Polymeric Nanomaterials – An Overview

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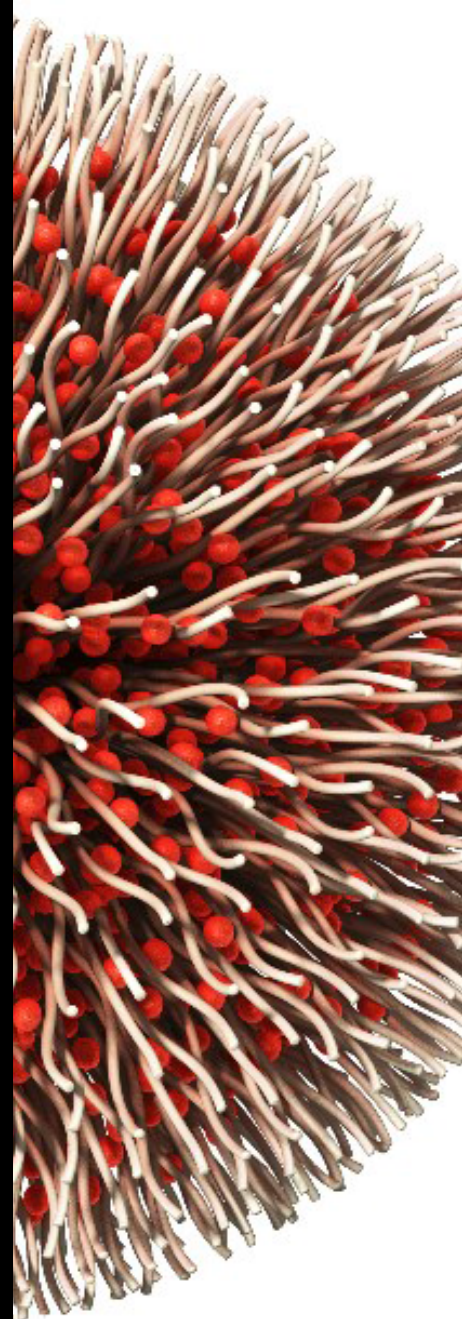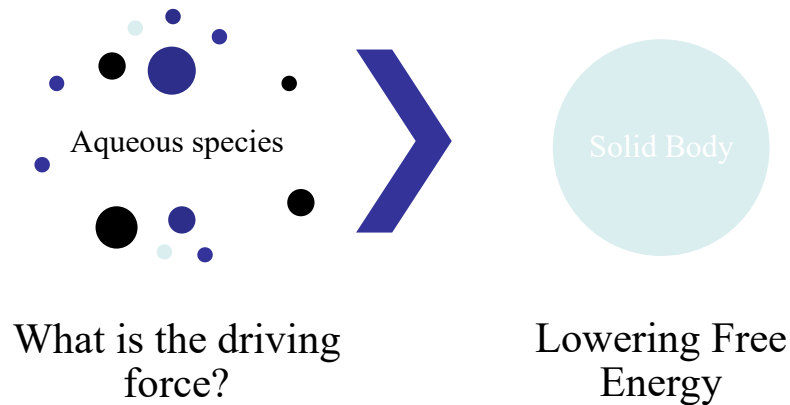
Overview

- **Classical Nucleation Theory**
  - Nucleation
  - Growth
  - Size Control

- **Synthesis of Polymeric NPs**
  - Nanoprecipitation
  - Flash Nanoprecipitation
  - Precipitation polymerization

Classical Nucleation Theory

Crystallization From Solution

Aqueous species

Solid Body

What is the driving
force?

Lowering Free
Energy

Crystallization is a phase transition process during which matter is transformed from a *high free energy*, disordered state to a crystal phase characterized by the regular arrangement of its building units to a *low free energy* state.

Solubility & Supersaturation

- A **saturated solution** is in thermodynamic equilibrium with the solid phase at a specified $T > c = c^*$

- Solutions where $c > c^*$ can be prepared (exm: by slow cooling), such solutions are called **supersaturated**

- The state of supersaturation is essential for all crystallization operations!!
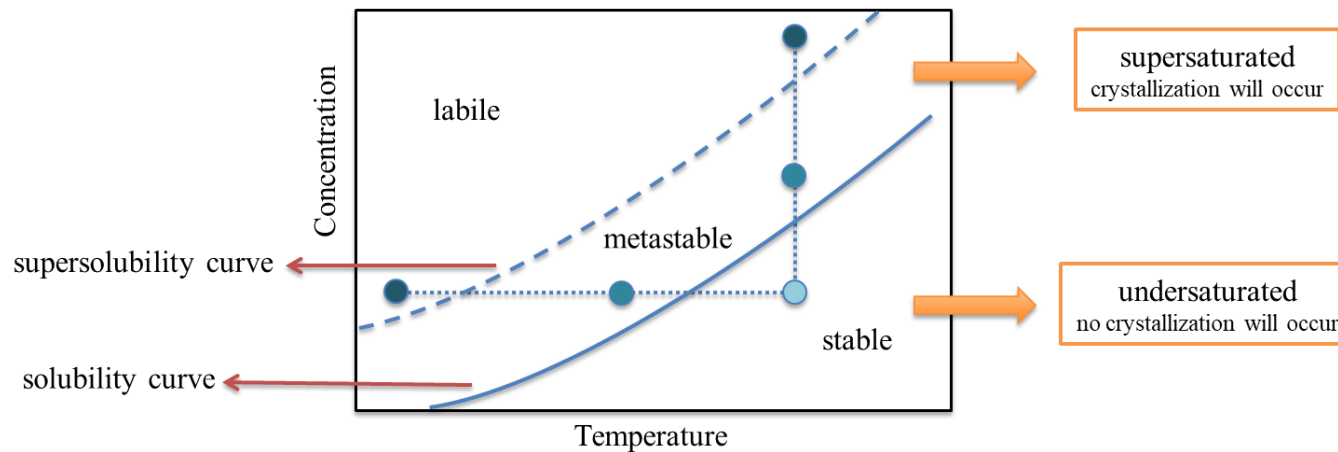

Stable zone: undersaturated- crystallization is impossible

Metastable zone: supersaturated- spontaneous crystallization is probable

Labile zone: supersaturated- uncontrolled spontaneous crystallization

Nucleation

- First step in the formation of the new phase

- According to CNT, nuclei form via the dynamic and stochastic association of monomeric units that overcome a free energy barrier at a critical size and result in a phase separation in the system.
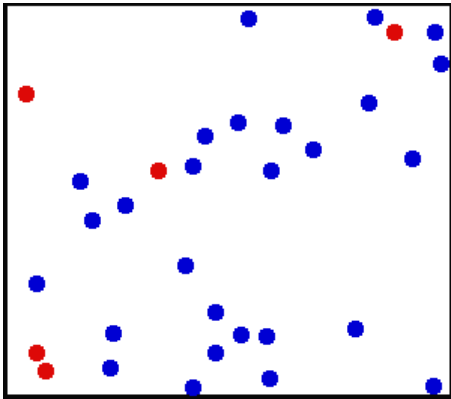
- Stochastic process

