Polymere Therapeutika WS 2009/2010

Skript vom 10.11.2009

- Formulation of drugs by matrixes (controlled release)
  - Tablets, pills (oral delivery), deposits, transdermal applications
  - Protection (acid), slow release for longer drug levels
  - Drug release by erosion or diffusion from polymeric or porous materials

- Drug transport by particle-based systems
  - Parenteral administration (i.v.; i.p.)
  - Non-covalent transport
  - „Self assembly“ – systems, such as micelles, Liposomes
  - Polymeric nanoparticles

- Polymer-drug conjugates
  - Parenteral administration (i.v.; i.p.)
  - Covalent conjugates (stable or cleavable linkers)
  - PEGylation
  - Other macromolecular carriers
  - Additionally „self assembly“ possible

Drug transport by particle-based systems

- Drug transport by particle-based systems
  - Non-covalent transport of drugs
  - Polymeric nanoparticles
  - Micelles, Liposomes

„Self-assembly“

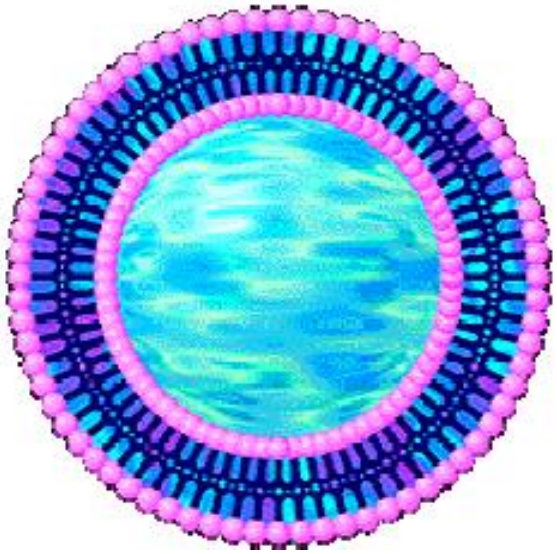
Self assembly is typically approach via one of two methods:

1. Using a molecule that has a hydrophilic head and hydrophobic tail to form a shell to entrap drug molecules (**micelles, liposomes**)
2. Electrostatic interaction to entrap drug molecules (**polyelectrolyte nanoparticles**)

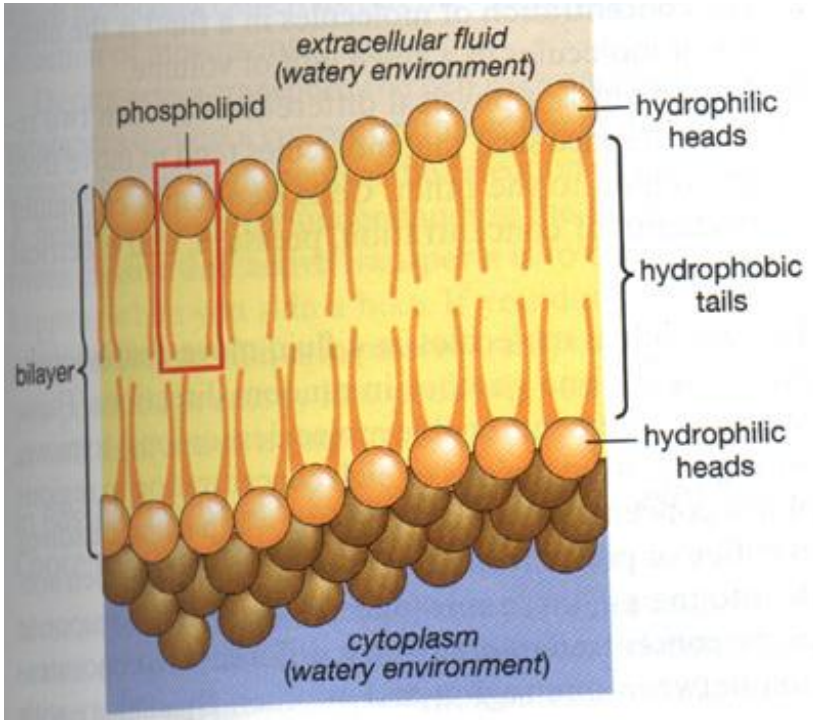
Self assembly

- Liposomes

Bilayer
(phopholipids)



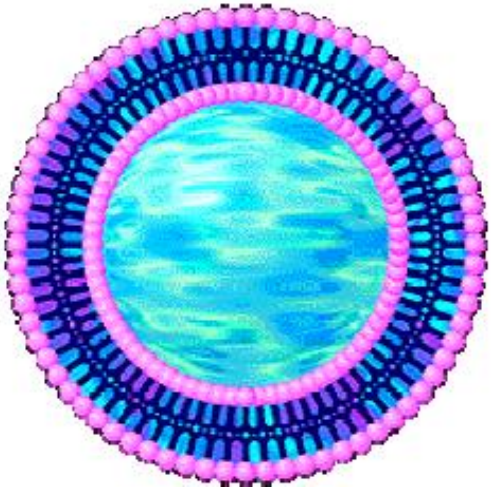
Compare with cell membrane



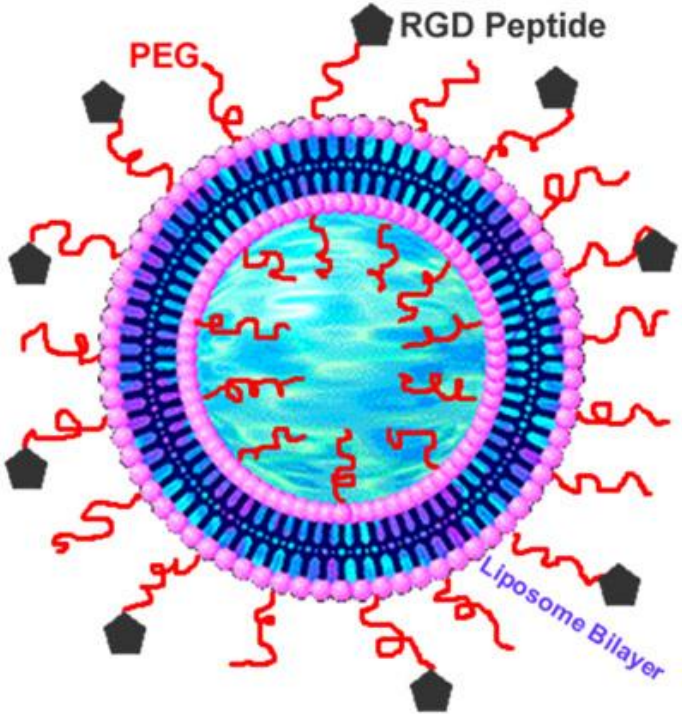
Self assembly

- Liposomes

Bilayer
(phopholipids)



