Production of monodisperse latex particles

- Heterogeneous polymerisation processes for latex particles
- Emulsion polymerisation process for monodisperse polystyrene NP
- Poly-(n-butyl-2-cyanoacrylate) NP for medicine and pharmacy
- Miniemulsion process - theoretical and experimental approach

Lecture series: Nanoparticle Technology
Heterogeneous polymerisation techniques of particle formation

polymerisation

monomers → polymer

auxiliaries (e.g. initiators, buffer, emulsifier, stabiliser)

Homogeneous systems: bulk polymerisation, solution polymerisation → bulk polymeric mass

Heterogeneous systems: emulsion polymerisation, suspension polymerisation, dispersion polymerisation, precipitation polymerisation, miniemulsion polymerisation → latex particles

emulsion polymerisation
emulsifier free emulsion polymerisation
dispersion polymerisation
precipitation polymerisation

nucleation and growth

polymer latex particles

polymer latex

0.01 μm 0.1 μm 1.0 μm 10 μm 100 μm 1000 μm
Suspension polymerisation process (Perl polymerisation)

I  monomer droplets before reaching identity point
   - monomer sparely soluble in water,
   - monomer redispersion by agitation, stabilisation of droplets (0.15-5 mm) by polyvinylalcohol or BaSO₄ (emulsion)
   - initiator (e.g. AIBN) soluble in monomer, polymerisation inside monomer droplets (suspension)

II monomer droplets after reaching identity point
   - secondary perls
   - primary perls

redispersion by agitation
creaming
redispersion
coalescence
agglomeration
degglomeration
polymerisation
interfacial tension
**Precipitation polymerisation process**

- monomer dissolves in continuous phase - homogeneous solution (e.g. water-based polymerisation of acetonitrile, polymerisation of styrene in hexane or ethanol)
- initiator is soluble in continuous phase
- initiation and polymerisation in the homogeneous phase - homogenous nucleation (primary particles)
- agglomeration of nuclei - coagulative nucleation (particles are polydisperse 0.1 - 1000 μm)
- polymerisation medium is a precipitant for the resulting polymer

**Dispersion polymerisation process**

- monomer dissolves in continuous phase - homogeneous solution (e.g. water-based polymerisation of acetonitrile, polymerisation of styrene in hexane or ethanol)
- initiator is soluble in continuous phase
- initiation and polymerisation in the homogeneous phase - homogenous nucleation (primary particles)
- presence of stabilizer !!! - sterical stabilisation - (spherical particles 0.1 - 1000 μm
- without sufficient stabilisation - agglomeration of primary particles - coagulative nucleation
- polymerisation medium is a precipitant for the resulting polymer
Emulsion polymerisation process

Theory according Fikentscher and Harkins

I Period of particle formation (Nucleation)
Inside the O/W emulsion, there are micelles (5-10 nm), surfactant stabilized monomer droplets (1-10 µm), and initiator. Monomer is solubilised inside micelles. Initiator forms radicals, later with in water sparingly soluble monomer (styrene 4 g/L at 70°C) oligo-radicals. These oligo-radicals are stabilized by surfactant (swollen micelles), or solubilised in monomer containing micelles. Polymerisation starts, formation of small latex particle. Ratio of monomer/water is 0.1–0.5, temperature from 40°C to 80°C. Disappearance of micelles.

II Period of growth
Latex particles grow until monomer droplets in emulsion are gone. Increasing surface area of the latex particle adsorbs more surfactant molecules, no micelles. Disappearance of droplets.

III Period of final polymerisation
Rest of monomers in the latex particles (50-300 nm) are polymerized.
Emulsion polymerisation process

- **number of latex particles**
  - depends on rate of radical formation, rate of increase in volume of polymer particle, interfacial area occupied by surfactant molecules, total concentration of surfactant in the micelle

- **rate of polymerisation** - \( r = k_3 \left( f \cdot \frac{k_1}{k_4} \right)^{1/2} [I]^{1/2} [M] \)

- **degree of polymerisation** - \( P = k_3 [M] \cdot t \) with \( t \) interval of successive entries of radicals in monomer-polymer particle

Emulsifier free emulsion process

- **monomer dissolves sparsely in continuous phase** (styrene - 4 g/L in water at 70°C)
- **initiator (e.g. potassium peroxodisulphate) is soluble in continuous phase**
- **Initiator forms radicals, later in water with the monomer oligo- and macro-radicals (e.g. potassium alkoxy sulphate radicals)**,
- **homogenous nucleation (primary particles) - stabilized by polymer (charged by sulphate groups on surface)**
- **without sufficient stabilisation - agglomeration of primary particles - coagulative nucleation particles**
- **polymerisation medium is a precipitant for the resulting polymer**
- **ratio monomer to water much smaller than in normal emulsion polymerisation**
**Free radical polymerisation process of styrene**