- Brownian motion

- Ions/molecules come together and apart until the formation of stable nucleus

Types of Nucleation
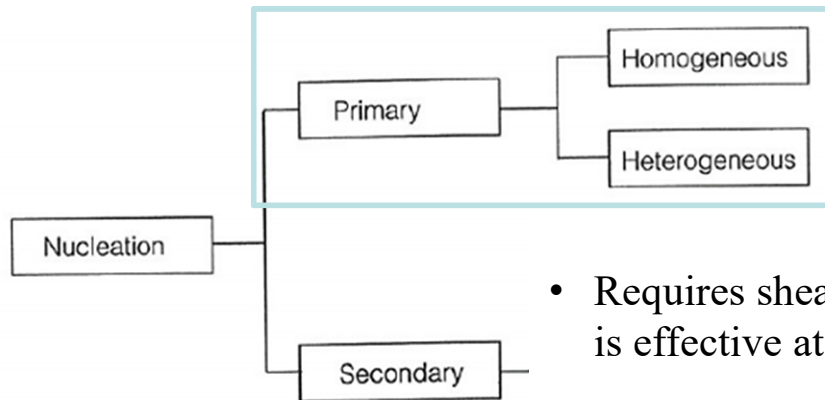
- Requires shear force to be active on particles that is effective at micron size range.

- Negligible for nanoparticle formation.

Primary Homogeneous Nucleation

A crystal forms via ***formation of a stable nucleus*** with a critical size where its bulk energy balances the energetic costs of creating a surface; and subsequently grows via ***monomer-by-monomer attachment of its building units***, that can be atoms, molecules or ions.
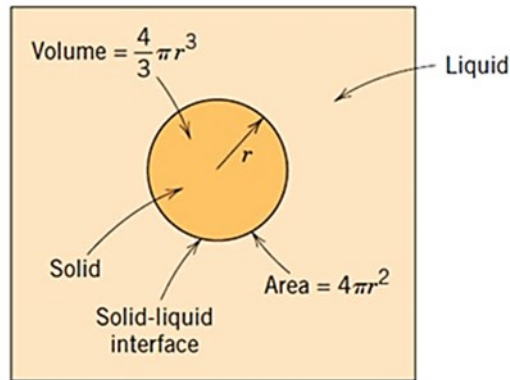
$$\Delta G = \Delta G_V + \Delta G_S$$
$$\Delta G = \Delta G_v V + \gamma A$$

(-)   (+)

Primary Homogeneous Nucleation

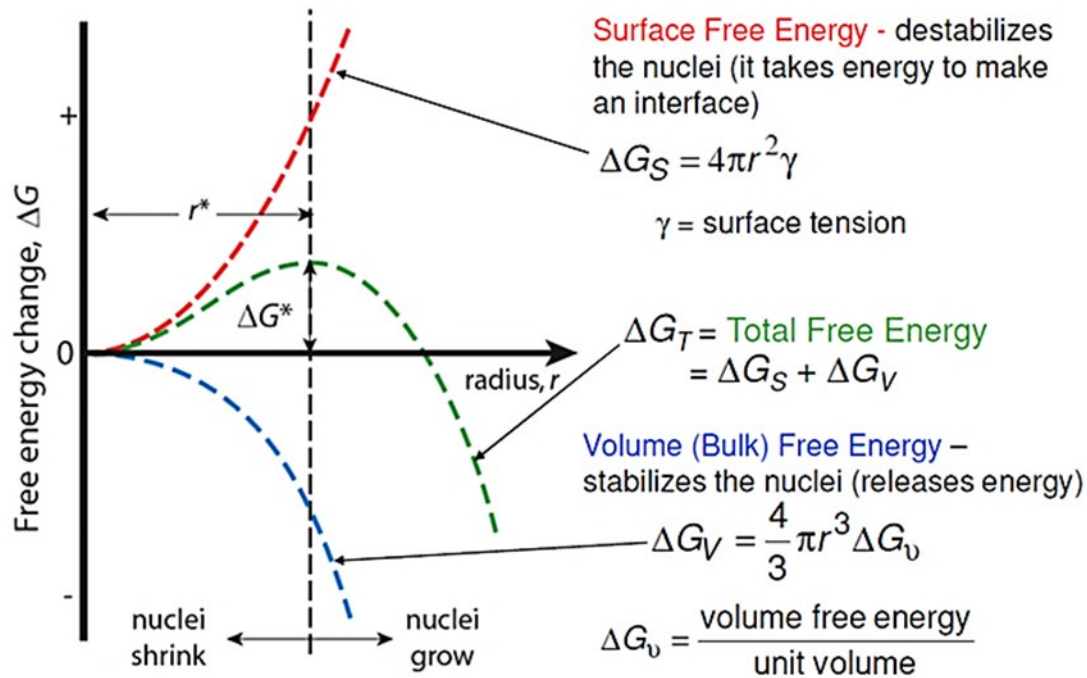Surface Free Energy - destabilizes the nuclei (it takes energy to make an interface)

$$\Delta G_S = 4\pi r^2 \gamma$$

γ = surface tension

ΔG_T = Total Free Energy
$$= \Delta G_S + \Delta G_V$$

Volume (Bulk) Free Energy – stabilizes the nuclei (releases energy)

$$\Delta G_V = \frac{4}{3}\pi r^3 \Delta G_\upsilon$$

$$\Delta G_\upsilon = \frac{\text{volume free energy}}{\text{unit volume}}$$

r^* = critical nucleus: for $r < r^*$ nuclei shrink; for $r > r^*$ nuclei grow (to reduce energy)

Primary Homogeneous Nucleation

- The nucleation rate, J, can be expressed as an Arrhenius reaction equation, commonly used for thermally activated processes

$$J = A\exp\left(\frac{-\Delta G^*}{kT}\right)$$

$$J = A\exp\left[-\frac{16\pi v_m^{\,2}\gamma^3}{3\upsilon^2\left(kT\right)^3\left(\ln S\right)^2}\right]$$

