



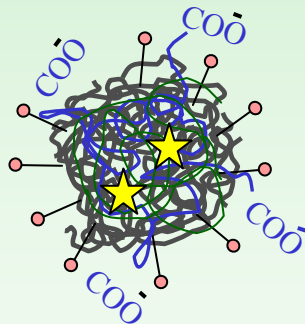
MAX-PLANCK-GESellschaft



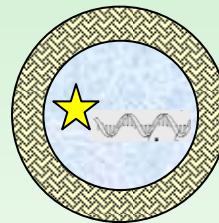
Formation of smart nanocapsules for defined slow or sudden release

Anna Musyanovych and Katharina Landfester

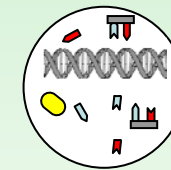
Max Planck Institute for Polymer Research, Mainz, Germany



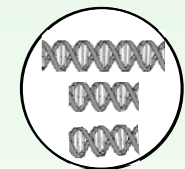
Functionalized nanoparticles
from degradable and non-
degradable materials



Capsules for hydrophilic
compounds



PCR

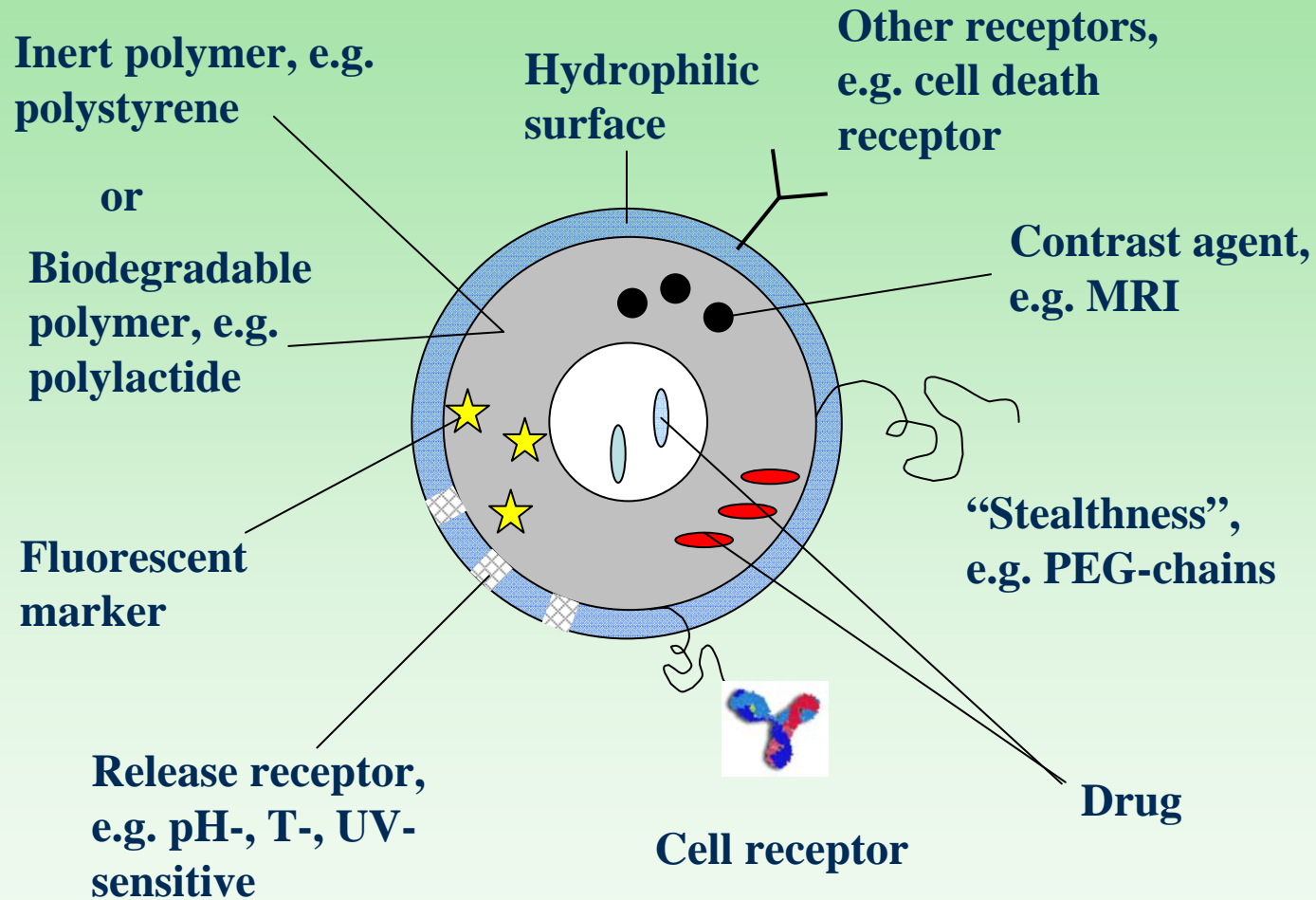


Bio-reactions with a
single molecule inside a
droplet



MAX-PLANCK-GESellschaft

Criteria for “perfect” nanocarrier

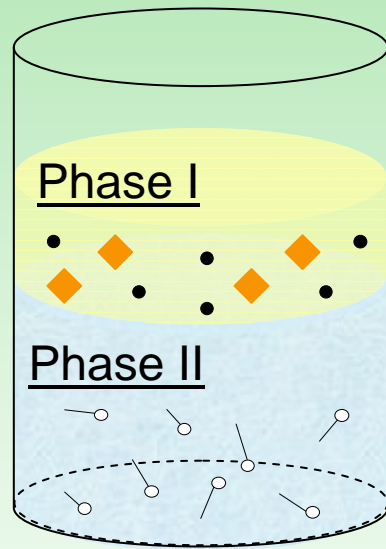


Principle of the miniemulsion process

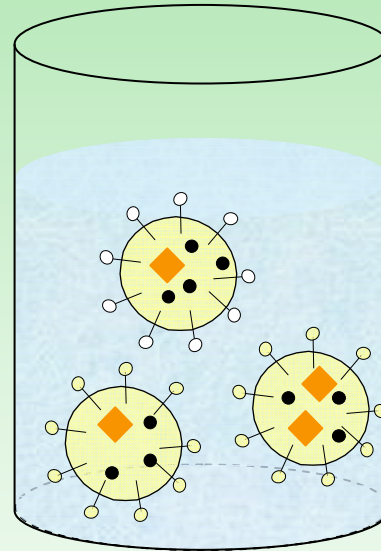


Formulation of small and stable droplets by using high shear (e.g. ultrasound)

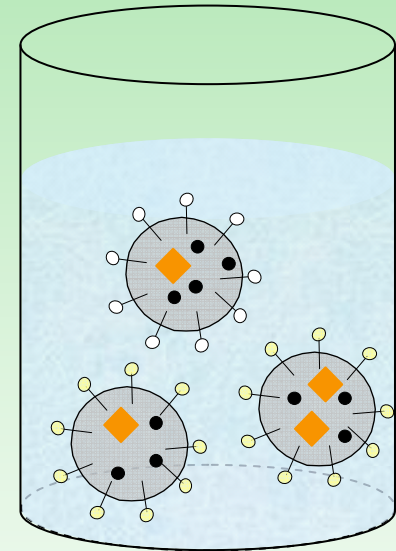
Reactions in confined geometries



high speed stirring, ultrasound



reaction



Narrowly distributed nanodroplets
Size range: 50-500 nm

1:1 copy
(nanoreactor)

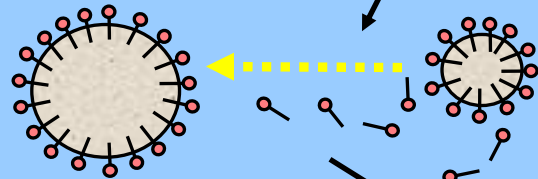
Growth of droplets



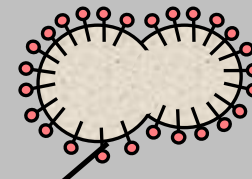
Ostwald ripening:

Coalescence:

diffusion of oil through the water phase

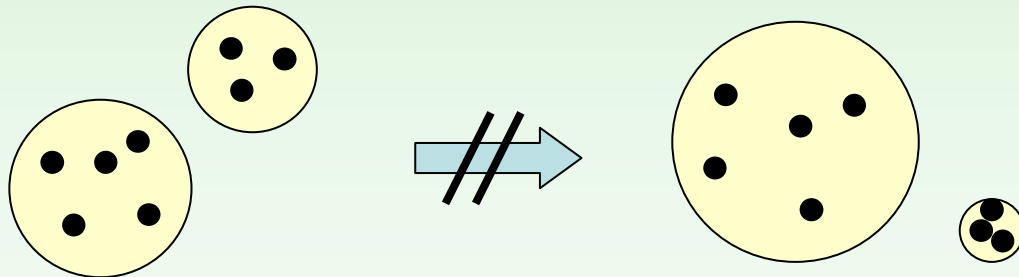


collision and fusion of oil droplets



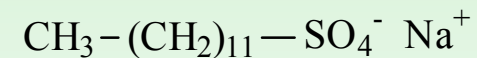
Suppression of Ostwald ripening:

Addition of a co-stabilizer with low solubility in a continuous phase

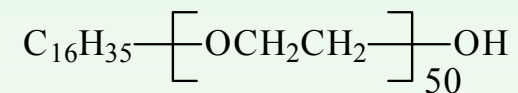


Suppression of coalescence:

Effective surfactants



Sodium dodecylsulfate (SDS)



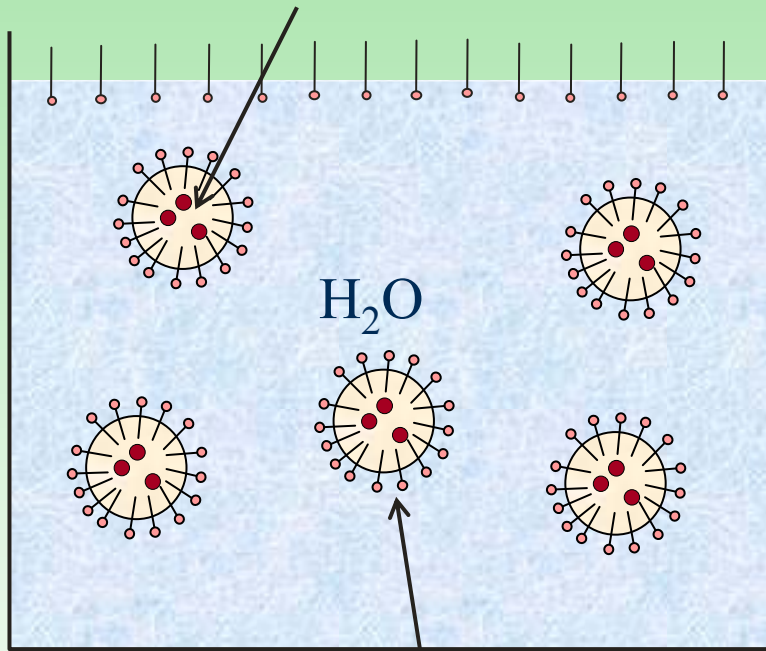
Lutensol AT50

Force: Same chemical potential in each droplet

Direct and Inverse miniemulsions



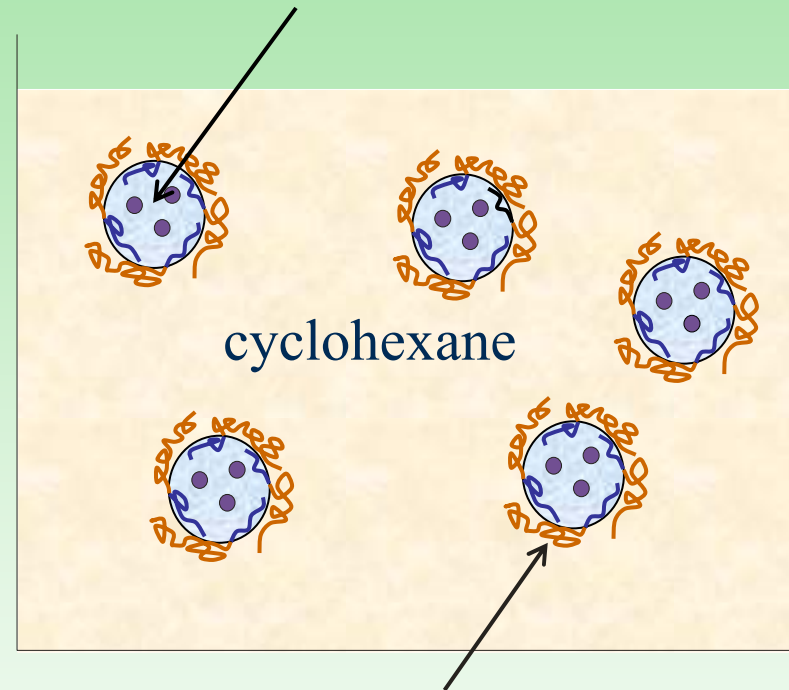
non-polar phase
and *hydrophobe*



surfactant

e.g. sodium dodecylsulfate (**SDS**)
cetyltrimethylammonium chloride
(**CTMA-Cl**)

polar phase
and *lipophobe* (e.g. salt)



surfactant

block copolymer
e.g. poly[(ethylene-*co*-butylene)-*b*-(ethylene oxide)]

Polystyrene functionalized nanoparticles



Langmuir, 2007, 23(10), 5367-5376.