Drug delivery system



Drug entrapment inside (hydrophilic)
Drug entrapment within bilayer (hydrophobic)

Surface modification (e.g with PEG)
Loading with targeting molecules (e. g. receptor-binding peptides)

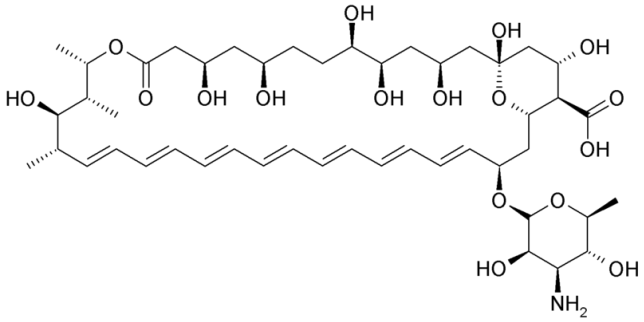
Self assembly

- Marketed Liposome products

AmBisome® (Gilead Sciences)

Amphotericin B (Membrane intercalated)

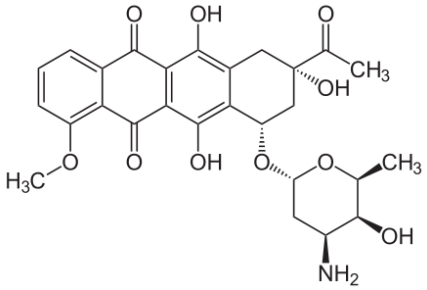
Antifungal drug to treat infections



DaunoXome® (Gilead Sciences)

Daunorubicin (Encapsulated)

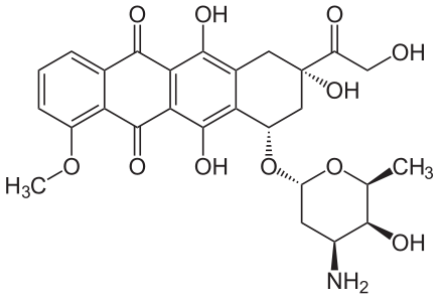
Karposi‘s Sarcoma



DOXIL® (J&J ALZA)

Doxorubicin (Encapsulated),
Liposome with PEG layer

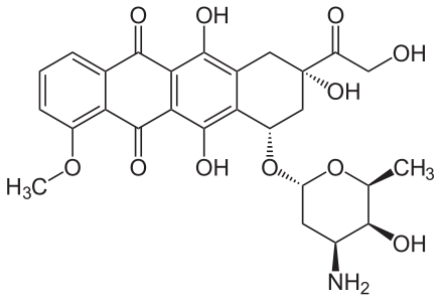
Treatment of ovarian cancer



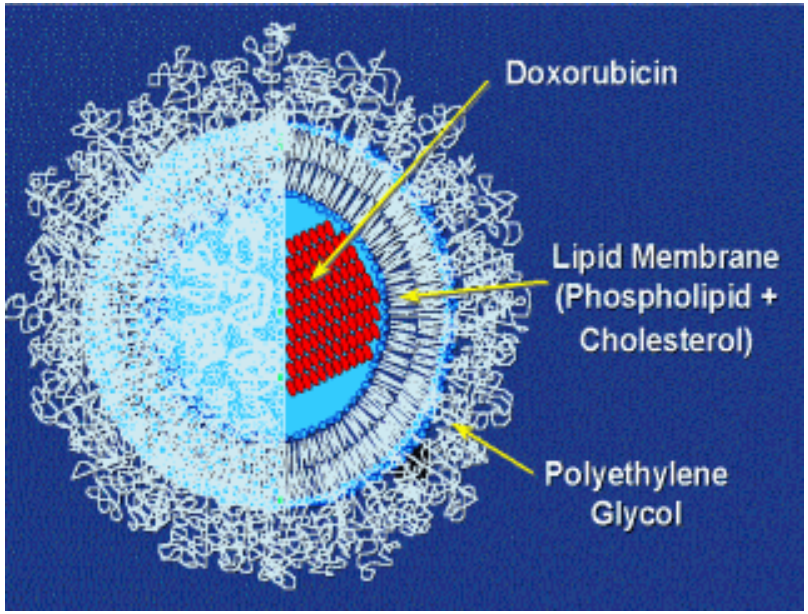
DOXIL
(doxorubicin HCl liposome injection)

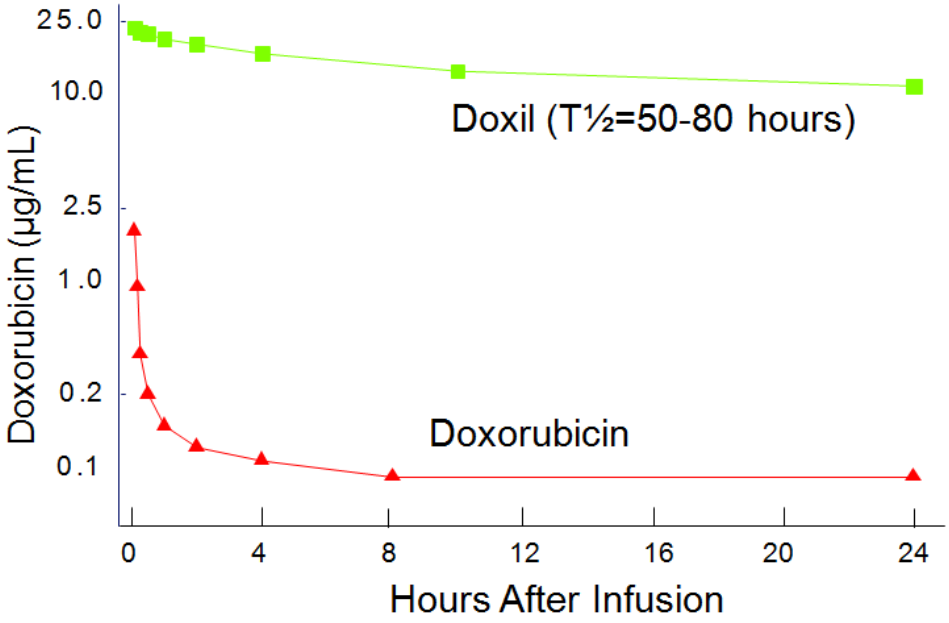
Self assemby

- DOXIL (Doxorubicin-Liposomal)