The pre-exponential factor A
- deals with the kinetic factors of nucleation

$$A = zf^*C_0$$

Zeldovich factor

corrects for the fraction of critical size nuclei that dissolve rather than grow

concentration of nucleation sites

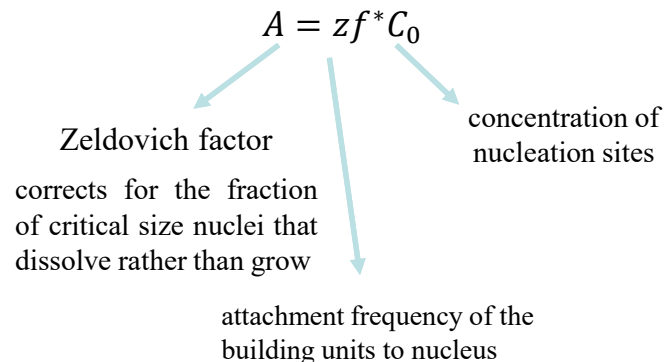attachment frequency of the building units to nucleus

Effecting variables: γ, T, S

Kinetic Factor

- The energy barrier for homogeneous nucleation is usually too high to enable precipitation (i.e. critical radius is too large).
- Thus, in practice primary homogeneous nucleation almost never occurs!

D. Kashchiev, G. M. van Rosmalen: **Review: Nucleation in solutions revisited (2003)**
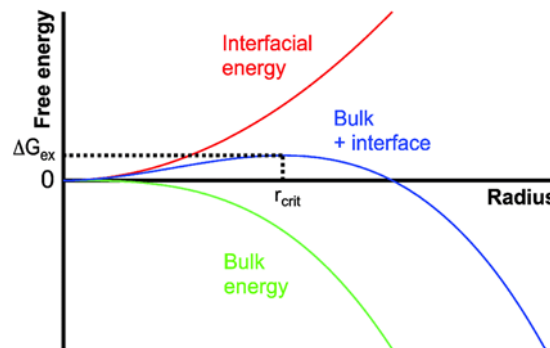
Ostwald's Rule of Stages

- Thermodynamically metastable phases associated with *lower energy barriers of formation* can initially appear in a supersaturated system as a *coaction of thermodynamic and kinetic factors*
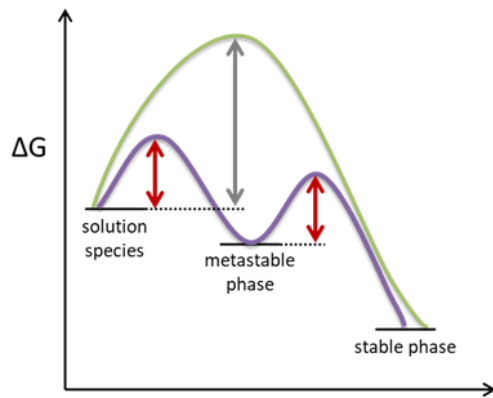
metastable phase -> higher solubility -> lower bulk free energy

lower interfacial energy

kinetically favorable

- Given the sufficient time and the free energy of activation, they eventually transform into the more stable phase

$$\Delta G = G_{stable} - G_{metastable} < 0$$

- The driving force for this transformation is the minimization of the total free energy of the system

Size Enlargement

- Enlargement of crystalline particles in solution is described by two processes according to the classical theory:

  i. crystal growth – monomer addition

  ii. agglomeration – crystal growth during contact which forms a bridge between two crystals

- The driving force for crystal growth is the lower chemical potential of the growth units as constituents of the solid, in equilibrium with its solution, than as solution species

- Thus, the activity based supersaturation can be defined in the same way for both processes and used as a measure of the driving force:

$$S = \left(\frac{IAP}{K_{sp,a}} \right)^{1/v}$$

Size Enlargement

- Although the fundamental driving force for nucleation and growth processes is the same, they follow different energy landscapes.
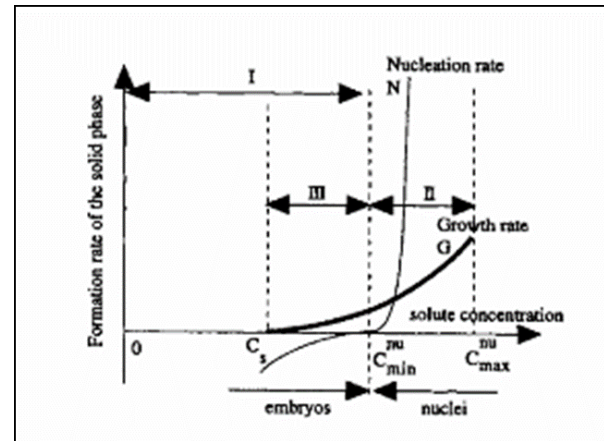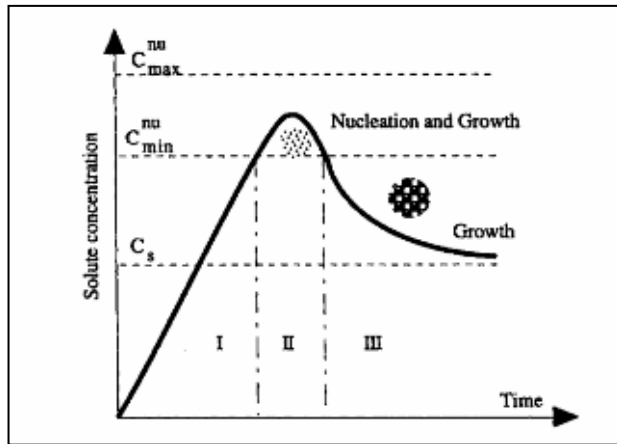

- When the activity/concentration of the solute is reduced below the value required for nucleation, only growth will be responsible for the relaxation of the supersaturated system towards $\Delta\mu = 0$ at $S = 1$.

Growth Rate

Growth rate law: $R = k(S - 1)^g$

Diffusion controlled	
Rough growth	**g=1**
Reaction controlled	
Spiral growth	**g=2**
Polynuclear growth	**g > 2**

- Experimental determination of the growth kinetics supported by microscopic examination of crystals often allows the determination of the prevailing growth mechanism.
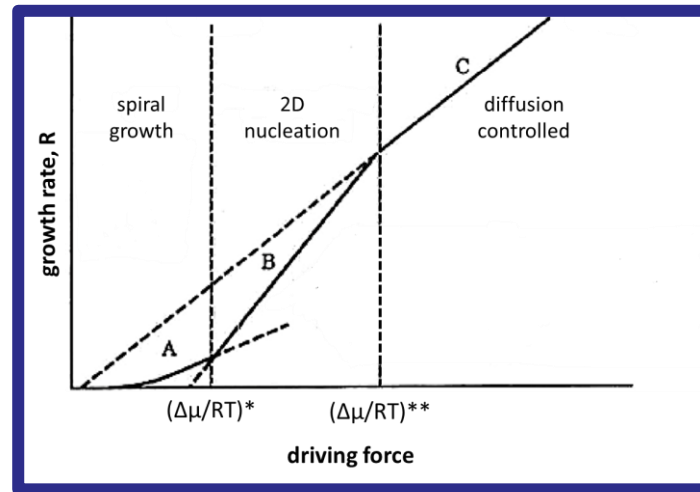
- Whichever the prevailing growth mechanism, the constant, k, is proportional to the solute concentration, i.e., soluble compounds grow faster than slightly soluble ones

Teng, H. H. et. al; *Geochimica et Cosmochimica Acta*, 64, **2000**, 2255-2264.