Colloid Polym. Sci., 2009, (in press).

Polystyrene functionalized nanoparticles



Oil phase

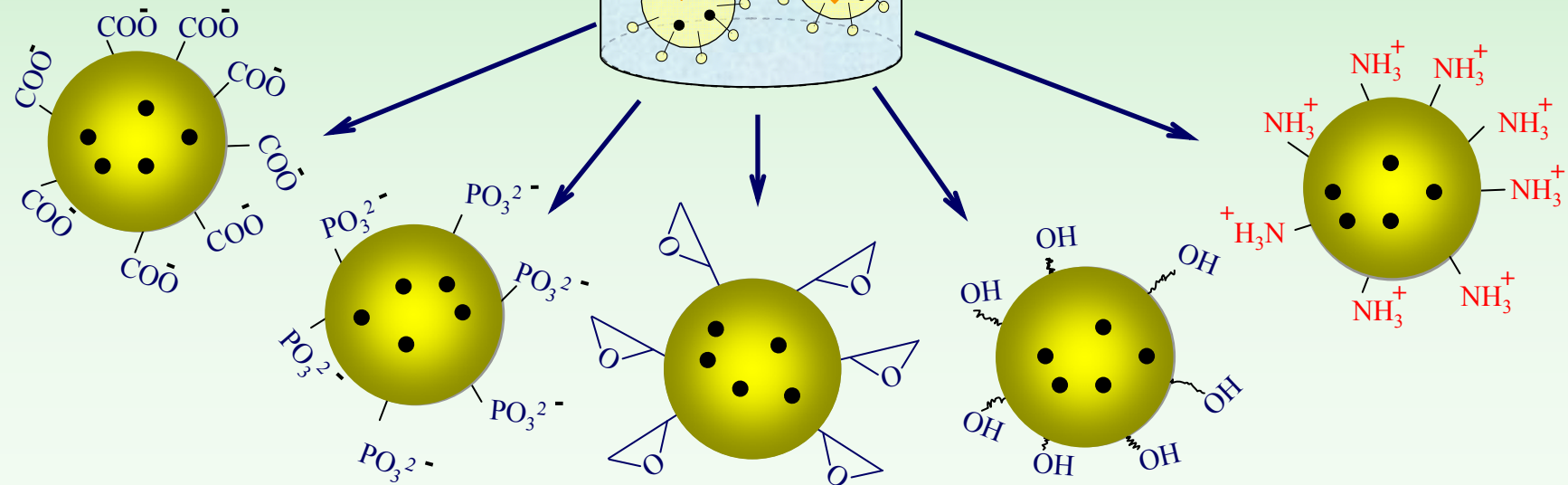
Styrene
Oil-soluble initiator
Oil-soluble fluorescent dye

Oil-soluble comonomer: e.g. acrylic acid, glycidyl methacrylate, etc.

Aqueous phase

Water
Surfactant
Dispersion of magnetite

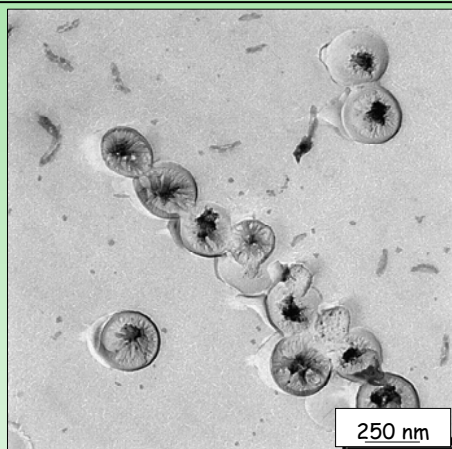
Water-soluble comonomer: e.g. PEG-acrylate, vinyl phosphonic acid, aminoethyl methacrylate, etc.



Encapsulation of materials in nanoparticles

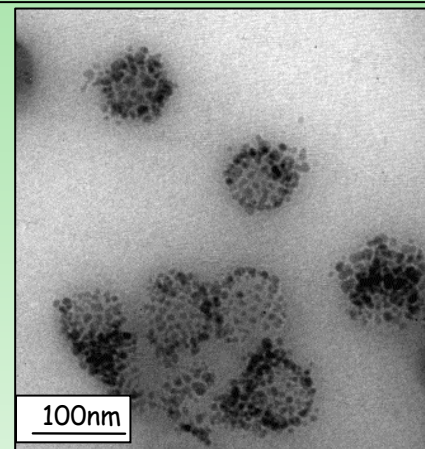


One colloid particle per polymer particle:
 CaCO_3 in PS



Macromol. Symp. **2000**, 151, 549.

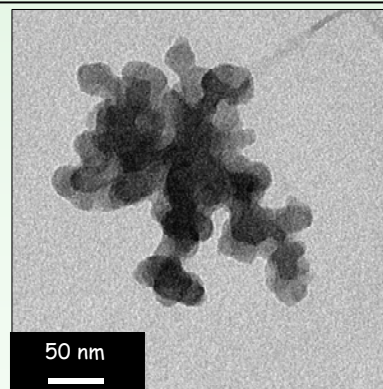
Many colloid particles per polymer particle:
 Fe_3O_4 in PS



Macromol. Chem. Phys. **2003**, 204, 22.



One aggregate per polymer particle:
Carbon black in PS



Macromol. Chem. Phys. **2001**, 202, 51-60.

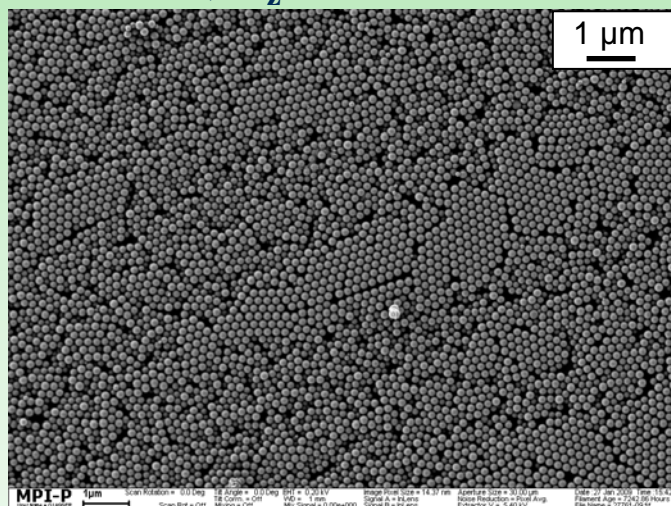
Characterization of functionalized nanoparticles



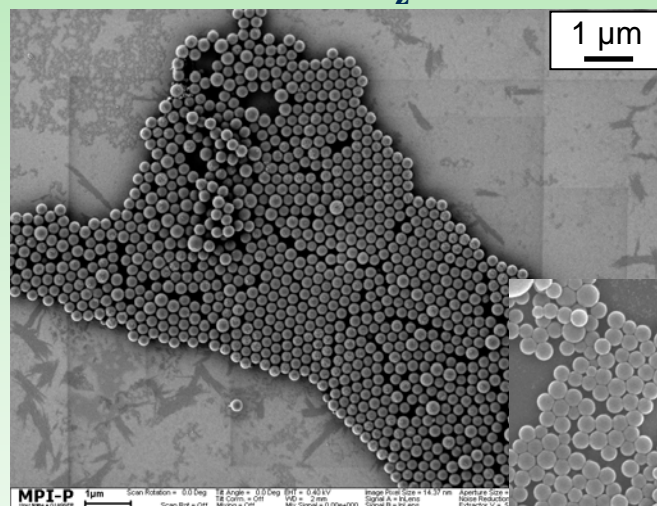
Particle size and surface groups density can be adjusted by varying the type and amount of surfactant/functional monomer

Poly(styrene-co-acrylic acid)

