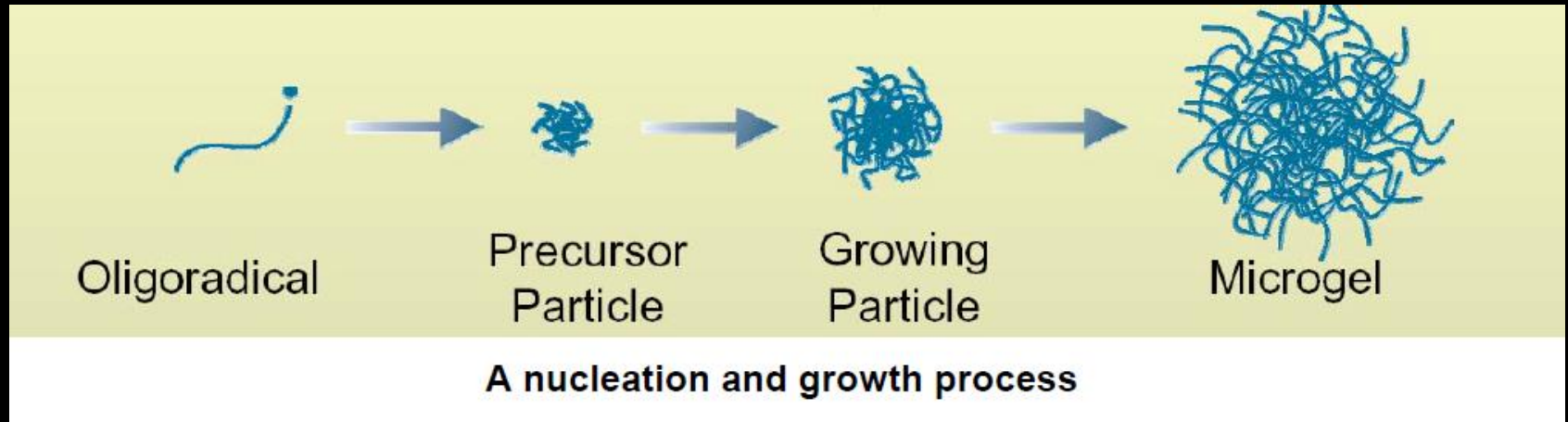
Hydrodynamic sizes of polymeric NPs as a function of concentration.

# Precipitation Polymerization

- Polymers like Poly(N-isopropyl acrylamide) (PNIPAm) dissolved in water undergo a coil-to-globule transition at temperatures exceeding its lower critical solution temperature (LCST) ( $\sim 32^{\circ}\text{C}$ )
- The LCST/cloud point can be tuned by altering the composition of a PNIPAm-containing block copolymer
- LCST also affected by the mobility of the PNIPAm chains