Particle Size and Size Distribution

Uniform Size Distribution

Nucleation Stage

For the synthesis of NPs with uniform size distribution, it is best if all nuclei are formed at the same time.

↓

When formed under the same conditions, all nuclei would have the same or similar size

↓

In addition, they will all have the same subsequent growth

Growth Stage

- The size distribution of particles can be further altered during the growth process

- Different growth mechanisms exert dissimilar outcomes on the size distribution in accordance with the correlation between the growth rate and the particle size

The formation of uniformly sized nanoparticles can be achieved if both processes are appropriately controlled.

Particle Size and Size Distribution

Ostwald Ripening

- When solid particles are dispersed in their own saturated solution **(aging)** there is a tendency for the smaller particles to dissolve and the solute to be deposited on the larger particles

- Particle size distribution ultimately changes towards that of a monosized dispersion
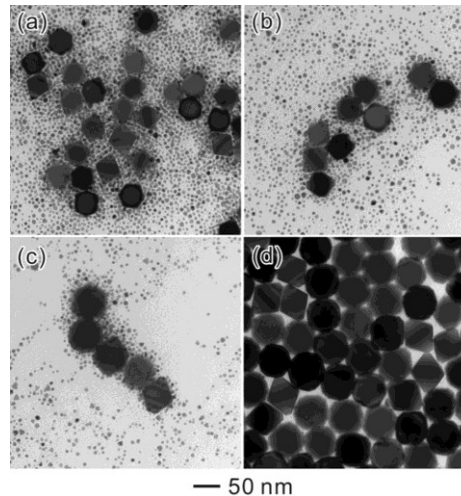
TEM images of Pd octahedra obtained after ripening for different periods of time: (a) 6 h, (b) 24 h, (c) 48 h, and (d) 72 h.
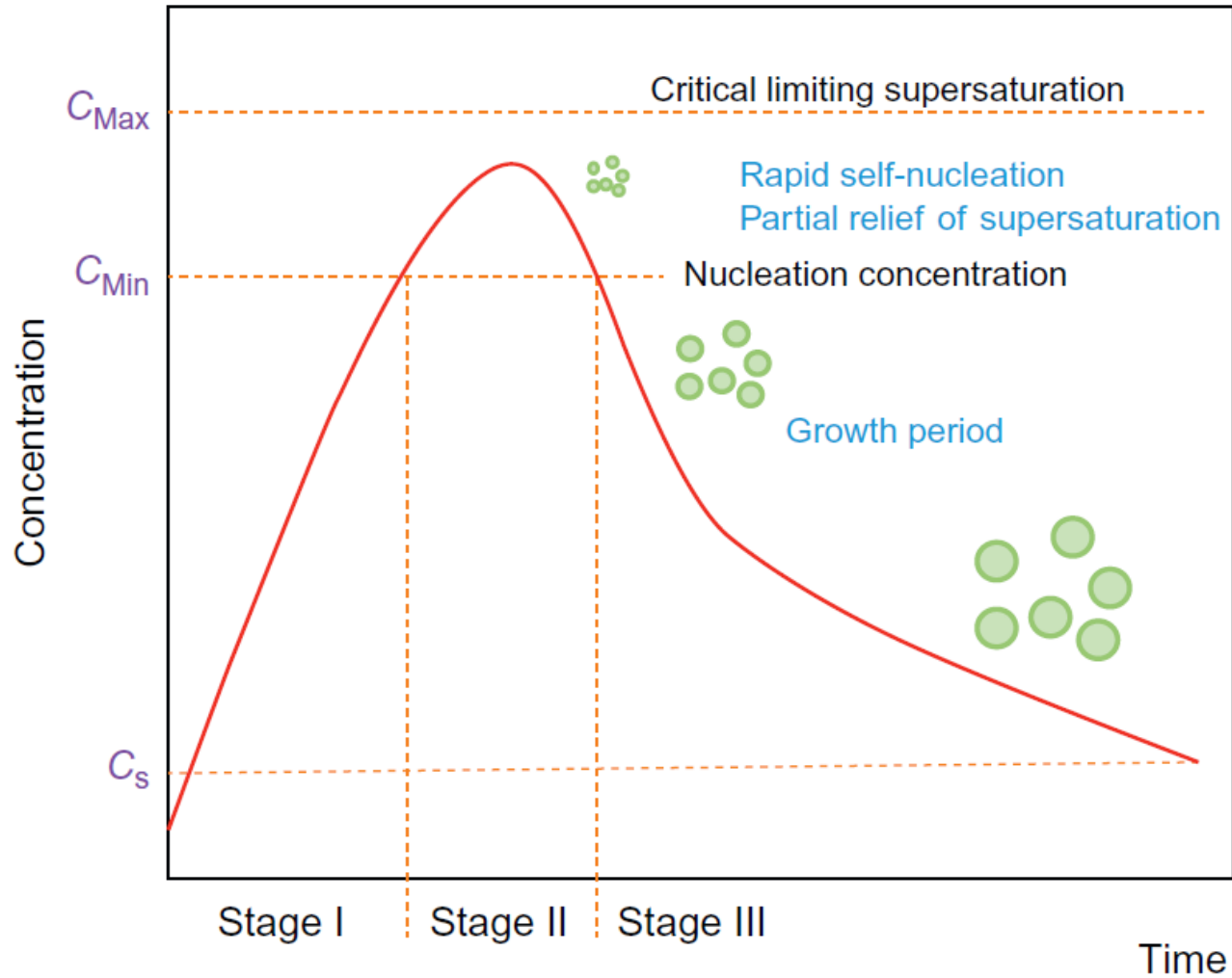
Recap