  - Doxorubicin verkapselt im Liposom
  - 15000 Doxorubicin-Moleküle pro Vesikel
  - PEGylierung der Liposomoberfläche
  - Lange Zirkulation im Blutkreislauf und langsame Aufnahme durch Leber
  - langsame, gezielte Freisetzung des Wirkstoffes
  - 6-fache Effizienz im Vergleich zu freiem Doxorubicin





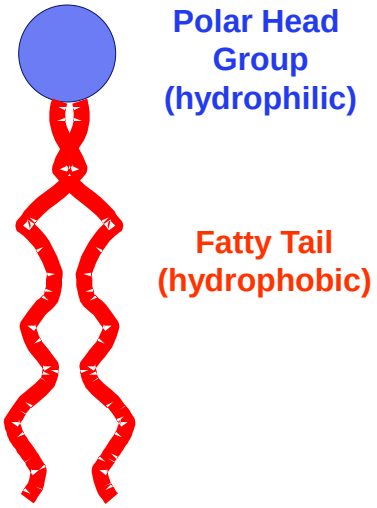
Self assembly

- Micelles

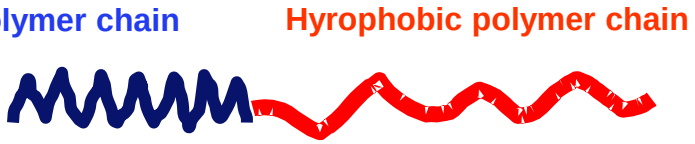
→ Entrapment by micelle formation can be obtained using lipids, surfactants and/or amphiphilic block copolymers

- Small unilamellar (10 to 50nm)
- Large unilamellar (50 nm to 1µm)
- Large multilamellar (100 nm to 20 µm)

Tensid



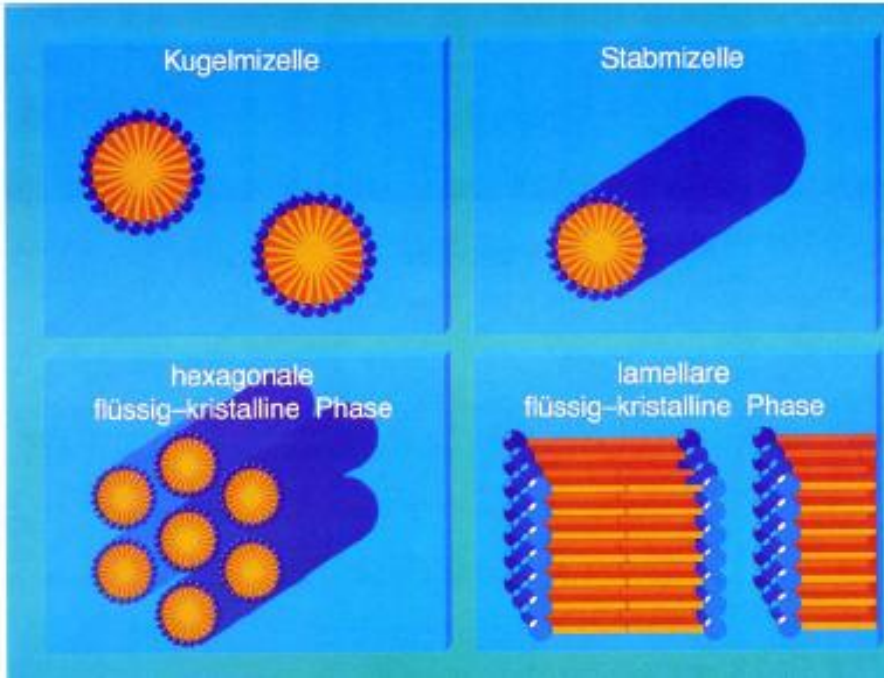
Diblock Co-polymer



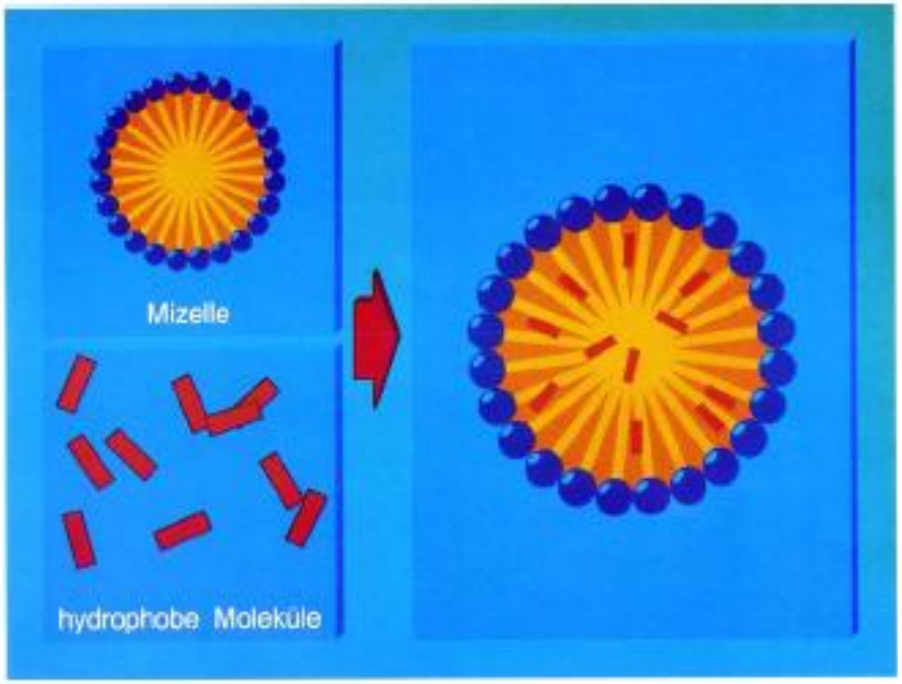
Self assembly

- Micelles

- Micellar architectures



- Entrapment of hydrophobic drug molecules



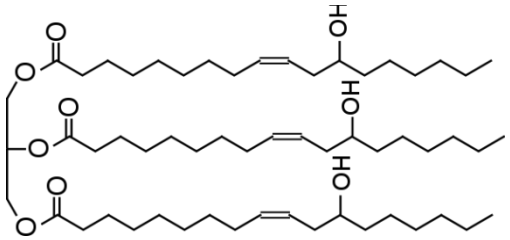
- **Emulgierung (z.B. O/W- oder W/O-Emulsion)**
- **Suspensionsstabilisierung**
- **Schaumbildung (Schaum = Dispersion Luft/Wasser)**