2 wt%, $D_z=165$ nm

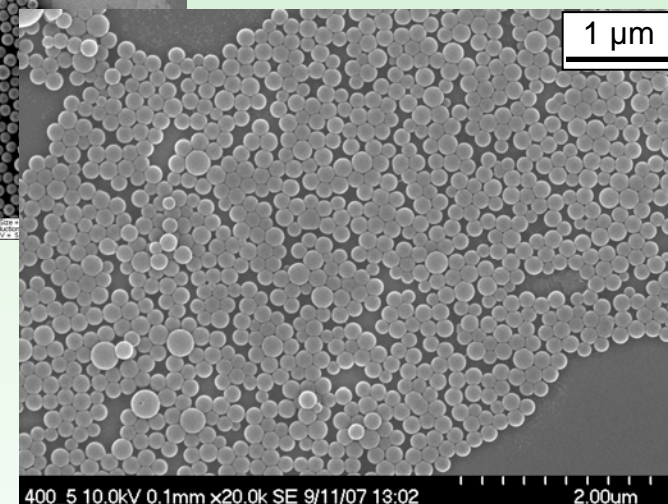


0.5 wt%, $D_z=220$ nm, 200 mg Lutensol AT50



0.5 wt%, $D_z=170$ nm

400 mg Lutensol AT50

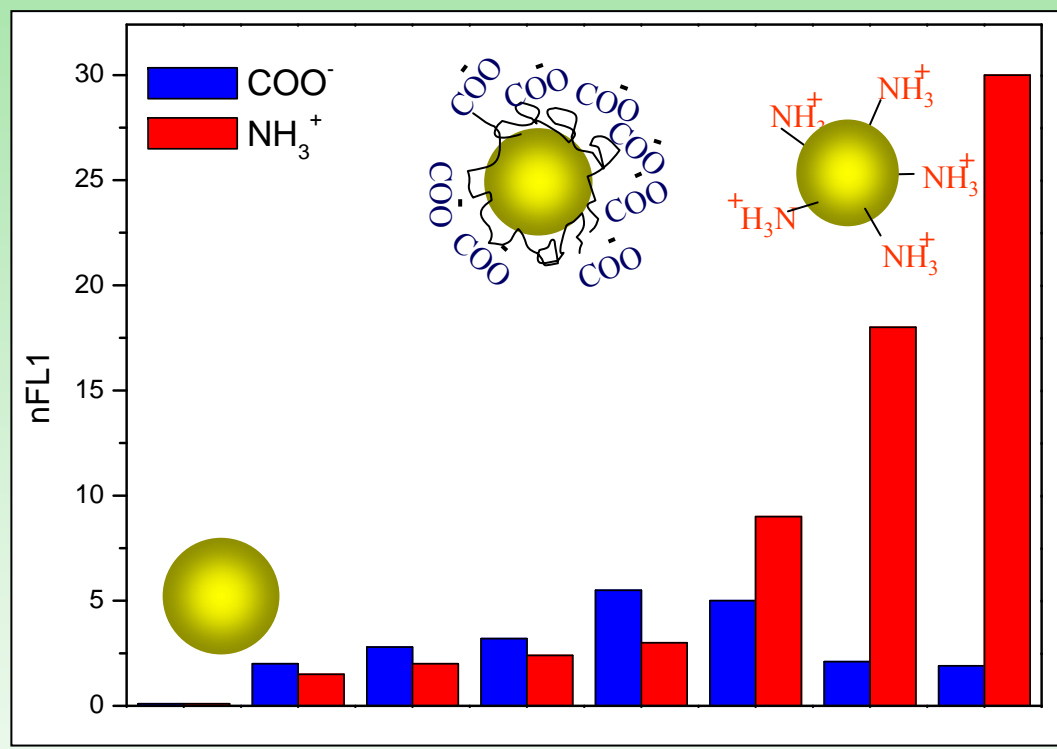
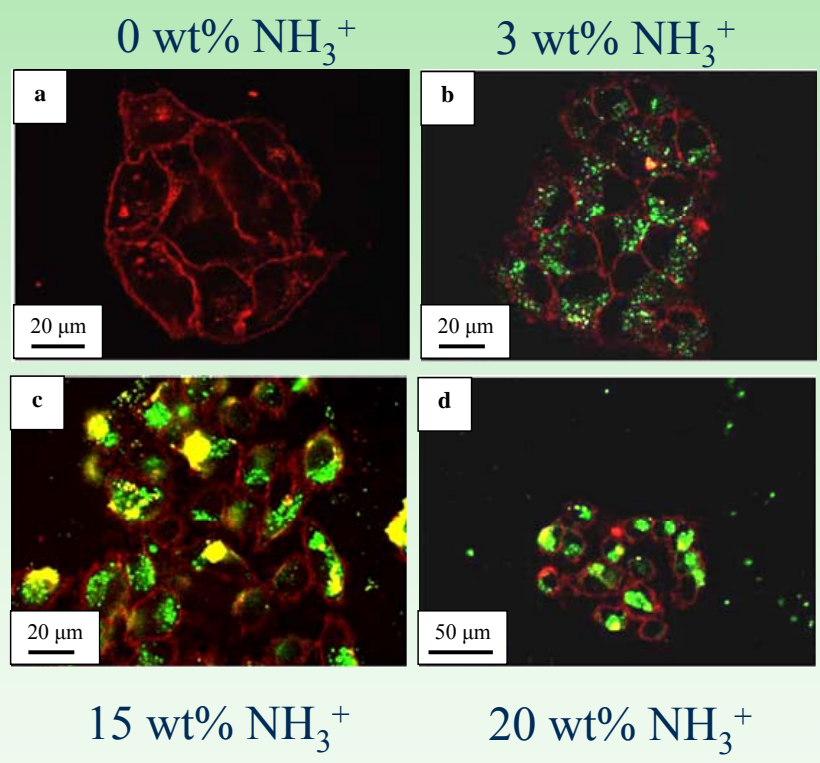


Particle - Cell interaction

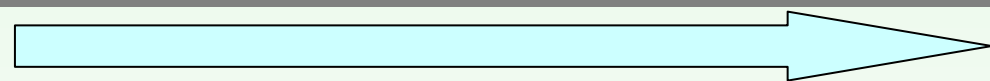


Surface functional groups density influence the cellular uptake

HeLa cells



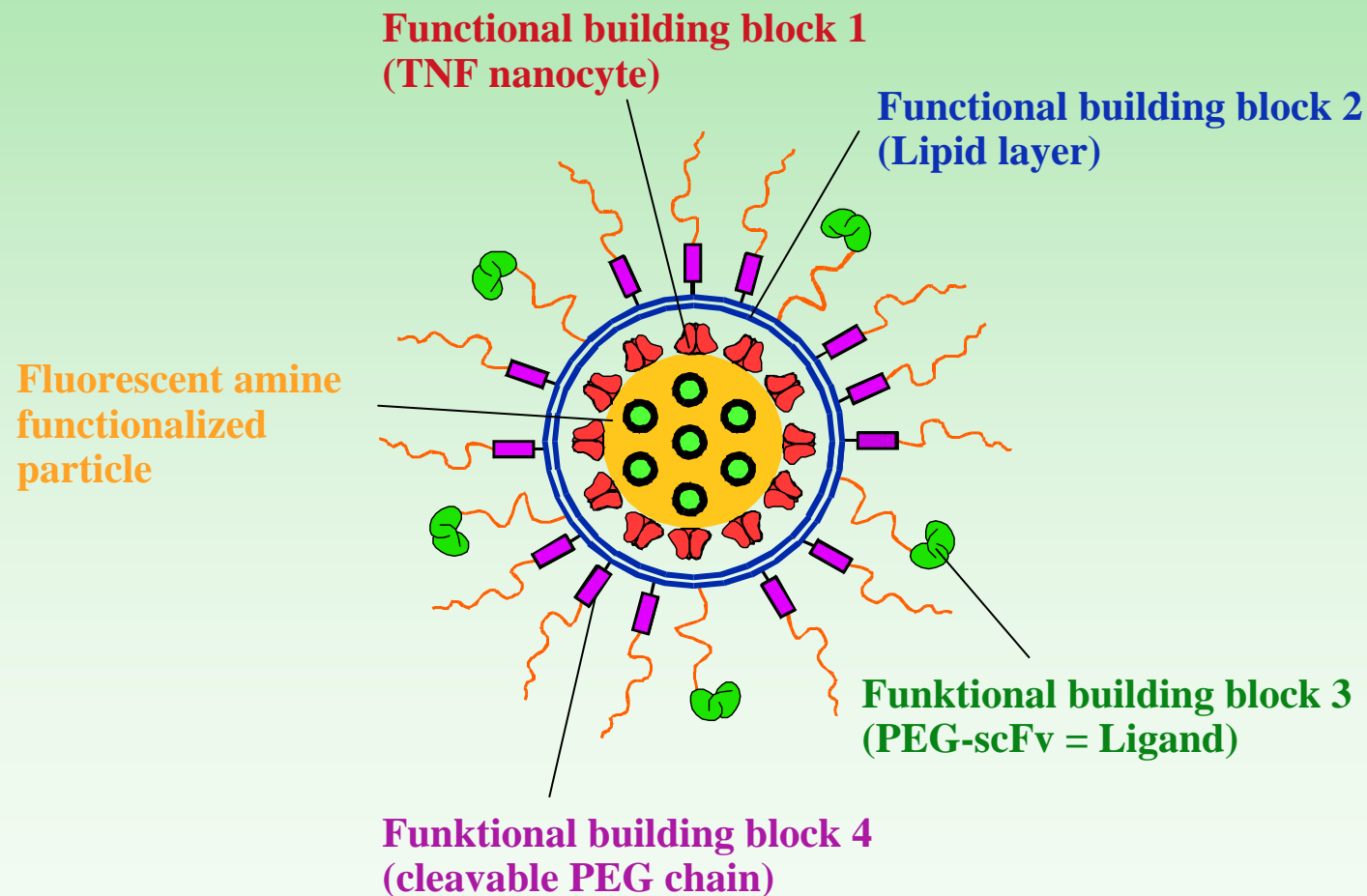
Increase of surface functional groups amount



Bioactive multifunctional composite particles



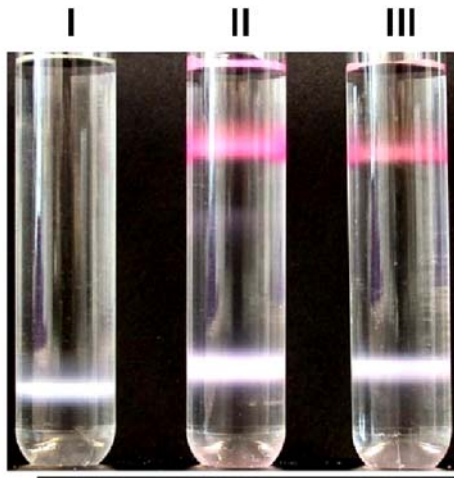
Induced drug release of the tumor necrosis factor TNF



Bioactive multifunctional composite particles



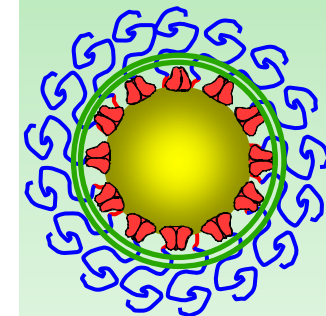
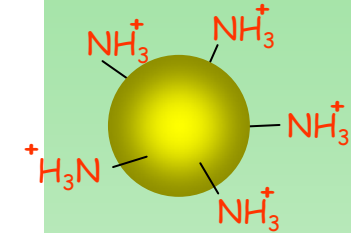
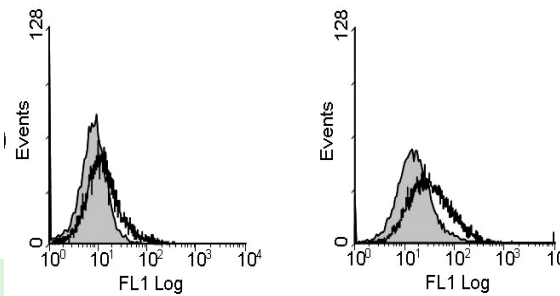
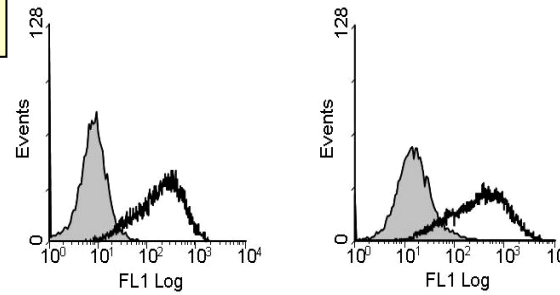
FACS



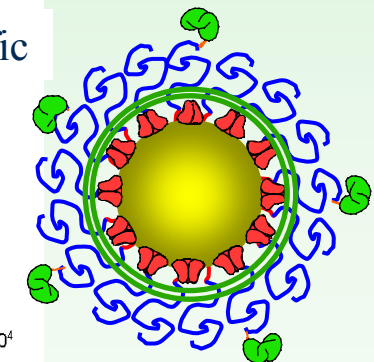
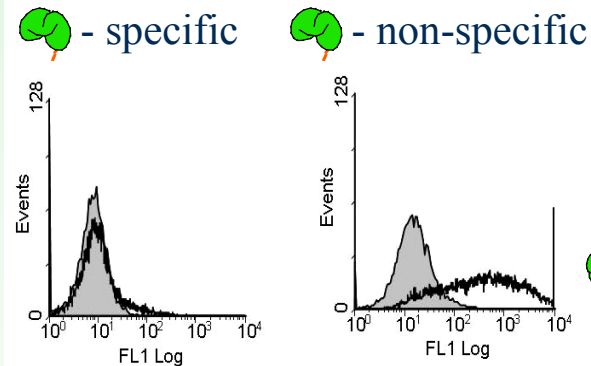
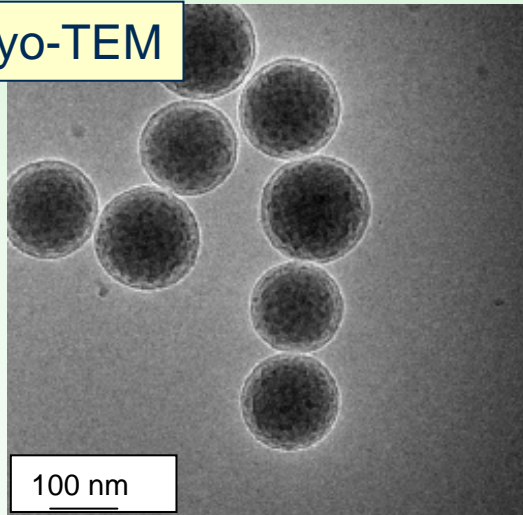
← free lipids/liposomes