1. Supersaturation

2. Nucleation

3. Crystal growth

4. Secondary growth

$$S = \frac{c}{c*}$$

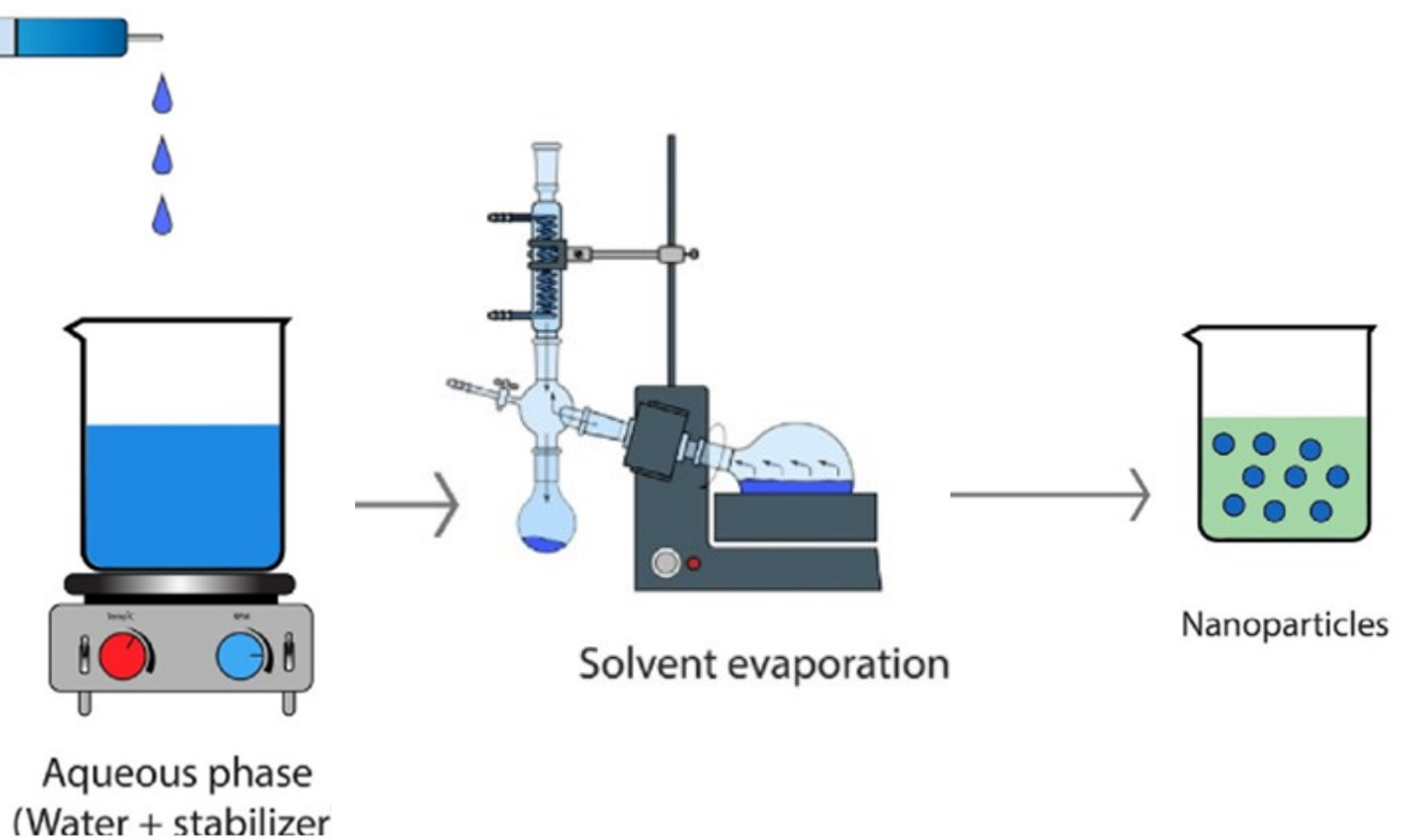$$\sigma = \frac{\Delta c}{c*} = S - 1$$

Recap

Lamer's Diagram

Synthesis of Polymeric NPs

Nanoprecipitation

Aqueous phase
(Water + stabilizer

Solvent evaporation

Nanoparticles

- 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.

Gibb's Marangoni Effect

- Mass transfer along an interface between two fluids due to a gradient of the surface tension.

- First identified by James Thomson: **Tears of wine phenomenon**
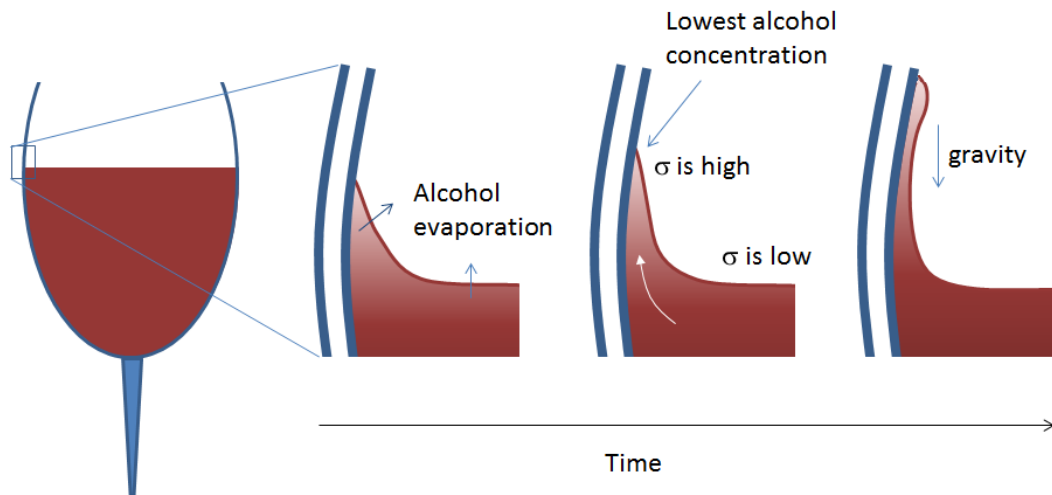
Mechanism

- Surface tension gradient tends to contract or stretch the interface resulting from a **contractile force**.