Self assembly

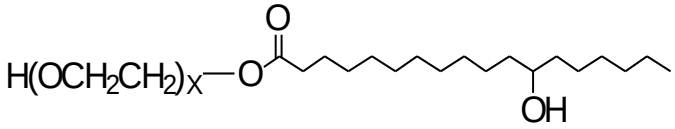
- Micelles, Surfactants

→ Solubilization of hydrophobic, insoluble drugs

Cremophor EL (BASF) Polyethylene glycol + Castor oil

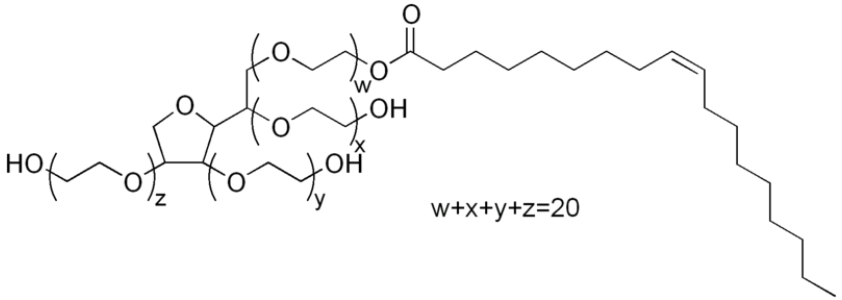


Solutol (BASF)



Polyethylene glycol Hydroxystearinsäure

Tween 80, Polysorbate 80



Self assemby

Adv Polym Sci (2006) 193: 67–101
DOI 10.1007/12_025

Published online: 8 November 2005

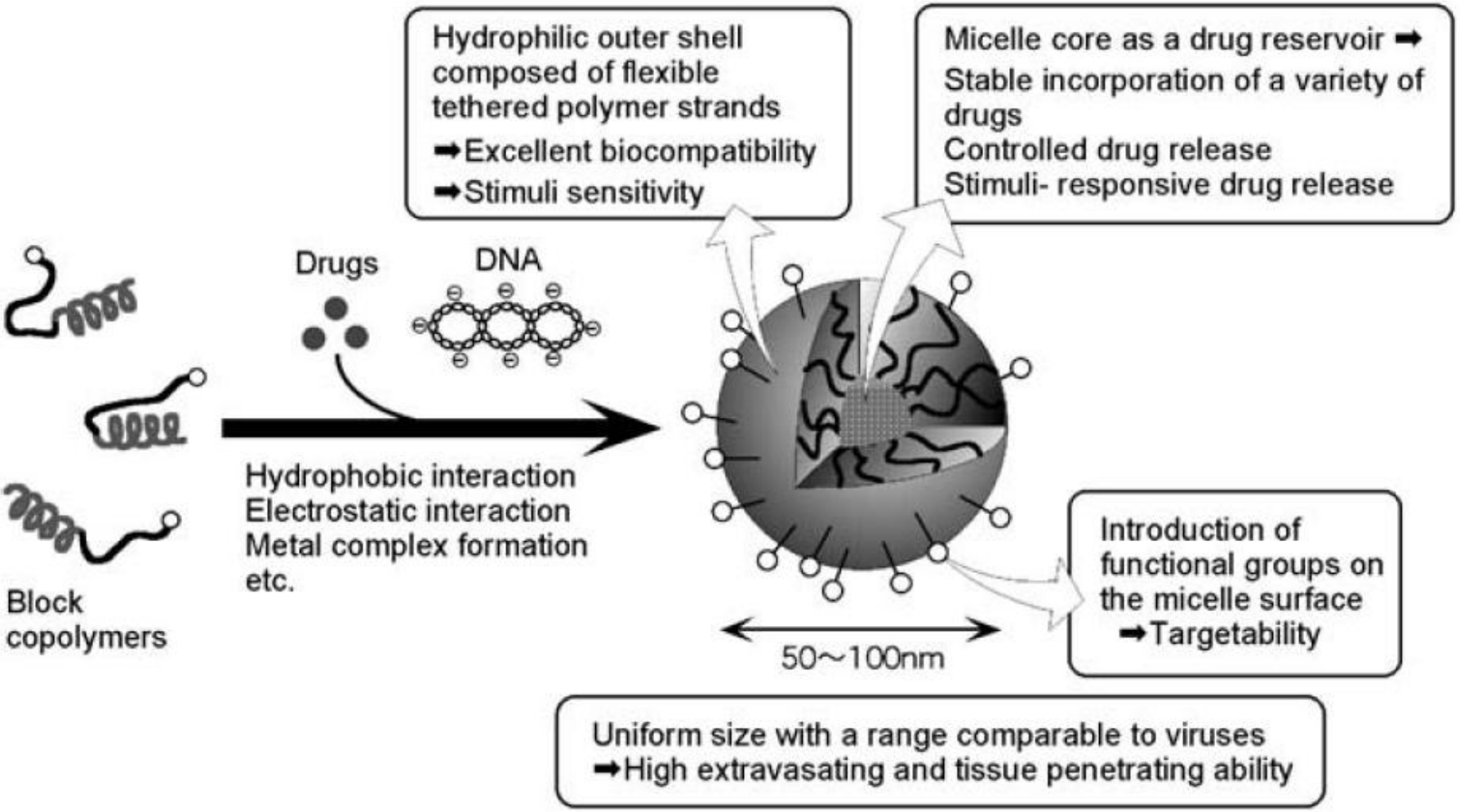
Nanostructured Devices Based on Block Copolymer Assemblies for Drug Delivery: Designing Structures for Enhanced Drug Function

Nobuhiro Nishiyama[1] · Kazunori Kataoka[1,2] (✉)