← lipid-encapsulated particles
← non-encapsulated particles

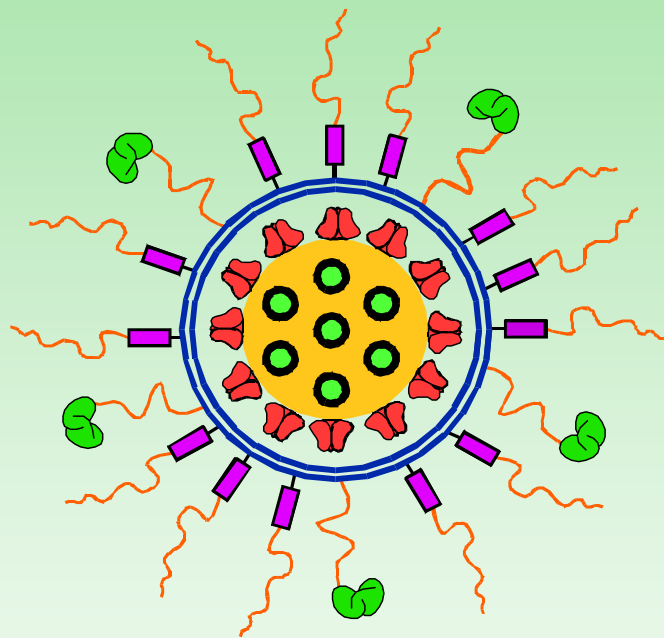
Gradient: 6%;15%



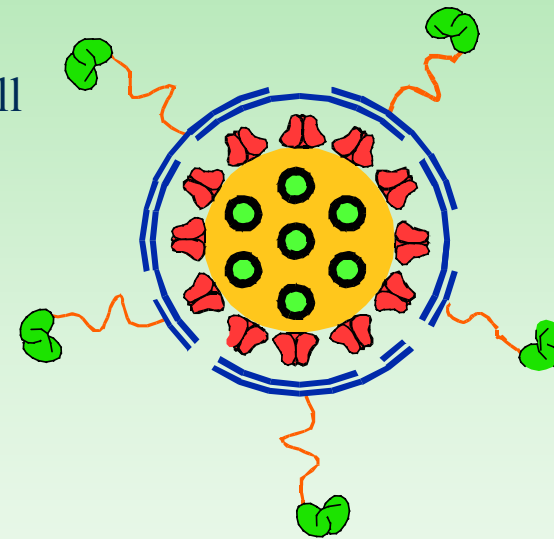
Cryo-TEM



Bioactive multifunctional composite particles



cleavage in cell
by enzyme



tumor necrosis factor becomes active

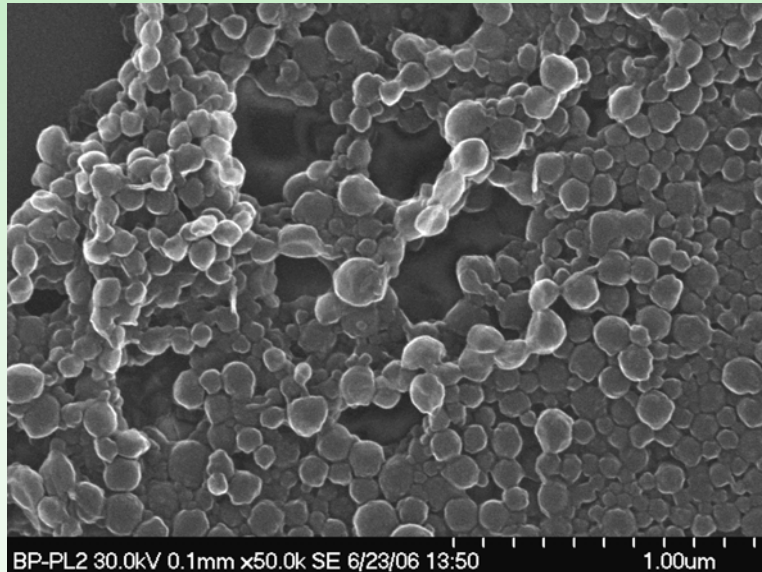
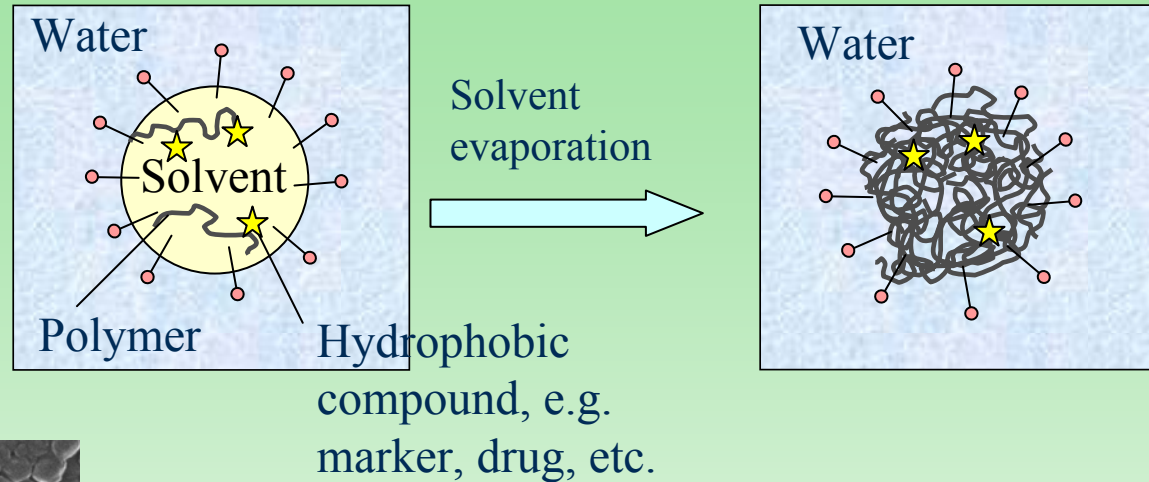
Polymer precipitation within a nanodroplet



Poly(L-lactide)

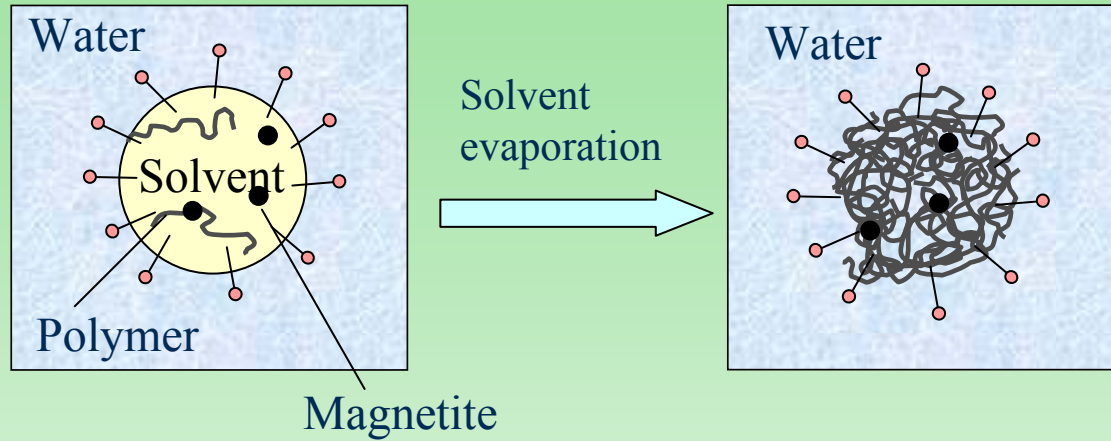
Poly(ϵ -caprolactone)

Poly(lactide-co-glycolide)



Particle size and size distribution mainly depend on the amount and type of polymer used

Biodegradable magnetite particles

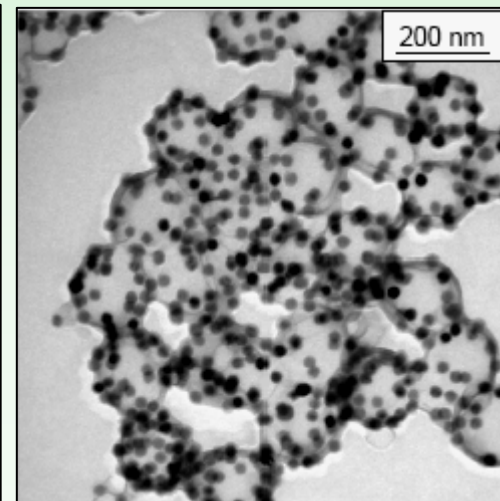
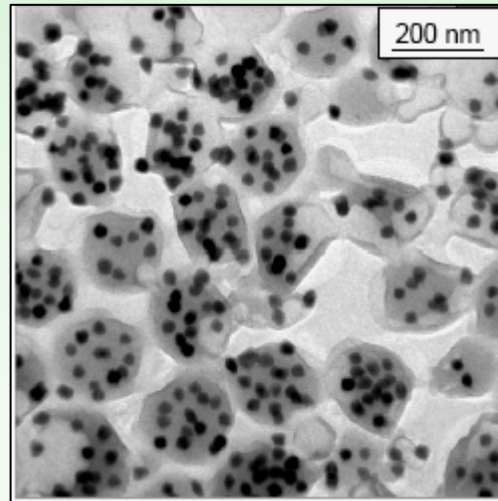
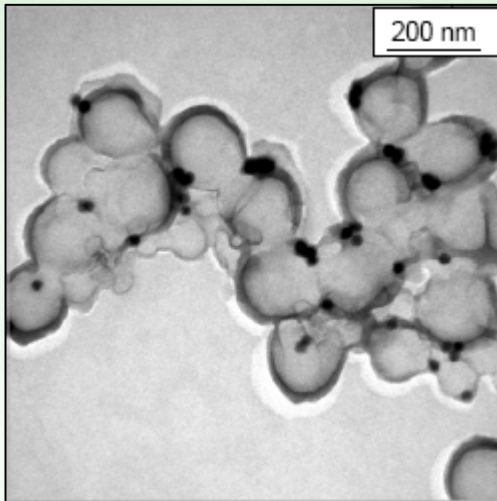


Effect of magnetite amount

6.7 wt%

20 wt%

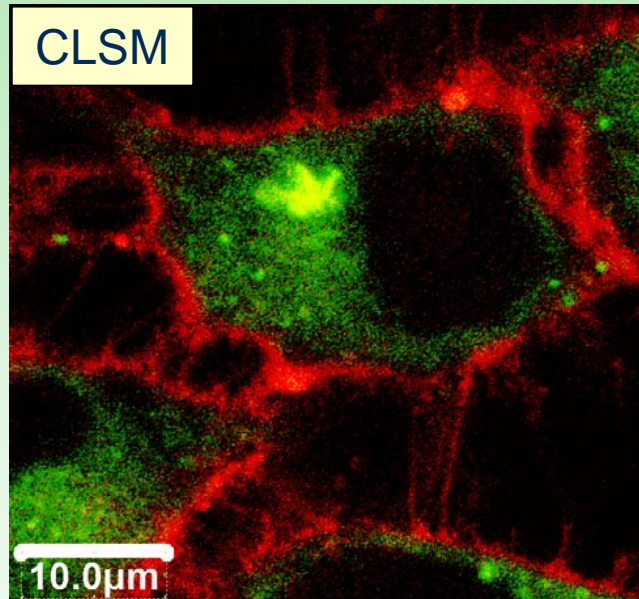
50 wt%



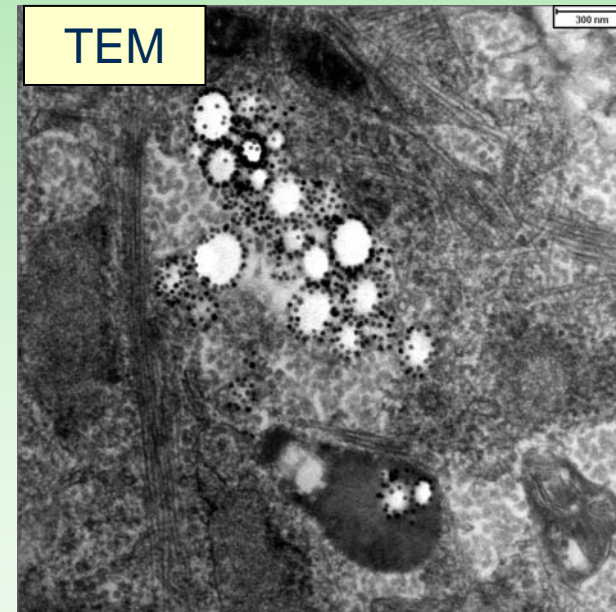
Degradation of nanoparticles



Release of fluorescent dye
from poly(L-lactide)
particles (HeLa cells)