- **Greater the surface tension: greater is the contractile force**

Mechanism

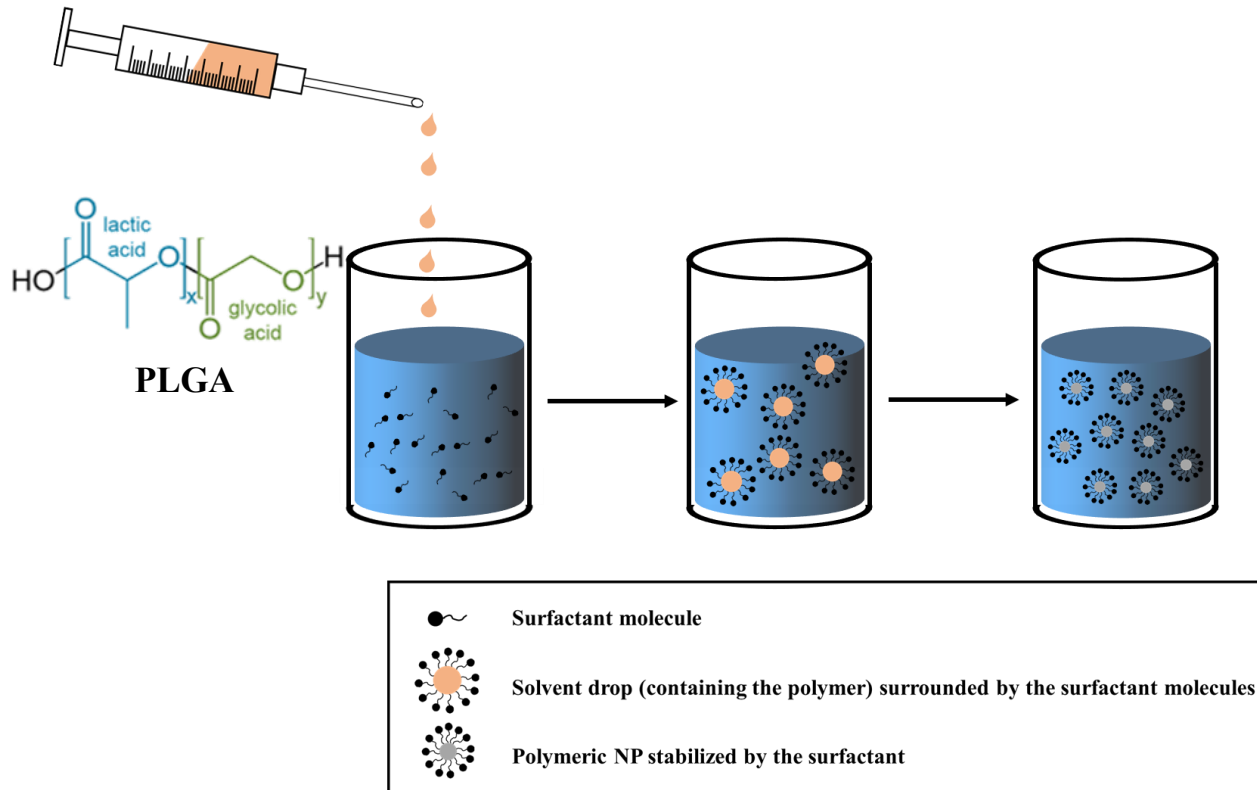| **Nucleation and Growth Theory**	**Gibbs-Marangoni Effect**

• Three Stages:
  – Nucleation
  – Growth
  – Aggregation
• Supersaturation determines nucleation rate, that is further determined by fluid dynamics and phase mixing.
• Higher mixing rate; Smaller NP size
	• Difference in surface tension that causes interfacial turbulence and thermal inequalities.
	• Thus, vortices are continuously formed and at the interface of both liquids.
	• Diffusion of solvent to a region of high surface tension causes precipitation of the polymer resulting in NPs due to **aggregation**.
	• NPs can be stabilised using a surfactant.

Parameters

- Stirring Rate

- Injection Rate

- Fraction of non-solvent phase

- Surfactant concentration

- Polymer concentration

- Polymer molecular weight

- Solvent selection

- Temperature

Lince et al; Journal of Colloid and Interface Science, **2008**, 505-515; Miladi et al., Nanoprecipitation Process: From Particle Preparation to In Vivo Applications, **2016**, 17-53

This is a drop of a **water-alcohol mixture**.

Polymer Coated Magnetic NPs

PLGA

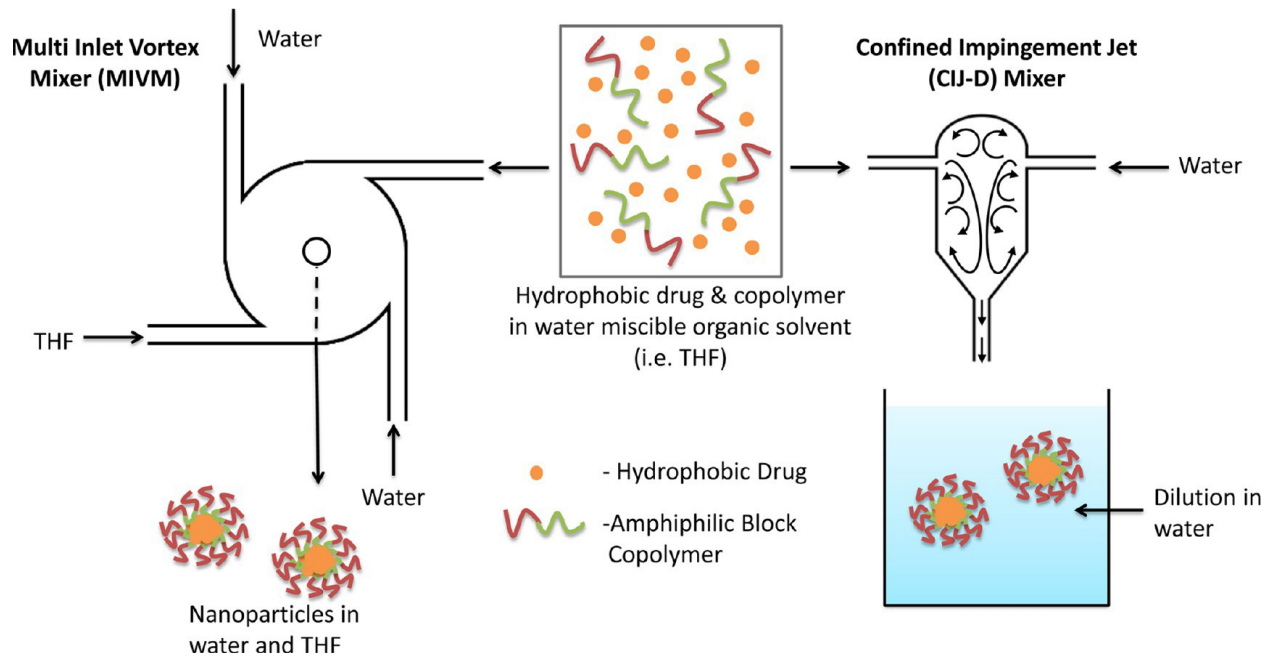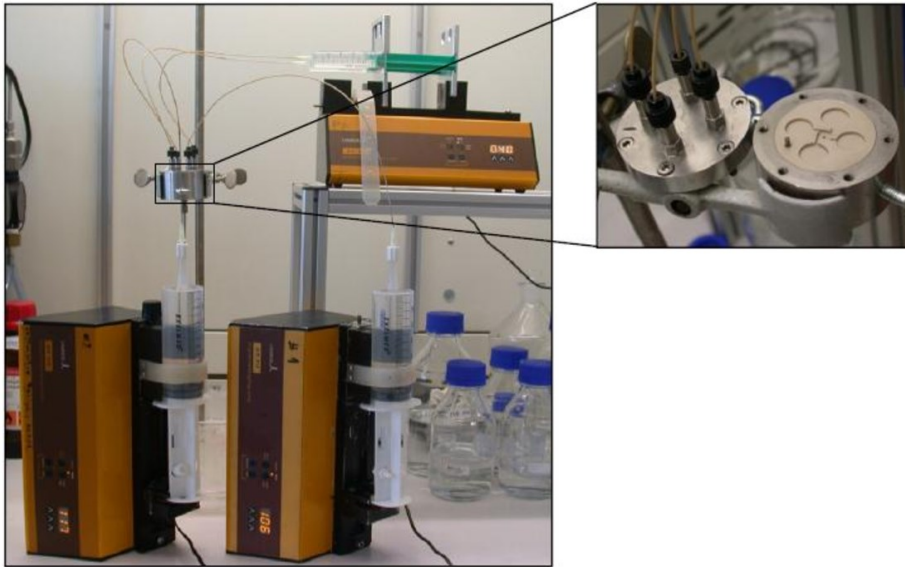|	Surfactant molecule
	Solvent drop (containing the polymer) surrounded by the surfactant molecules
	Polymeric NP stabilized by the surfactant