Y. Kakizawa, K. Kataoka
Advanced Drug Delivery Reviews 54 (2002) 203 –222

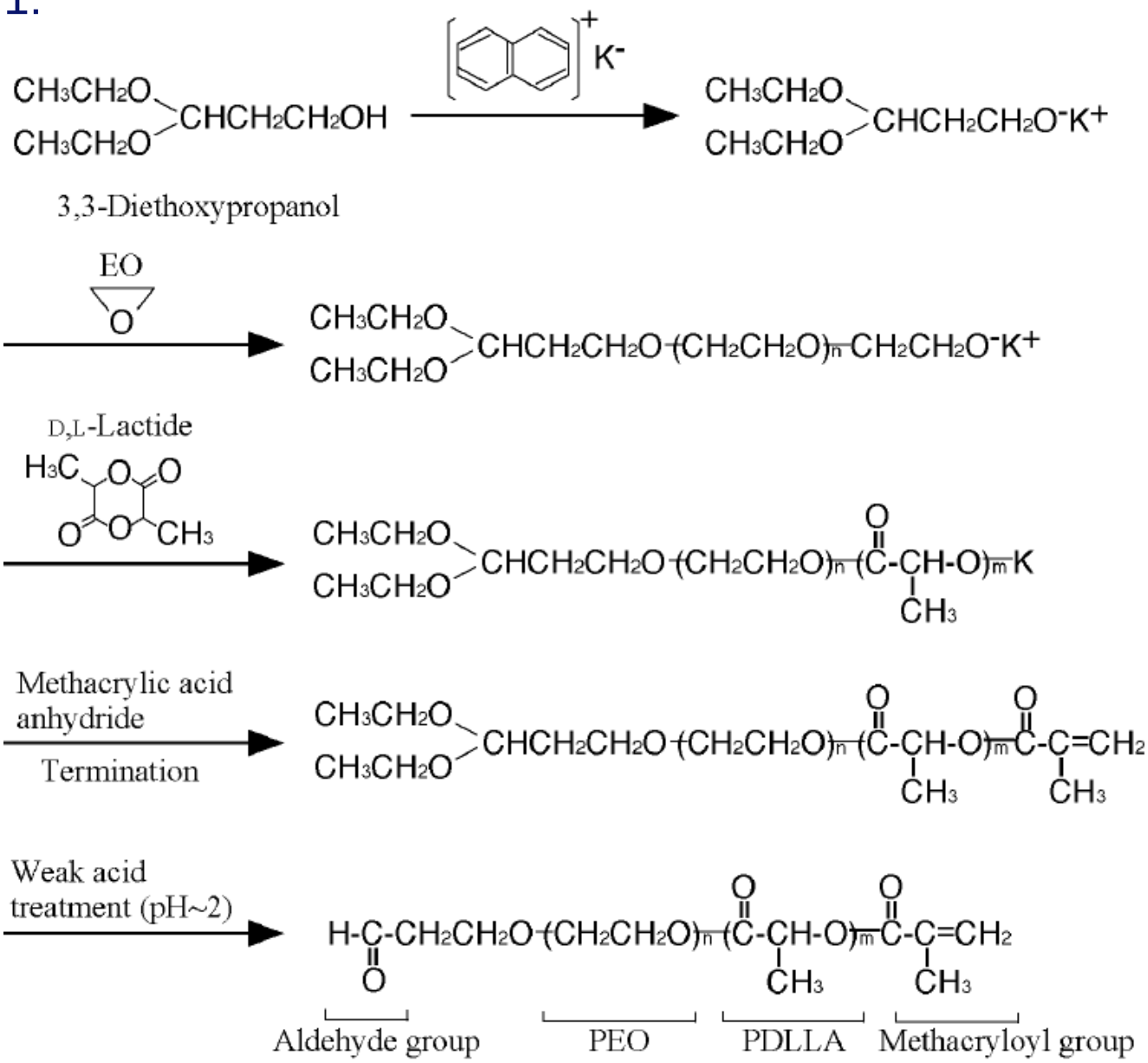
Self assemby

- Block Copolymers
  → Amphiphilic self assembly



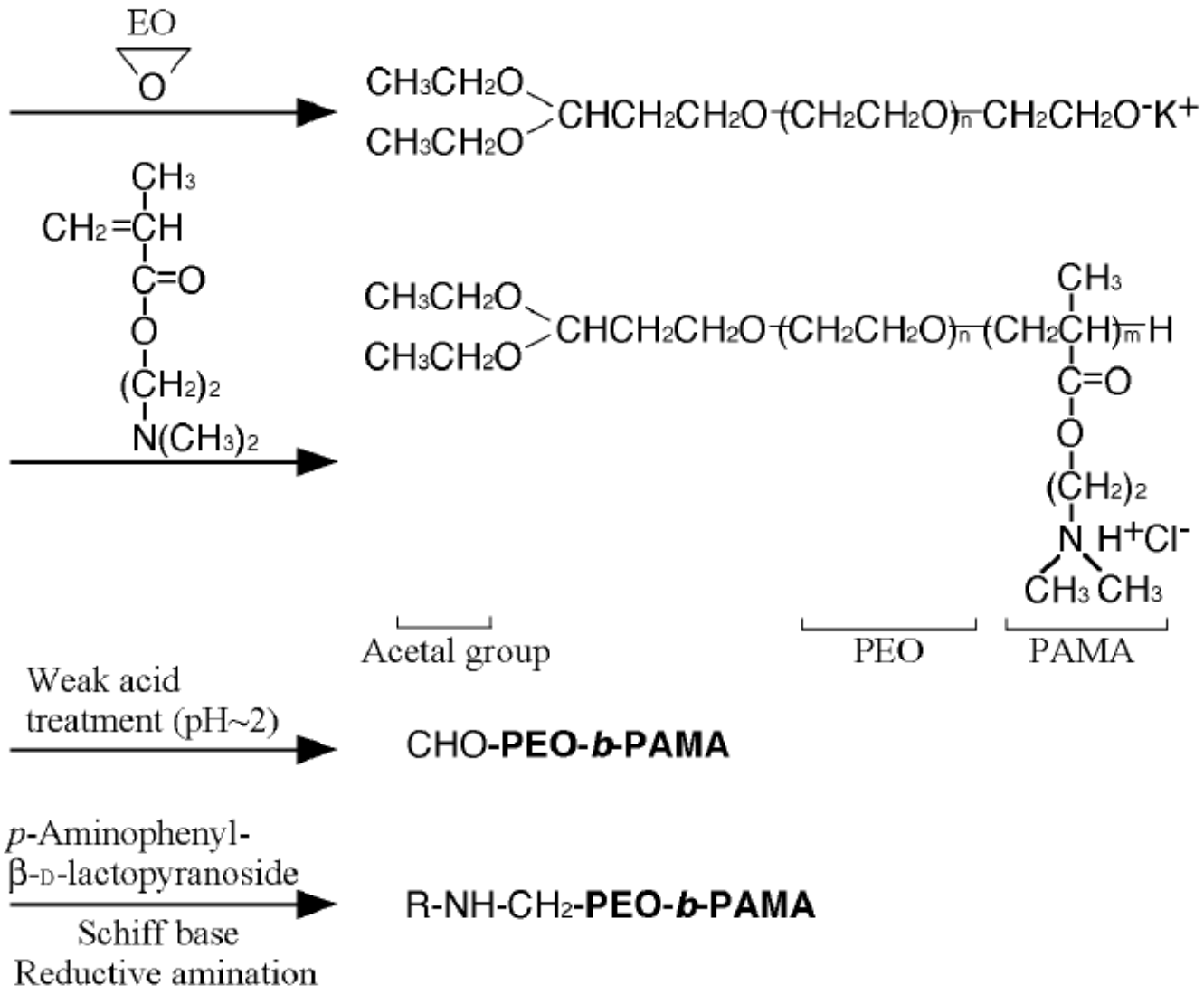
Self assemby

Synthetic example 1:



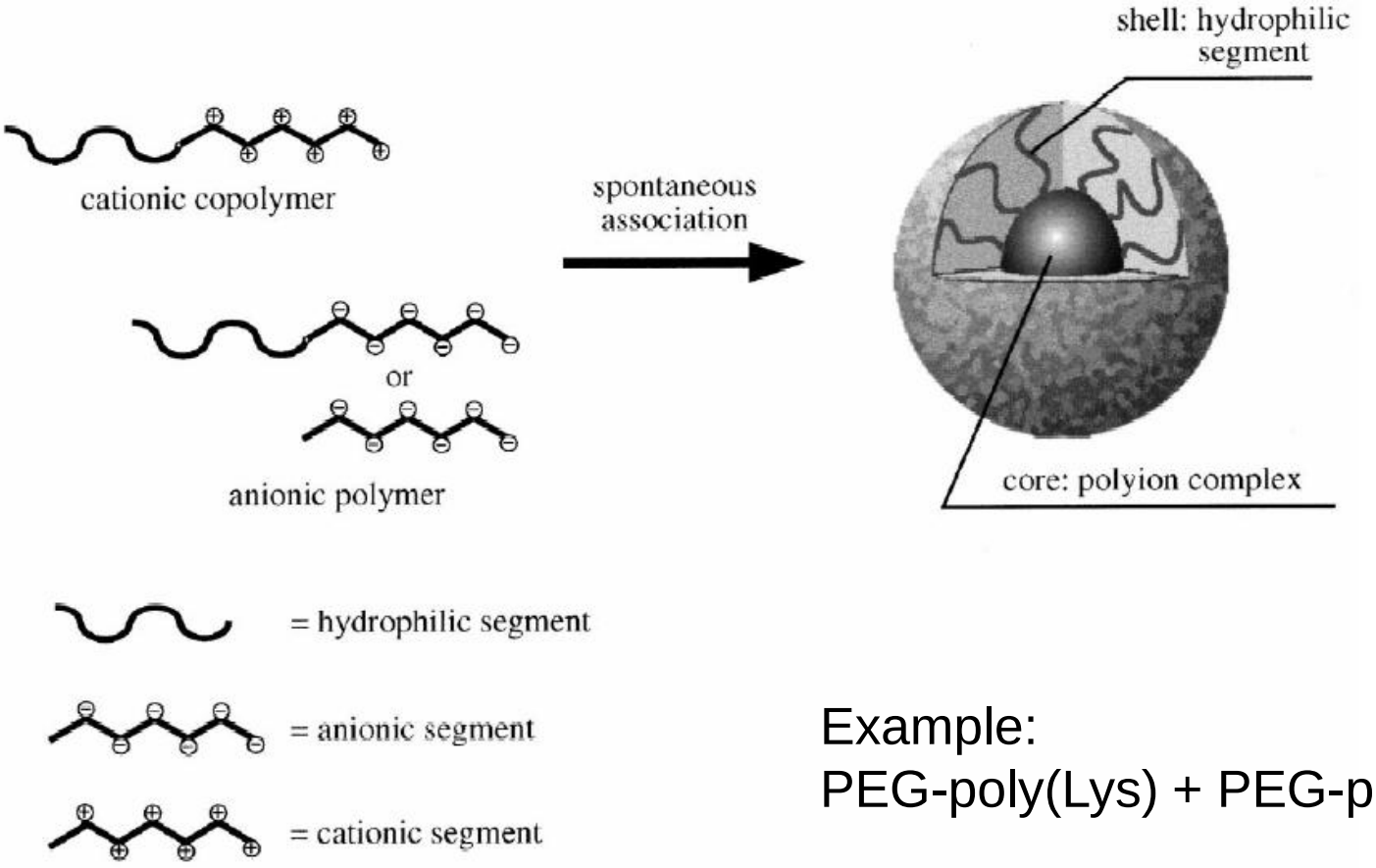
Self assemby

Synthetic example 2:



Self assemby

- Polyelectrolytes
  - → Charged self assembly



Example:
PEG-poly(Lys) + PEG-poly(Asp)

Y. Kakizawa, K. Kataoka / Advanced Drug Delivery Reviews 54 (2002) 203 –222

Polymeric nanoparticles

- Studied materials in R&D
  - Gums (Ex. Acacia, Guar, etc.)
  - Chitosan
  - Pullulan
  - Gelatin
  - Sodium alginate
  - Albumin

natural sources
mostly polysaccharides and proteins

  - Poly(2-hydroxy ethyl methacrylate)
  - Poly(N-vinyl pyrrolidone)
  - Poly(methyl methacrylate)
  - Poly(vinyl alcohol)
  - Poly(acrylic acid)
  - Polyacrylamide
  - Poly(ethylene-co-vinyl acetate)
  - Poly(ethylene glycol)
  - Poly(methacrylic acid)

synthetic origin:
polyethylene backbone

  - Polylactides (PLA).
  - Polyglycolides (PGA)
  - Poly(lactide-co-glycolides) (PLGA)
  - Polyanhydrides
  - Polyorthoesters
  - Polycaprolactone

esters
orthoesters
anhydrides

Polymeric nanoparticles

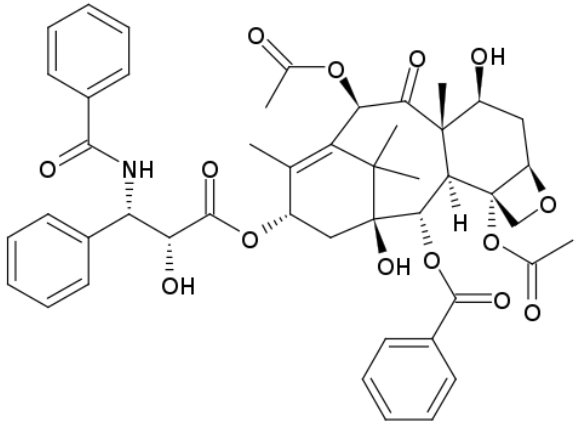
Technical process leading to nanoparticles

- Emulsification followed by solvent evaporation/cross-linking
- Emulsion polymerization
- Spray drying
- Supercritical fluid technology
- Electrospray method

- Drug entrapment or encapsulation
  - During particle preparation (drug has to be stable under the conditions)
  - Into final particle (drug has to penetrate/diffuse into particle)