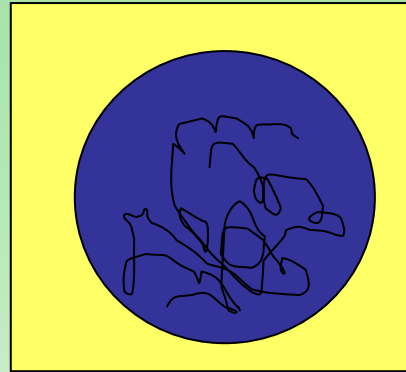


Release of magnetite
from poly(L-lactide)
particles (MSC)

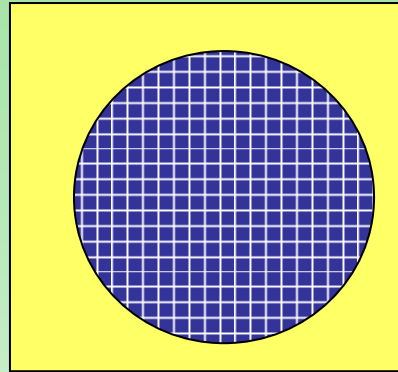


The rate of polymer degradation mainly depends on the type of surfactant, molecular weight and T_g of polymer

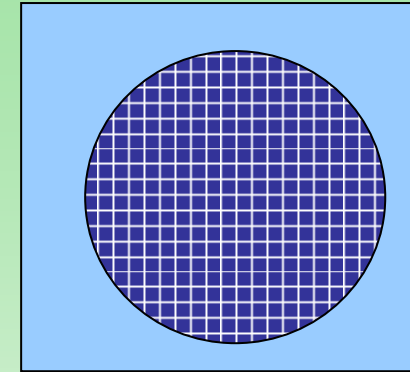
Crystallization in Gelatin Microgels



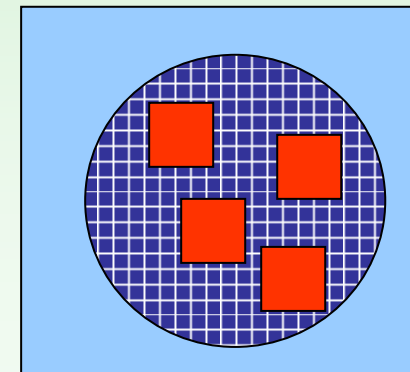
X-linking



Transfer
to H₂O

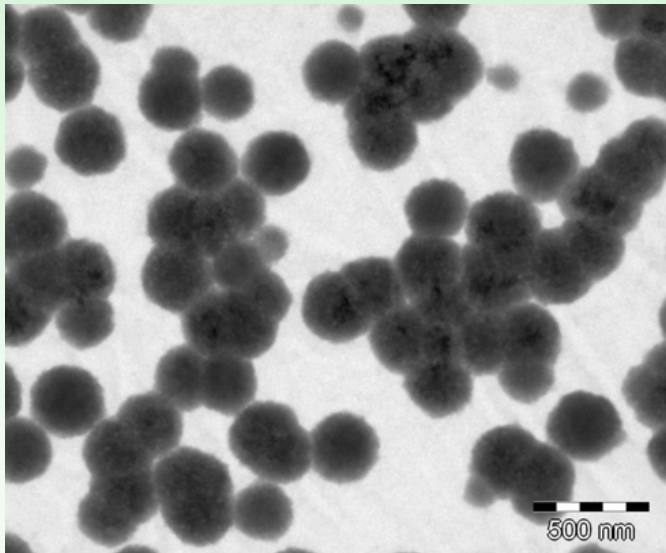


Loading with
CaCl₂+
crystallization
by Na₂HPO₄



Gelatine in water droplets

Particle size: 220 nm
Cross linking with glutaraldehyde

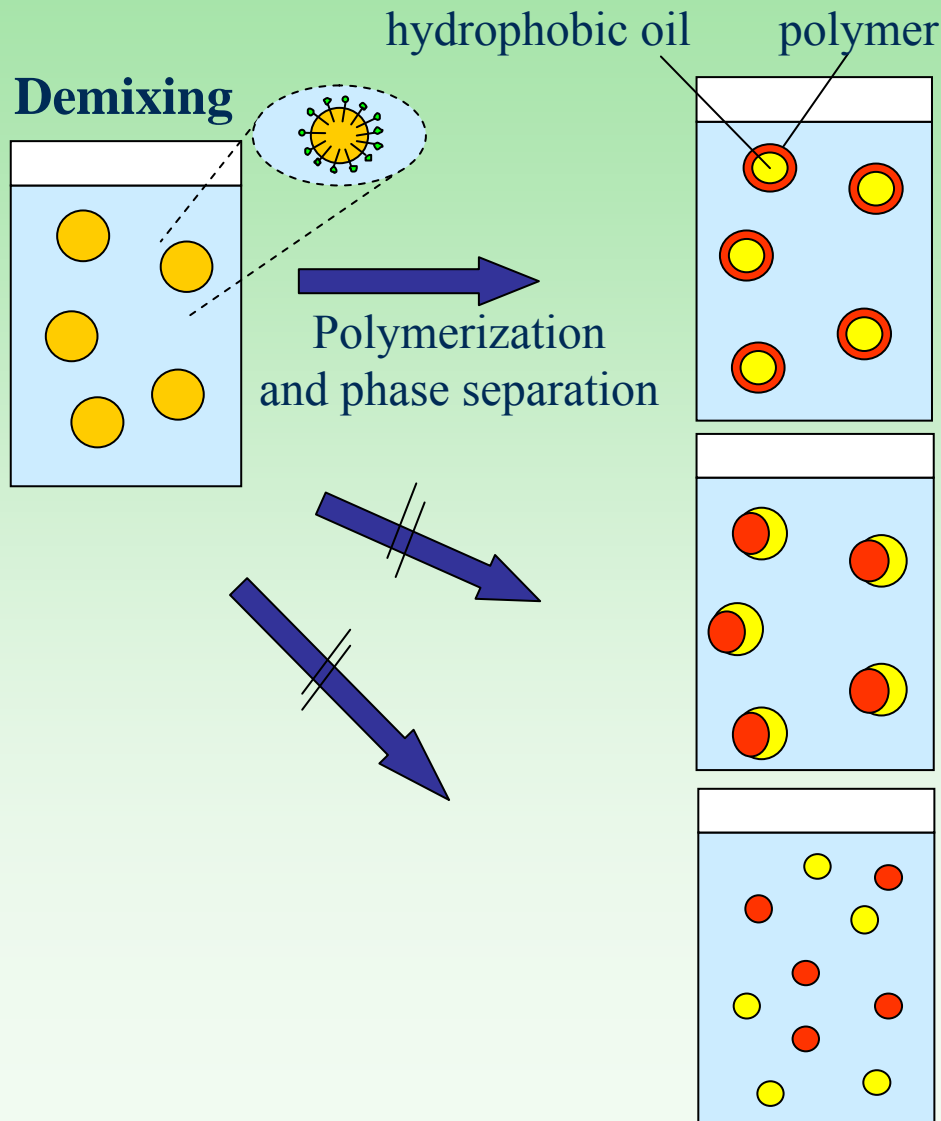


Apatite
 $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ in
gelatin microgels



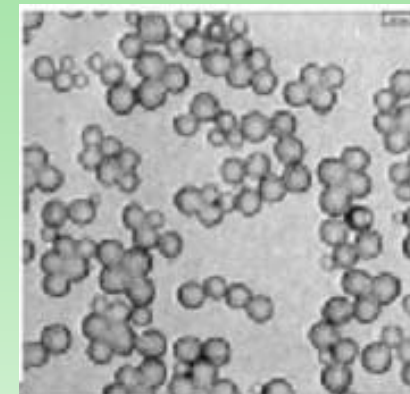
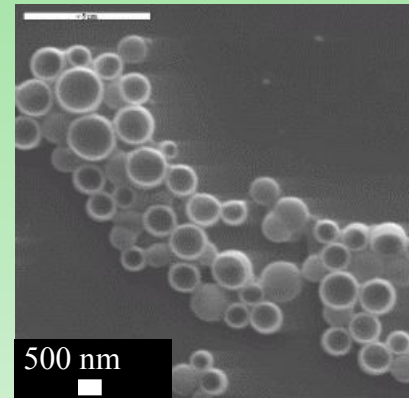
Encapsulation of liquids in miniemulsion

Capsules via phase separation



Styrene/ Hexadecane

PMMA/Parfume



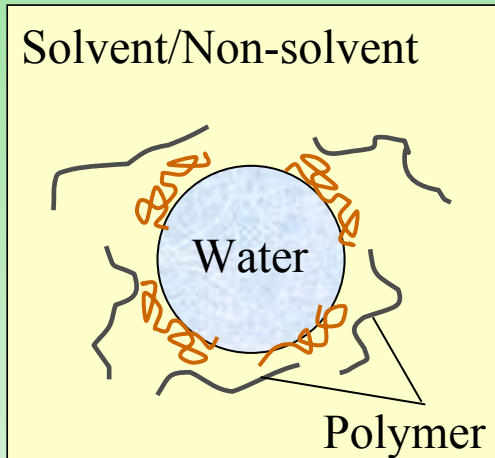
Final morphology depends on:

- the interfacial tension between three different phases (polymer, continuous phase, dispersed nanodroplet)
- kinetics of the polymerization vs phase separation
- miscibility of the phases

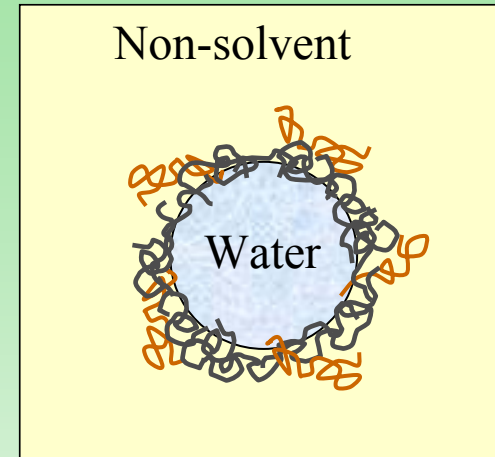
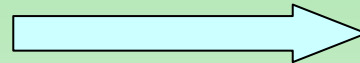
Capsules via polymer nanoprecipitation