2. 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
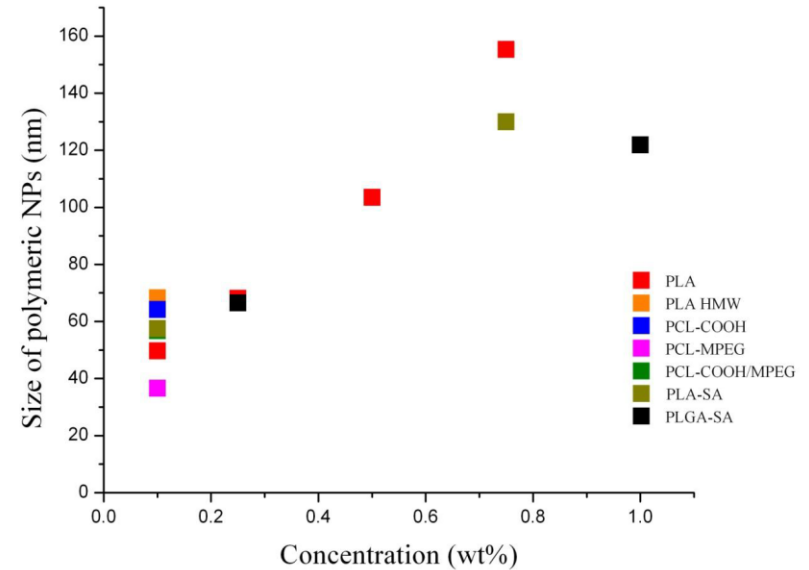
- Narrow particle size distribution

MIVM Setup

Multi Inlet Vortex Mixer (MIVM)

Water

THF

Water

Nanoparticles in water and THF

Hydrophobic drug & copolymer in water miscible organic solvent (i.e. THF)

● - Hydrophobic Drug

〜 -Amphiphilic Block Copolymer

Confined Impingement Jet (CIJ-D) Mixer

Water

Dilution in water

Pustulka et al. , Mol. Pharmaceutics, **2013**, 4367-4377

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) (~32 ^{0}C)

• The LCST/cloud point can be tuned by altering the composition of a PNIPAm-containing block copolymer

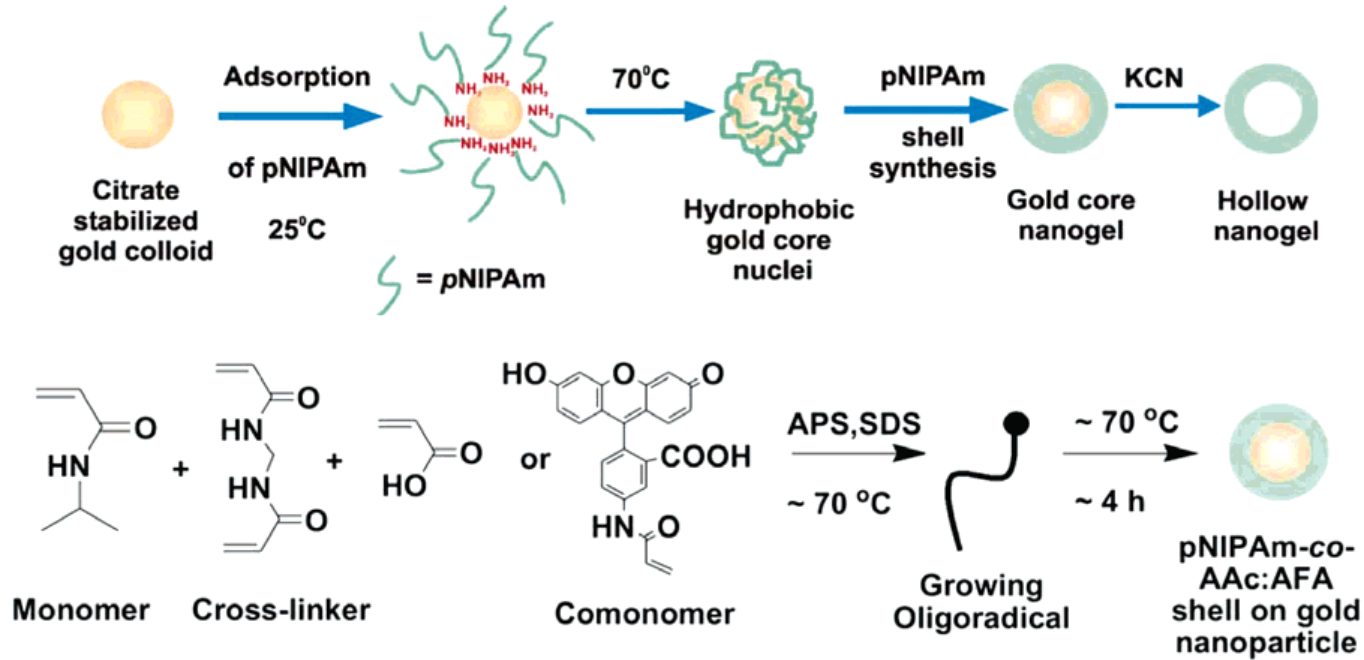• LCST also affected by the mobility of the PNIPAm chains