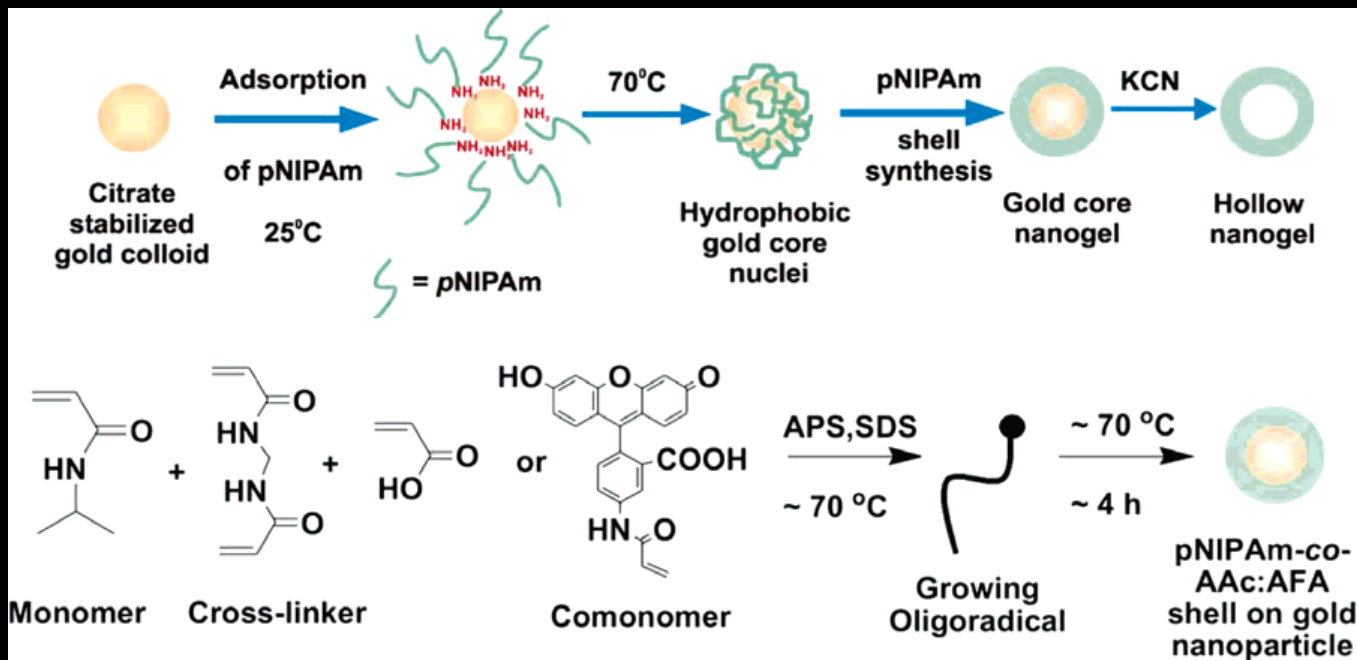


## Mechanism



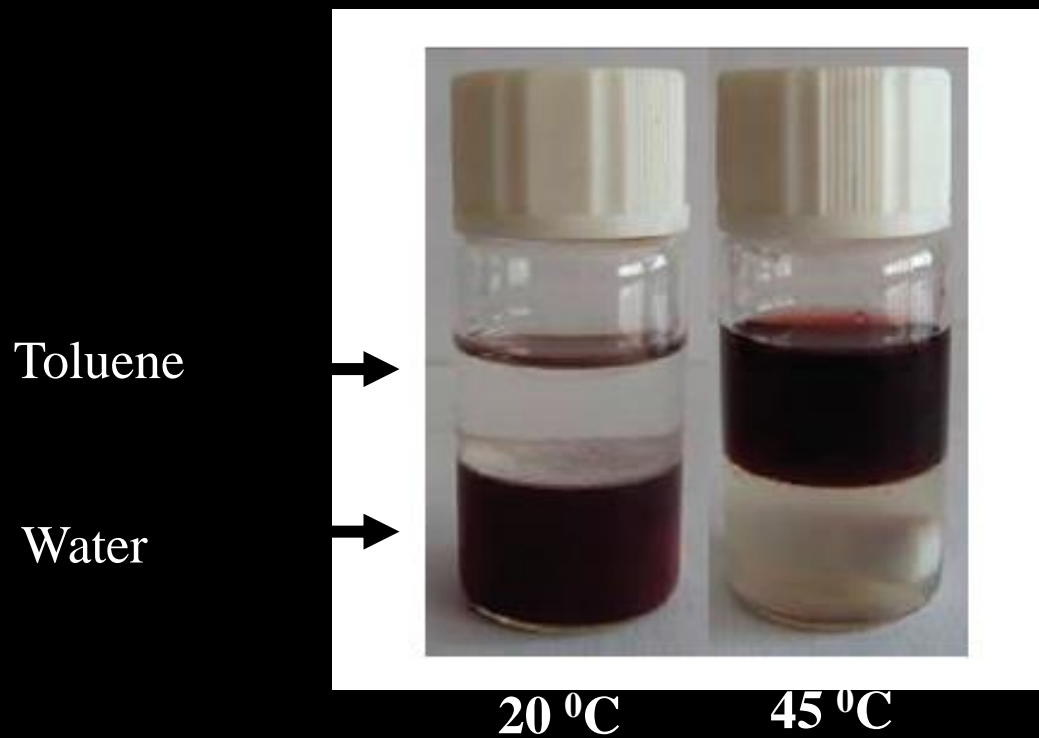
- Monomer + cross linking agent in water
- $T > LCST$
- Homogeneous nucleation on collapsed oligomers
- Oligomer and monomer addition, aggregation
- Low PDI, control of charge, size, cross-link density

## Au-pNIPAm





## Phase Transfer



Polarity and phase behavior of the Au NP constructs tunable via temperature

# Reader's Digest Version:

- Nanoprecipitation & Flash Nanoprecipitation
  - Fundamentals
  - Mechanisms
  - Parameters
- Nanogels
  - Mechanism
  - Functionalization