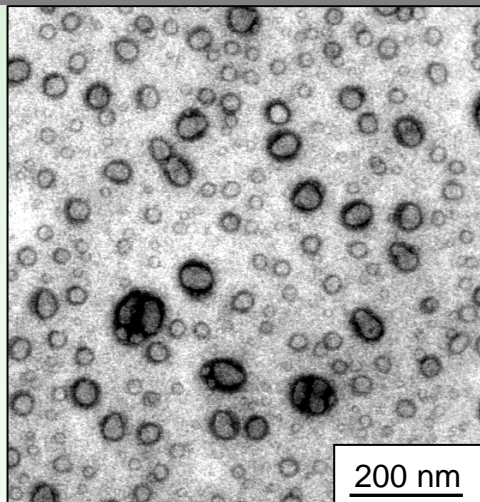
in inverse miniemulsion



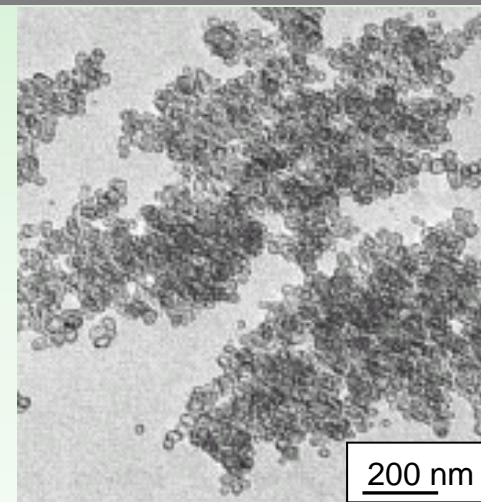
Solvent
evaporation



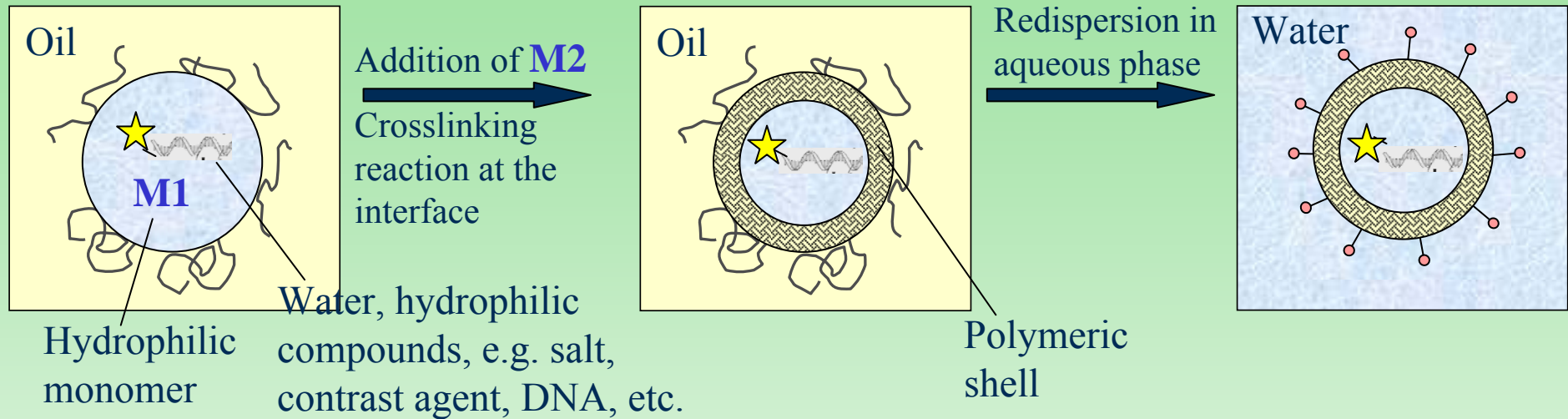
poly(L-lactide) capsules



poly(ϵ -caprolactone) capsules

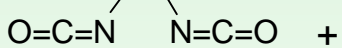


Capsules via reaction at the interface

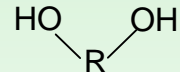


Crosslinking:

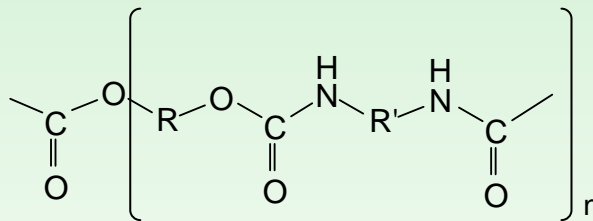
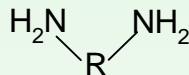
M2:



M1:

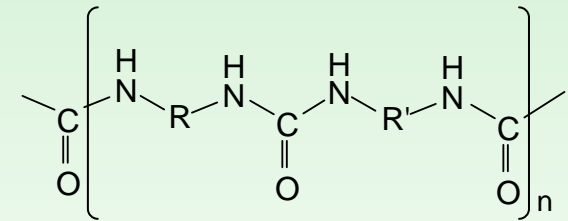


or



Polyurethane

or

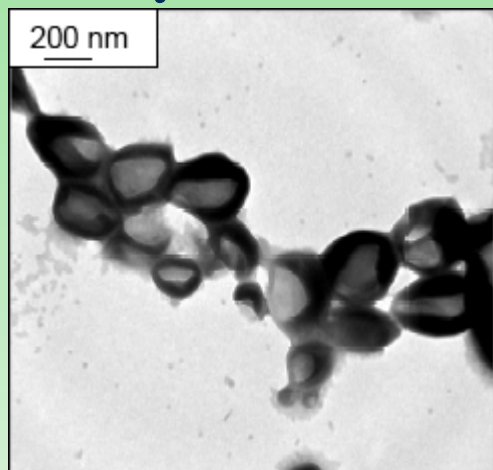


Polyurea

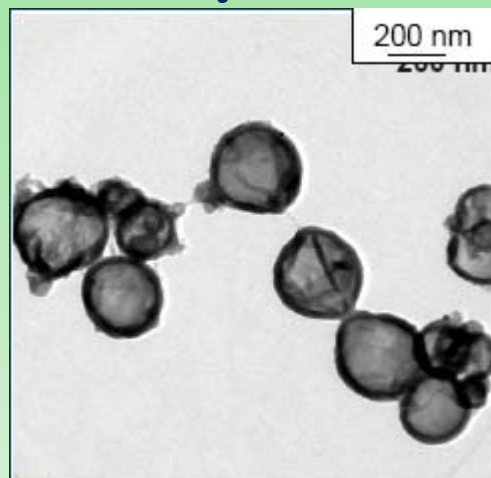
Capsules via reaction at interface



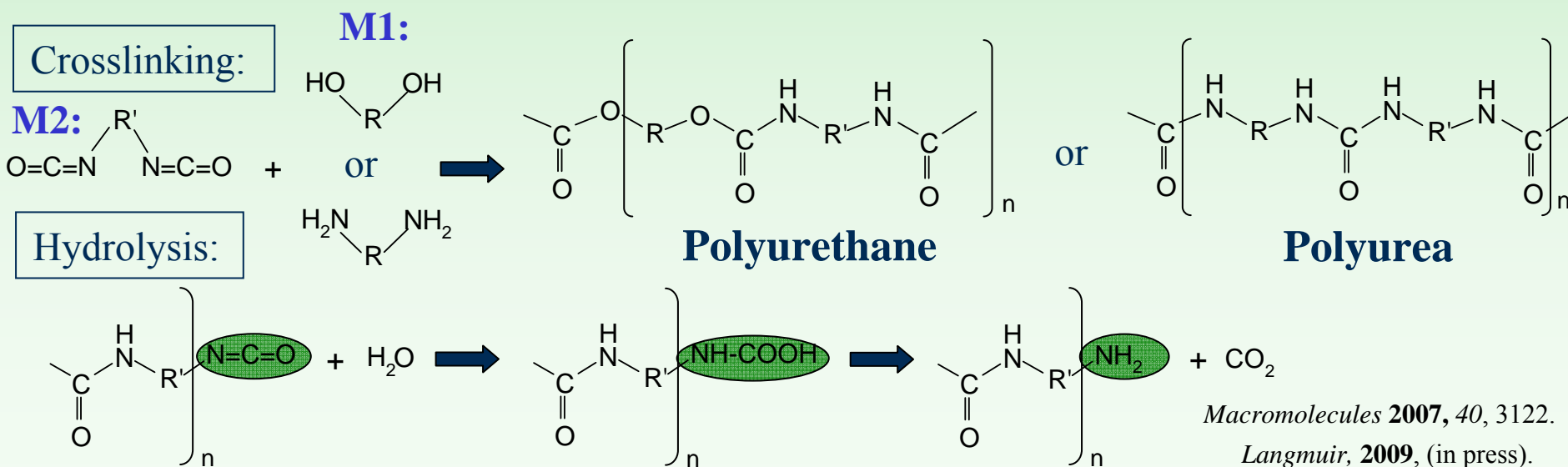
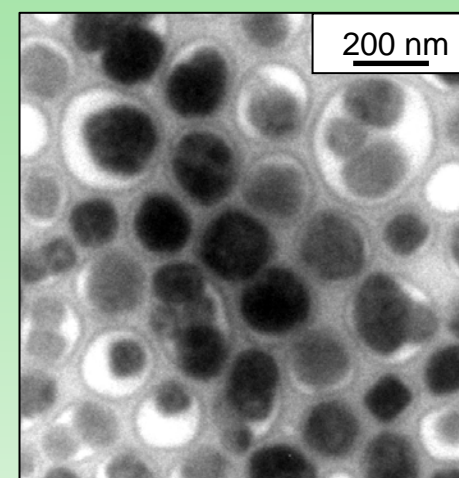
Polyurethane



Polyurea



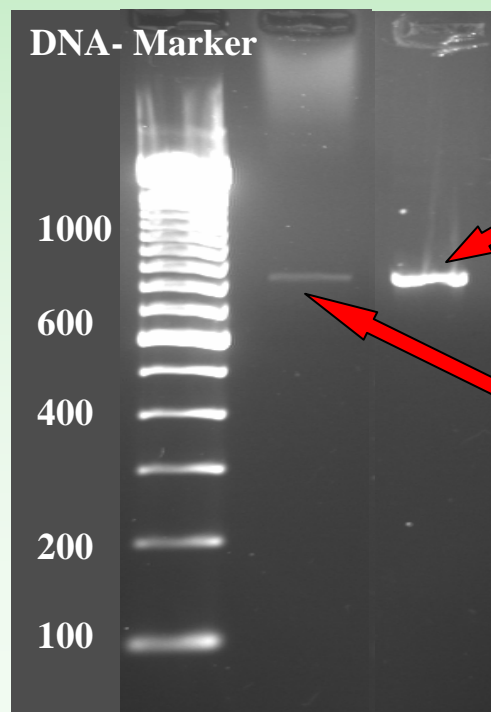
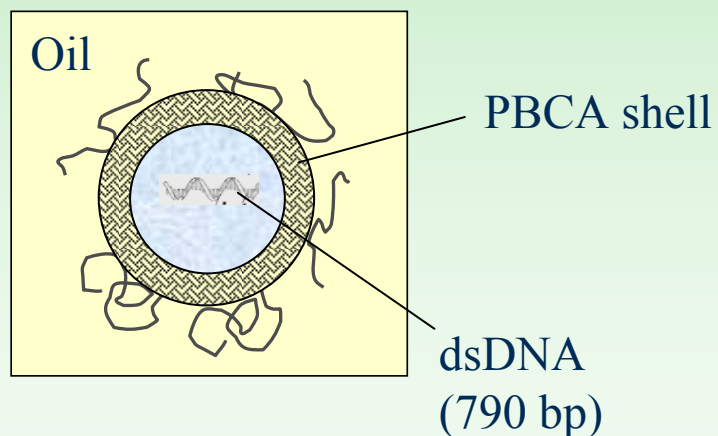
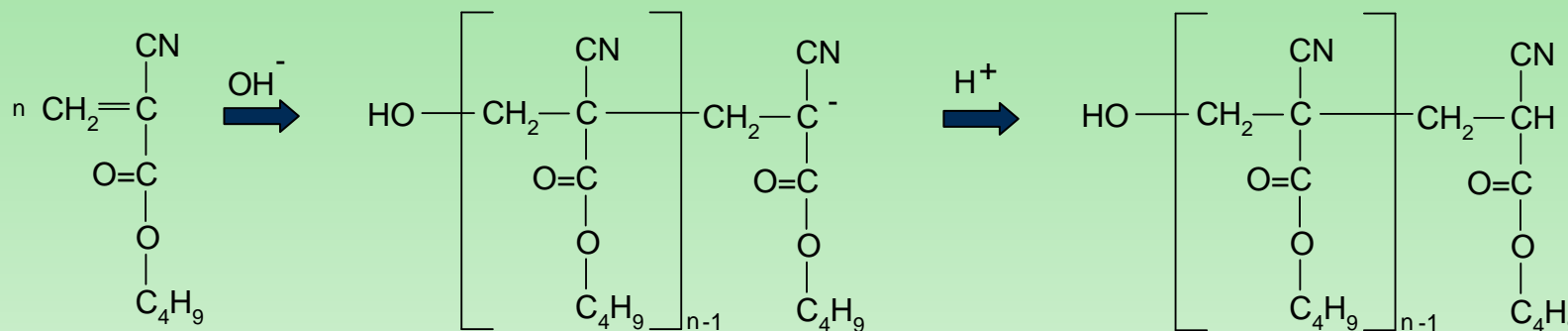
Crosslinked starch



Capsules via reaction at interface



Anionic polymerization of n-butylcyanoacrylate (BCA)