LCST

Mechanism

Oligoradical → Precursor Particle → Growing Particle → Microgel
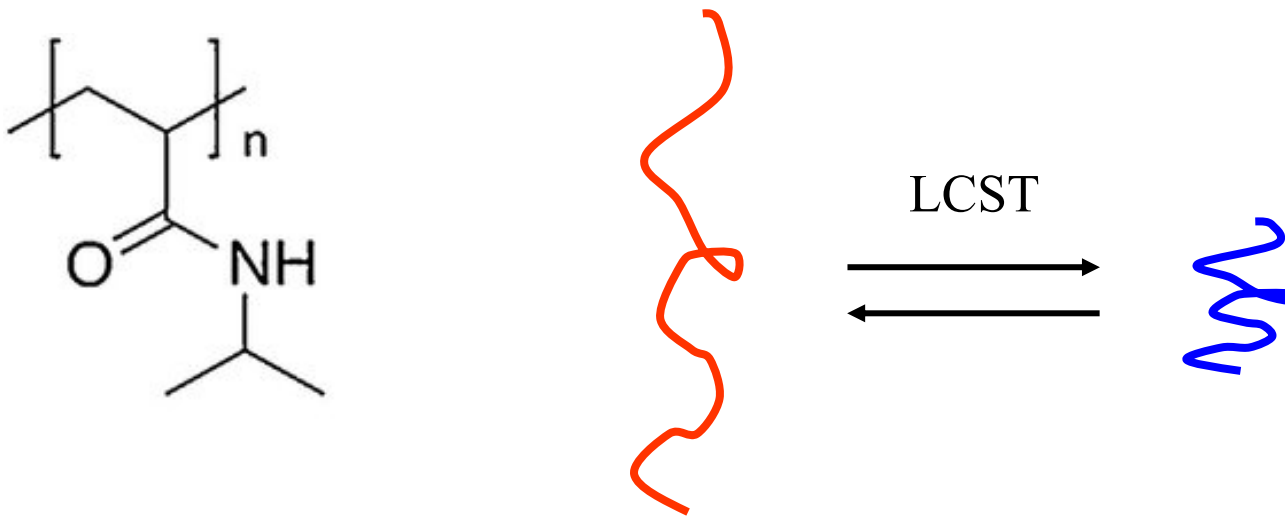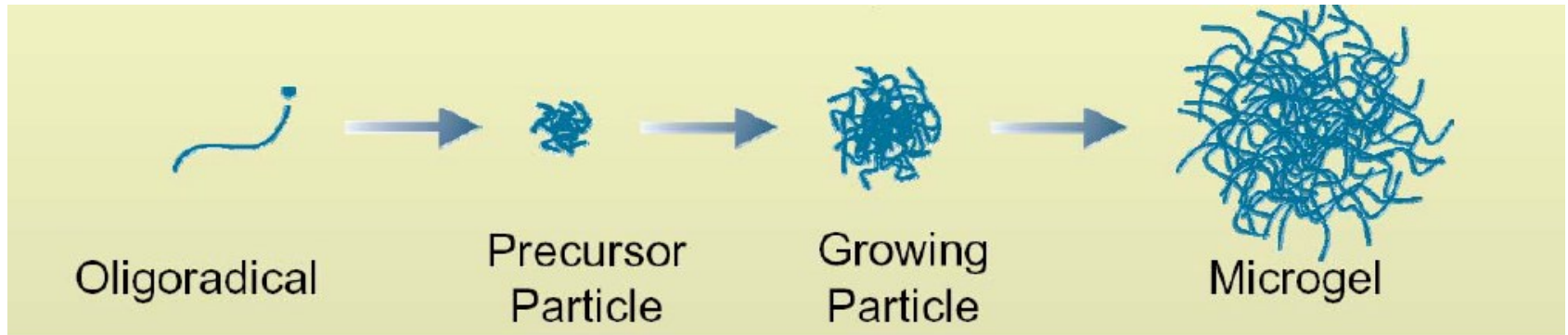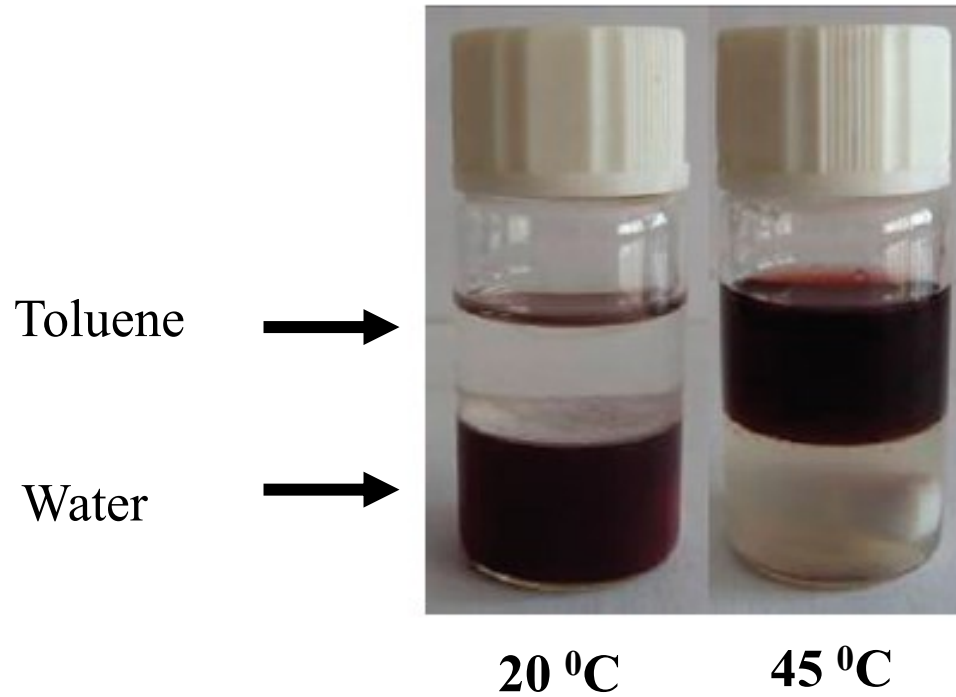
A nucleation and growth process

- 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

Singh, N., Lyon, L.A, *Chem. Mater.* **2007,** *19,* 719-726

Au-pNIPAm

Singh, N., Lyon, L.A, *Chem. Mater.* **2007,***19,* 719-726

Phase Transfer

Toluene →

Water →

20 ^{0}C   **45 ^{0}C**

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

Wen, Y., Jiang, X., Yin, G., and Yin, J., *Chem. Commun.*, **2009**, 6595-6597