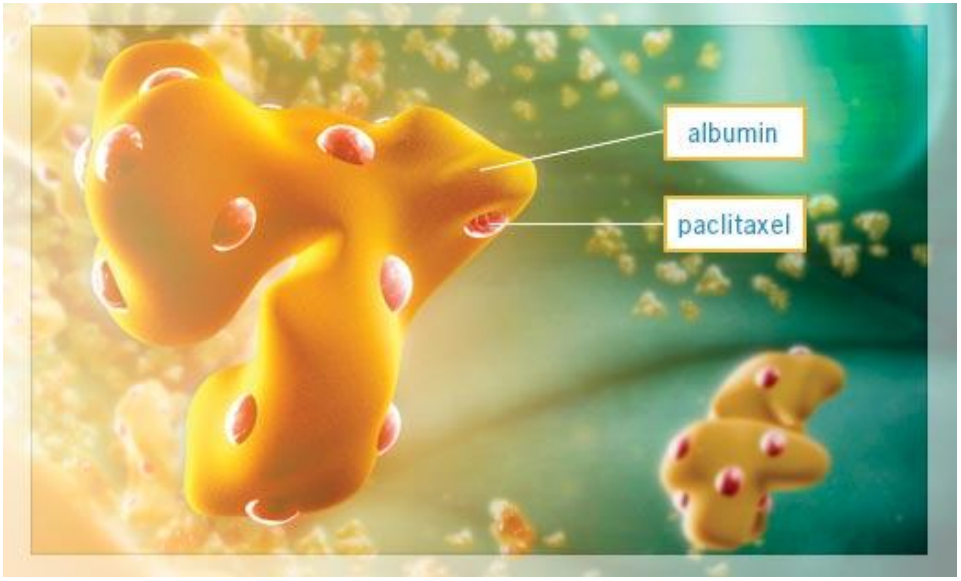
Polymeric nanoparticles

- Nanoparticular albumine
  - → Abraxane (Albumine-paclitaxel)



Injectable suspension for treatment of breast cancer after failure of chemotherapy

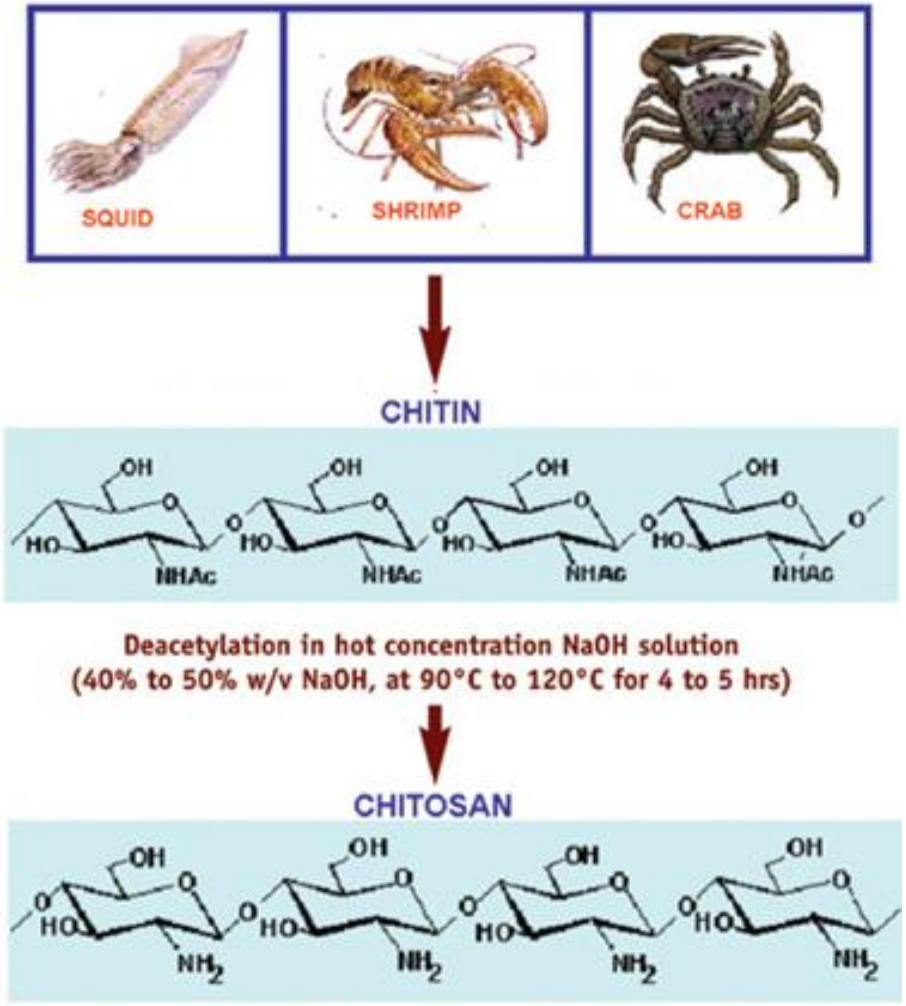
Albumin facilitates the administration of water-insoluble compounds
Allows delivery of a 49% higher dose of paclitaxel vs solvent-based paclitaxel



Polymeric nanoparticles

- Chitosan Particles

- Cationic polysaccharide
- Cheap production from natural waste material
- Poor solubility
- Processing into nanoparticles for drug delivery
- Combination with other polymers (coating)
- Modification of amino groups