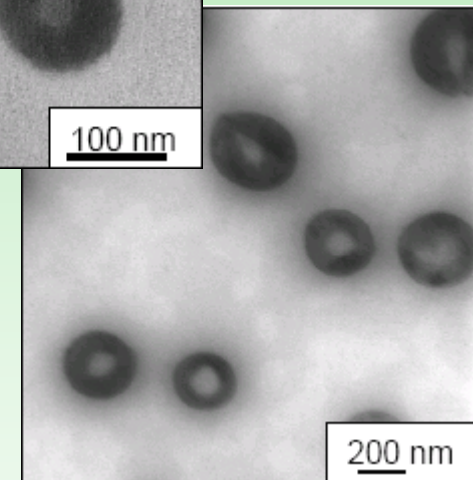
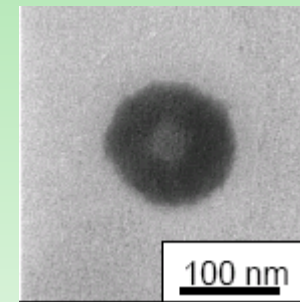
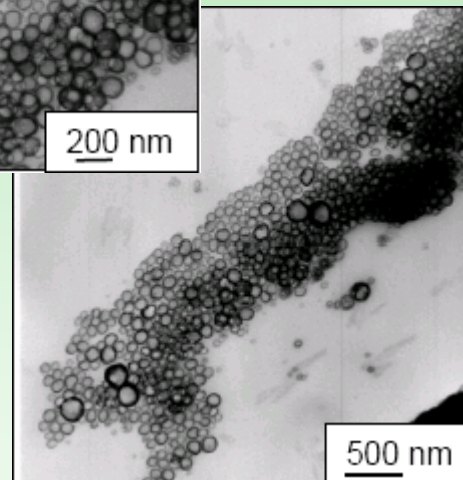
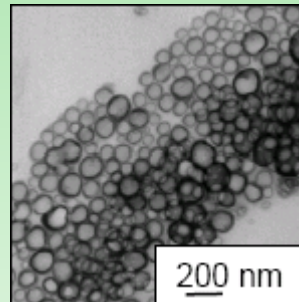
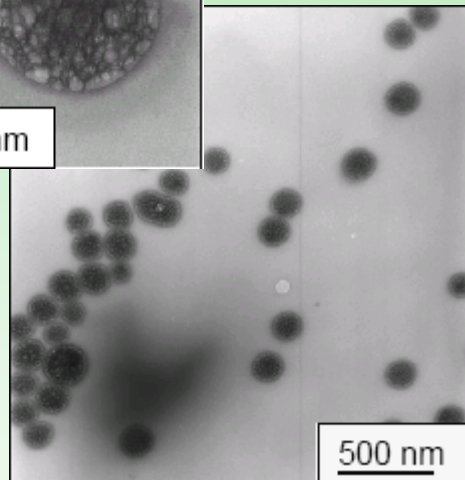
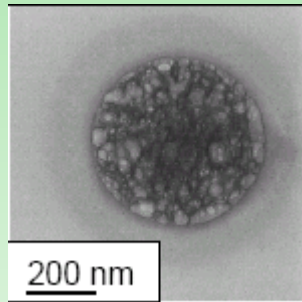
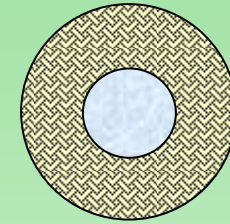
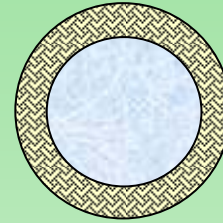
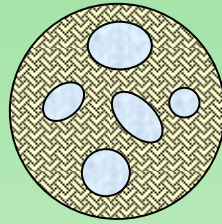


Amount of dsDNA inside the droplets

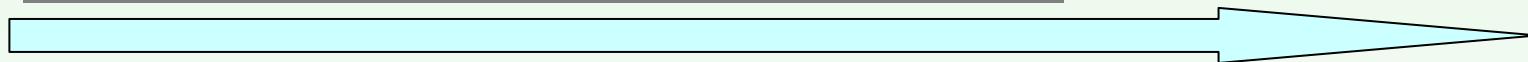
Amount of dsDNA inside the PBCA capsules

About 15% of encapsulated DNA is in a form of free chains

Capsules via reaction at interface



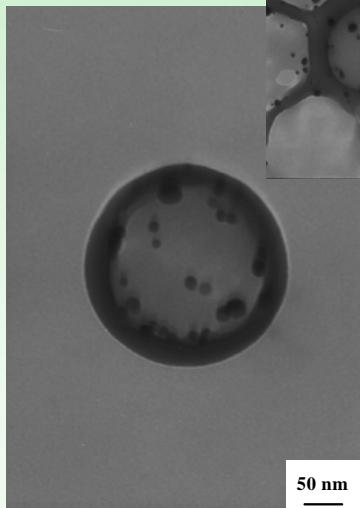
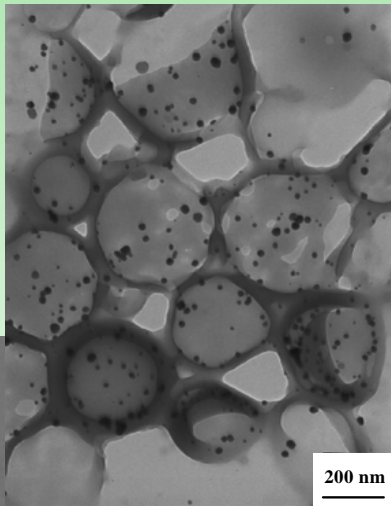
Increase of n-butylcyanoacrylate concentration



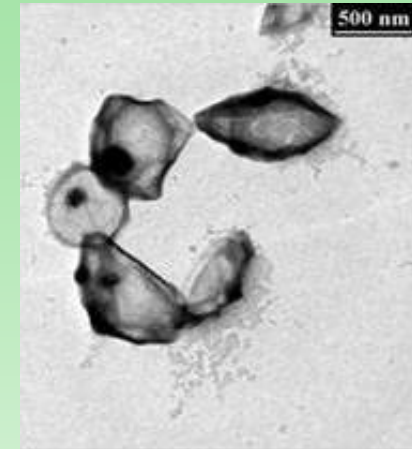
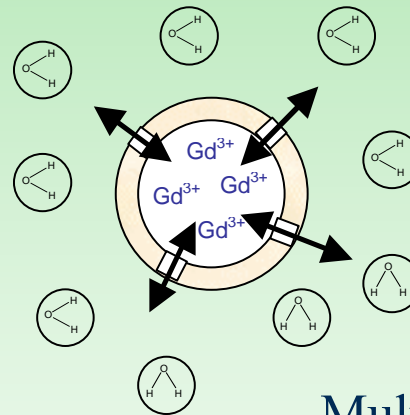
Capsules as nanocontainers



Reaction in the nanocapsule,
e.g. reduction of Ag^+ to Ag

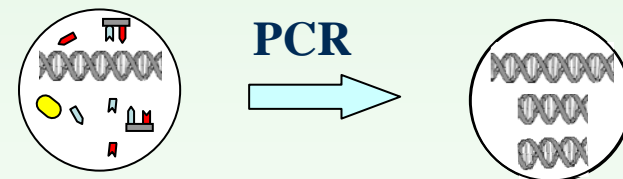


Hydrophilic Gd
complexes for magnetic
resonance imaging (MRI)
Biomedical application



Macromol. Chem. Phys. **2007**, *208*, 2229-2241.

Multiplication of dsDNA
inside the droplets



Macromolecules **2007**, *40*, 3122-3135.

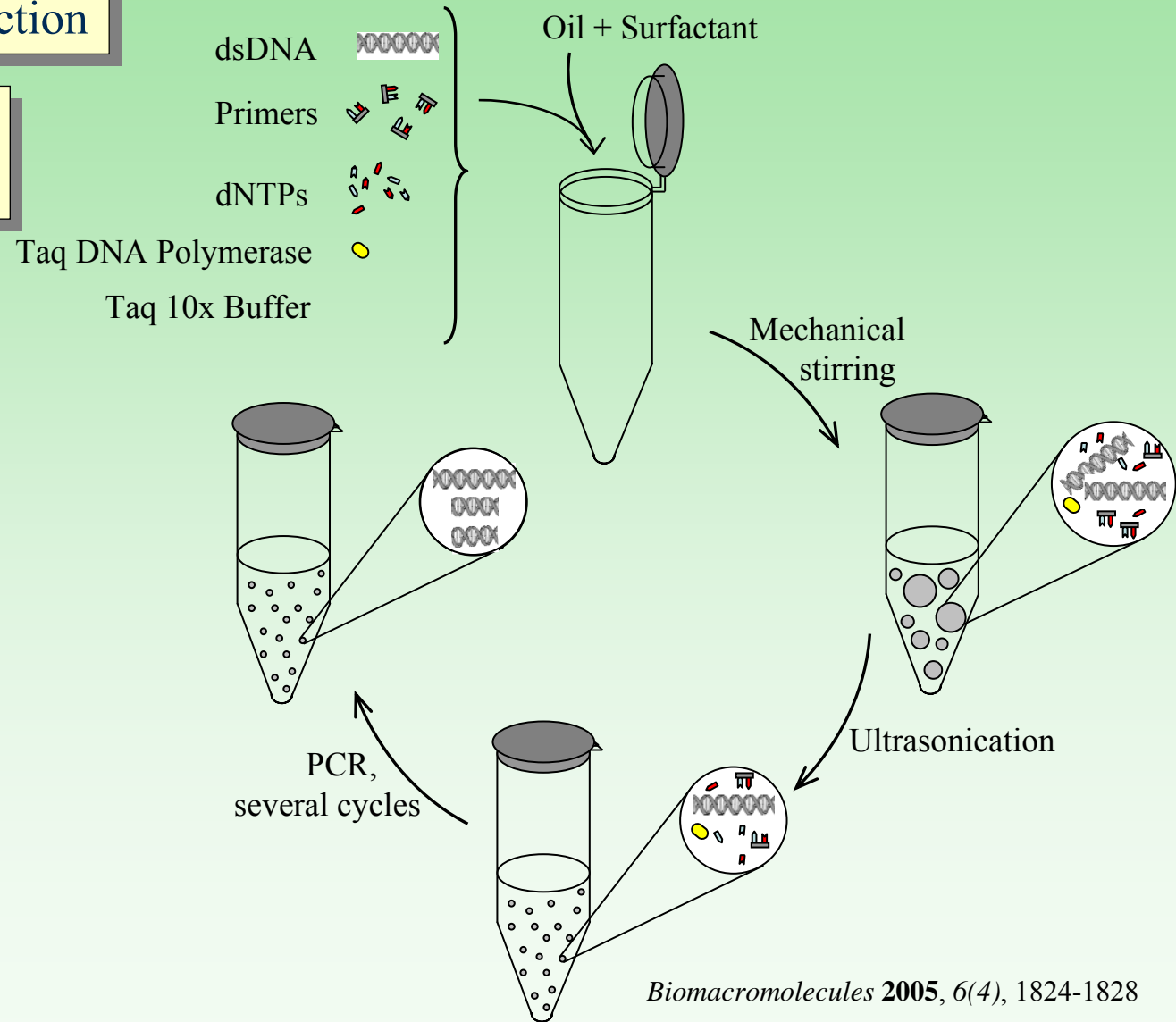
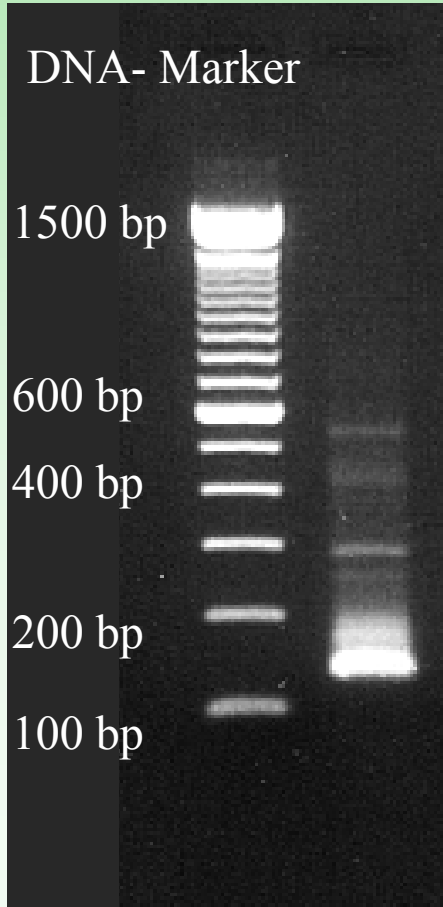
Biomacromolecules **2005**, *6*(4), 1824-1828

Droplets as “Bioreactors”



Polymerase Chain Reaction

DNA template: 286 bp
PCR – product: 135 bp

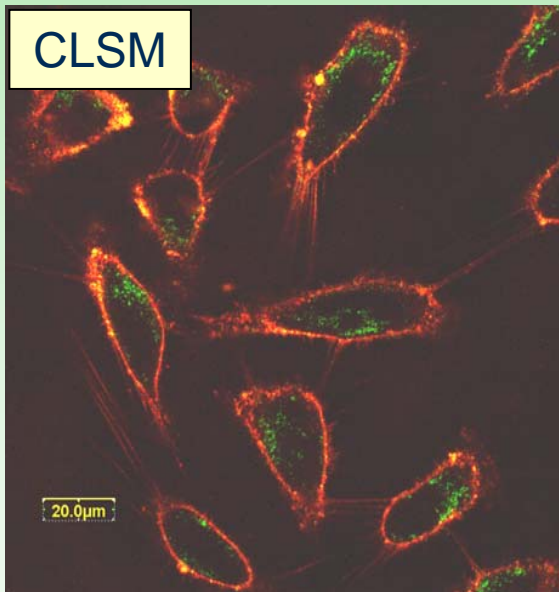


Cellular uptake



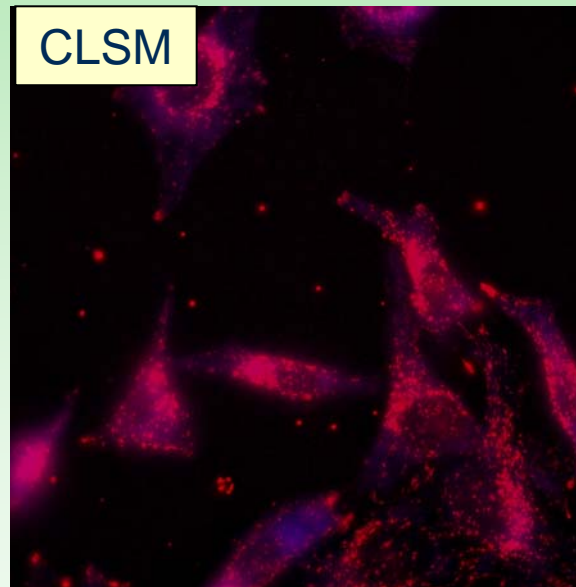
Polyurea capsules with fluorescein taken up by HeLa cells

CLSM



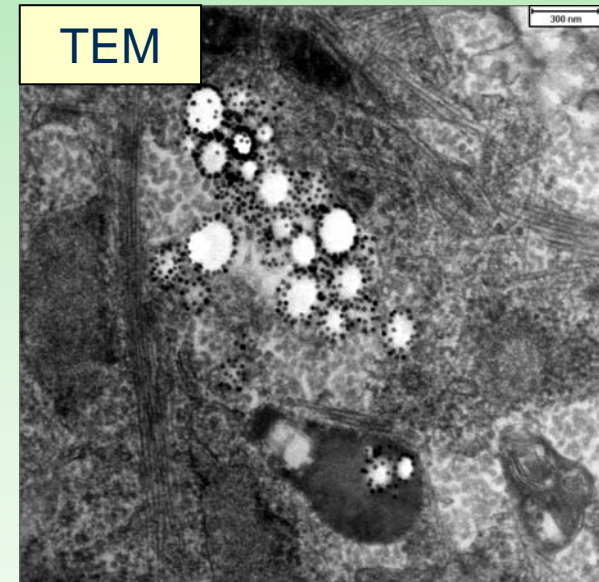
Crosslinked starch capsules with rhodamine taken up by HeLa cells

CLSM



Release of magnetite from poly(L-lactide) particles in MSC

TEM



Release mechanisms



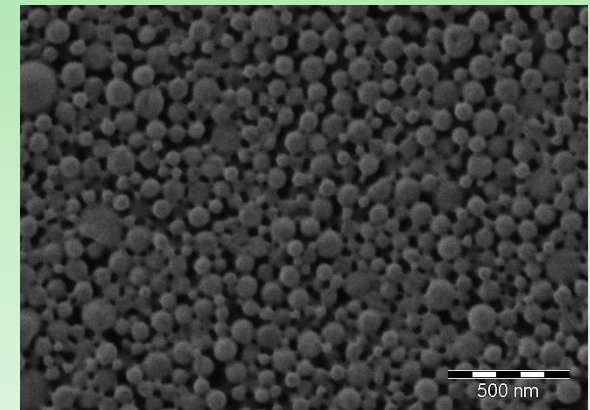
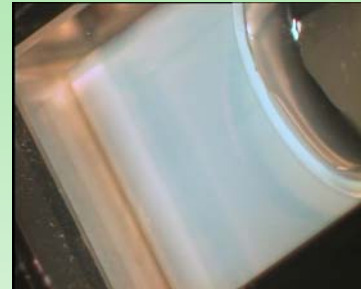
1. Slow release

- Diffusion from the nanocapsules: release depends on the shell thickness and type of polymer

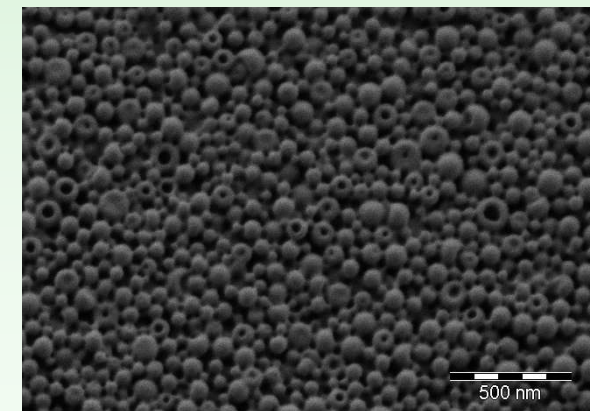
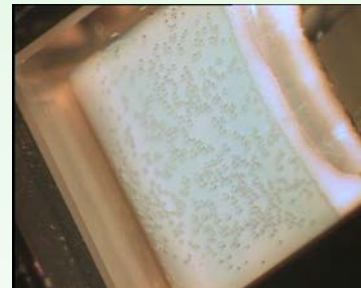
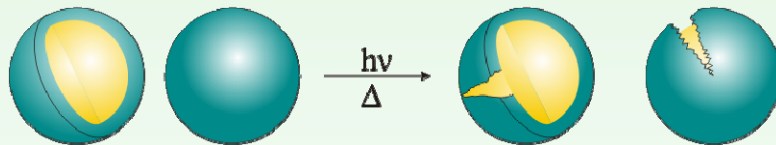
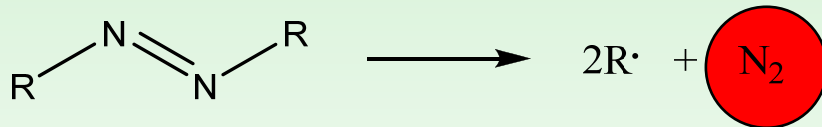
2. Fast release

- „switch“ e.g. by temperature, pH change, enzyme...

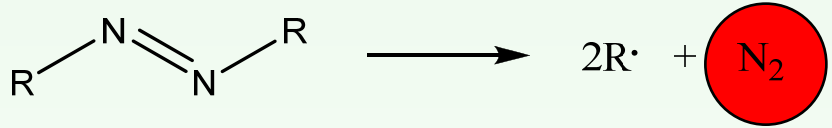
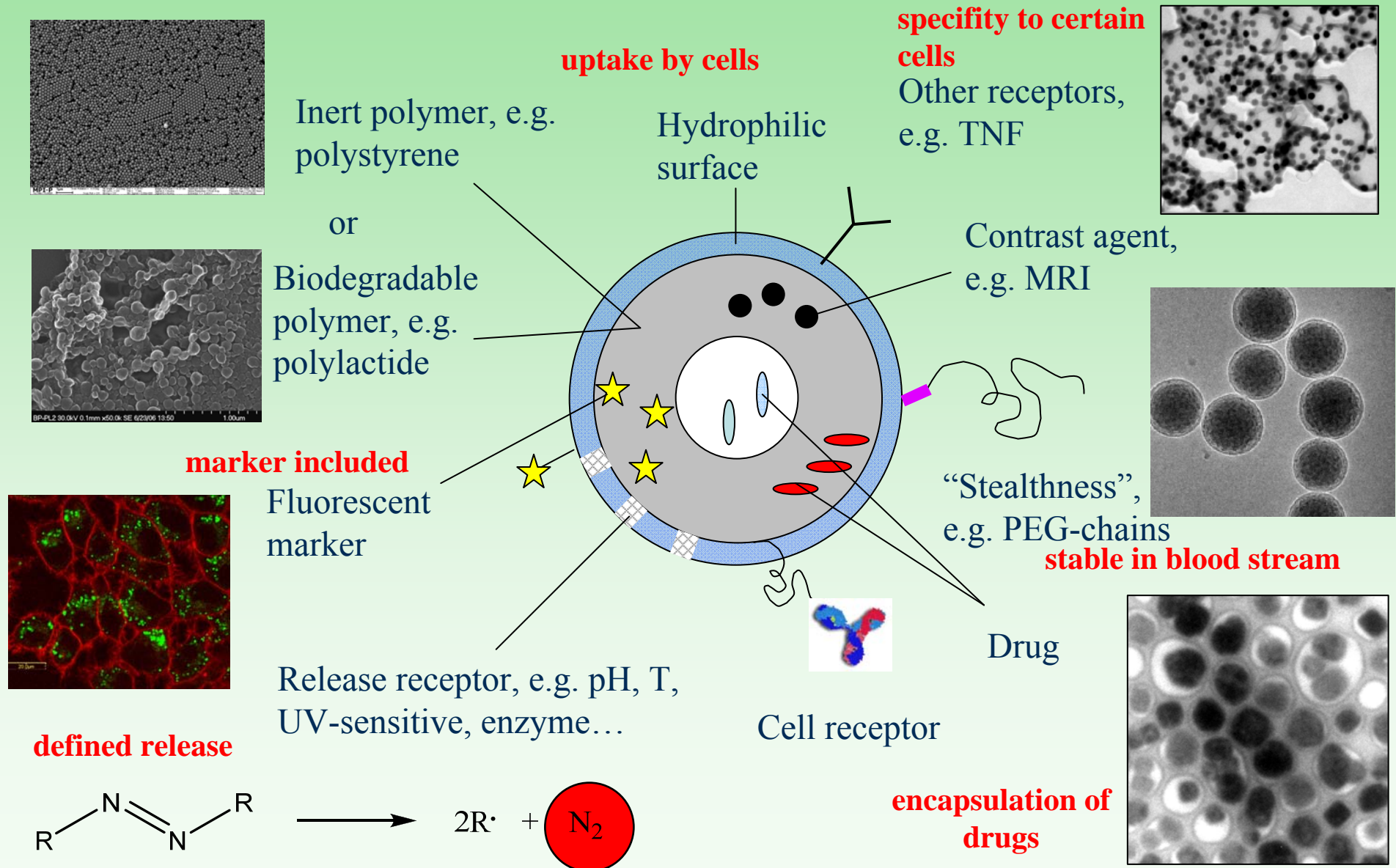
- Degradation of the nanocapsules: release depends on (bio)degradability



Incorporation of blasting agent inside the capsule



Summary





MAX-PLANCK-GESellschaft

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PCR)



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(Polyurethane capsules)



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(Polylactide composite particles)



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(PMMA capsules with blasting agents)

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