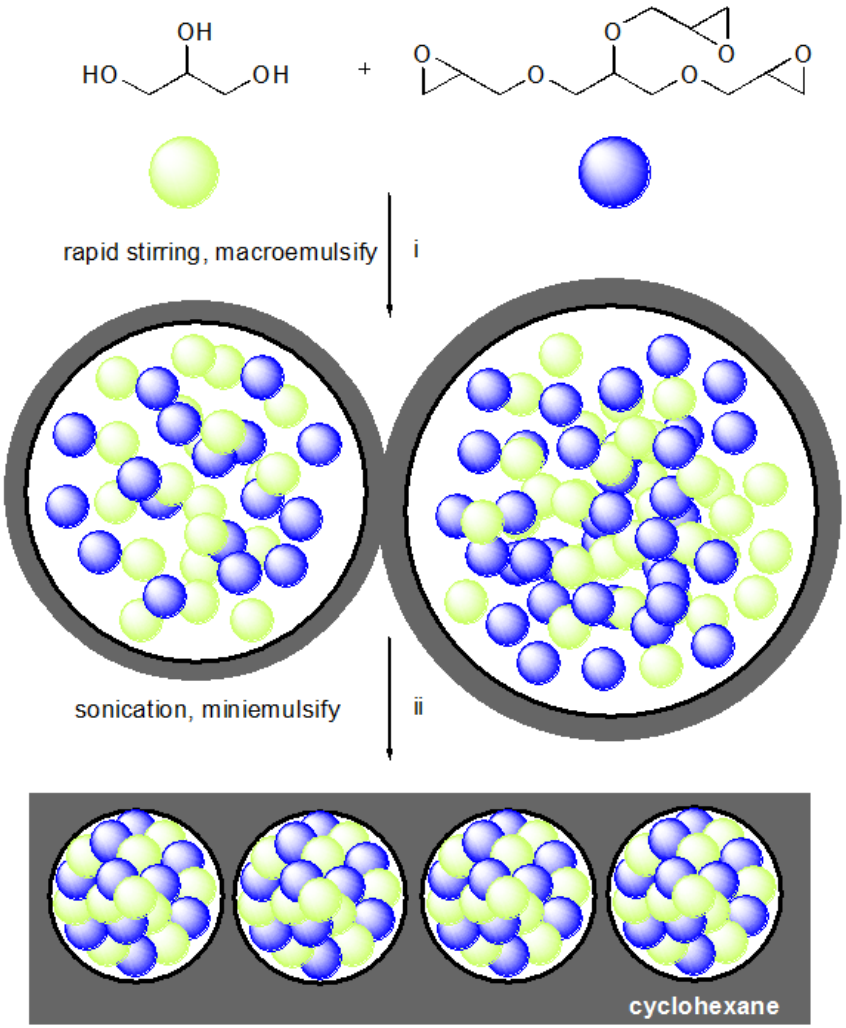


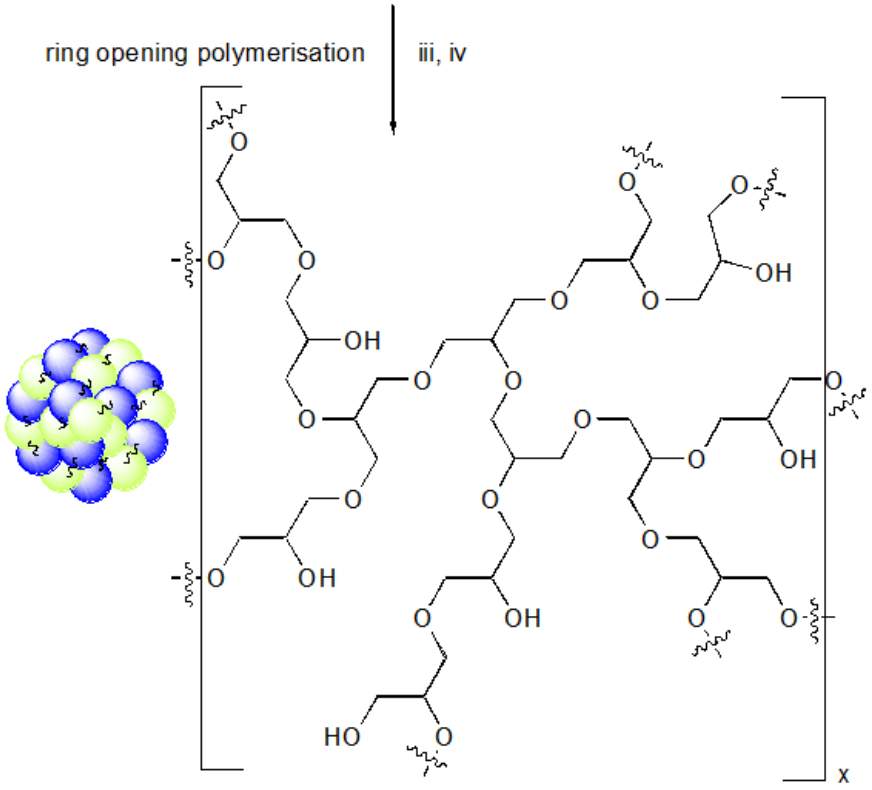
Int J Nanomedicine.
2006 June; 1(2): 181–187

Mini Rev Med Chem.
2009 Apr;9(4):463-9.

Polymeric nanoparticles

- Polyglycerol nanoparticles

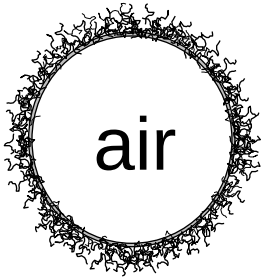


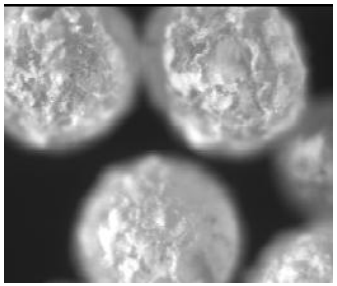


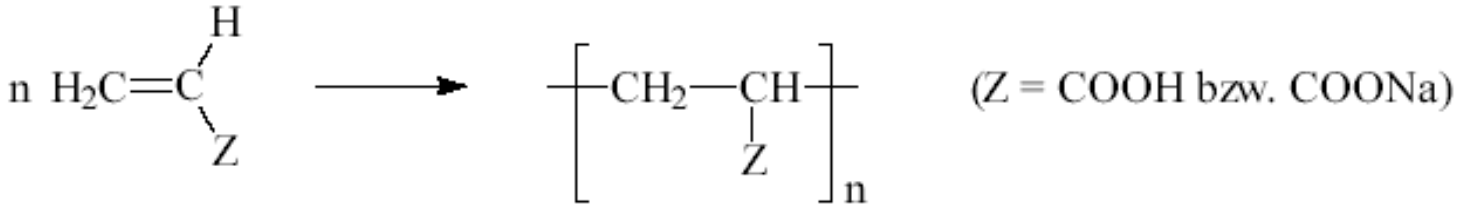
Research of AG Haag; Angew Chem Int Ed Engl. 2009;48(41):7540-5

Polymeric nanoparticles

- Ultrasound contrast agents
  → µm-sized gas-filled bubbles

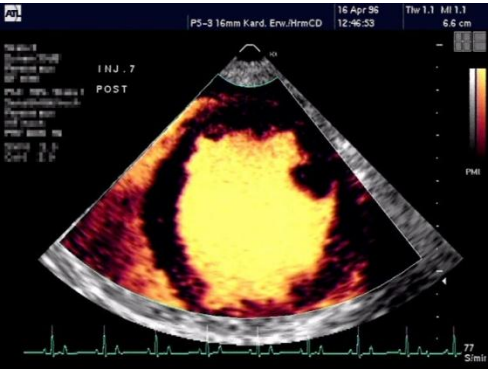






Acrylsäure bzw.
Natriumacrylat

Polyacrylsäure bzw.
Natriumpolyacrylat



anionic polymerization