**Initiation:** generation of free radicals

\[ I \xrightarrow{} 2 \cdot R \cdot \quad (1) \]

reaction with monomer to form growing chains

\[ R \cdot + M \xrightarrow{} R_1 \cdot \quad (2) \]

\[ r_1 = k_1 \cdot [I] \text{ with } k_1 = 6.89 \cdot 10^{-6} \text{ s}^{-1} \text{ for potassium peroxodisulphate in water at } 80 \degree C \]

**Propagation (growth):** monomer is added to radicals

\[ M_i \cdot + M \xrightarrow{} M_{i+1} \cdot \quad (3) \]

\[ r_3 = k_3 \cdot [M][M \cdot] \text{ with } k_3 = 176 \text{ L/(mol·s)} \text{ for styrene at } 60 \degree C, \]

\[ k_3 \text{ independent on chain length} \]

**Termination (stop):** bimolecular combination of two radicals

\[ M_i \cdot + M_j \xrightarrow{} M_{ij} \quad (4a) \]

disproportionation of two radicals

\[ M_i \cdot + M_j \xrightarrow{} M_i + M_j \quad (4b) \]

\[ r_4 = k_4 \cdot [M \cdot]^2 \text{ with } k_4 = 7.2 \cdot 10^{-7} \text{ L/(mol·s)} \text{ for styrene at } 60 \degree C \]

**Polymerisation rate:**

\[ r = k_3 \left( f \cdot \frac{k_1}{k_4} \right)^{1/2} [I]^{1/2}[M] \text{ with } f \text{ is the radical efficiency} \]
**Experimental set-up for the polystyrene emulsion polymerisation process**

**Process parameter**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>范围</th>
</tr>
</thead>
<tbody>
<tr>
<td>temperature:</td>
<td>55°C - 85 °C</td>
</tr>
<tr>
<td>duration:</td>
<td>2.0 - 24 hours</td>
</tr>
<tr>
<td>water:</td>
<td>100 - 150 mL</td>
</tr>
<tr>
<td>surfactant (sodium dodecyl sulphate):</td>
<td>0.06 - 1.2 g</td>
</tr>
<tr>
<td>initiator (potassium peroxodisulphate):</td>
<td>0.06 - 2.0 g</td>
</tr>
<tr>
<td>buffer (borax):</td>
<td>0.01 - 0.2 g</td>
</tr>
<tr>
<td>styrene:</td>
<td>9.0 g</td>
</tr>
<tr>
<td>co-monomer (sodium styrene sulphonate):</td>
<td>0.45 - 1.0 g</td>
</tr>
<tr>
<td>addition after 15 - 120 min</td>
<td></td>
</tr>
<tr>
<td>number of stirrer revolutions:</td>
<td>500 rpm</td>
</tr>
<tr>
<td>circumferential speed:</td>
<td>0.58 s⁻¹</td>
</tr>
</tbody>
</table>

**Diagram:**
- Discontinuous stirred tank reactor 250 mL
- Water
- Surfactant
- Buffer
- Styrene
- Initiator
- Polystyrene latex particle
- Characterisation: particle size distribution, zeta-potential
**Experimental process parameter for polystyrene latex particles**

*Tab. 1: Process parameter for the emulsion polymerisation process with SDS (for 150 mL water)*

<table>
<thead>
<tr>
<th>charges</th>
<th>SDS in g</th>
<th>KPS in g</th>
<th>borax in g</th>
<th>temperature in °C</th>
<th>process in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.18</td>
<td>0.06</td>
<td>0.01</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>S2</td>
<td>0.06</td>
<td>0.06</td>
<td>0.01</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td>S3</td>
<td>0.06</td>
<td>0.06</td>
<td>0.01</td>
<td>65</td>
<td>24</td>
</tr>
<tr>
<td>S4</td>
<td>0.06</td>
<td>0.06</td>
<td>0.01</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>S5</td>
<td>0.06</td>
<td>0.24</td>
<td>0.03</td>
<td>85</td>
<td>6</td>
</tr>
</tbody>
</table>

*Tab. 2: Process parameter for the emulsion polymerisation process with NaSS (for 150 mL water)*

<table>
<thead>
<tr>
<th>charges</th>
<th>SDS in g</th>
<th>Na SS in g</th>
<th>addition after min</th>
<th>KPS in g</th>
<th>borax in g</th>
<th>temperature in °C</th>
<th>process in hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF1</td>
<td>1.2</td>
<td>1.0</td>
<td>15</td>
<td>2.0</td>
<td>0.2</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>SF2</td>
<td>0.3</td>
<td>1.0</td>
<td>25</td>
<td>1.0</td>
<td>0.1</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>SF2a</td>
<td>0.3</td>
<td>0.45</td>
<td>40</td>
<td>0.4</td>
<td>0.04</td>
<td>85</td>
<td>3</td>
</tr>
<tr>
<td>SF2b</td>
<td>0.2</td>
<td>0.45</td>
<td>40</td>
<td>0.4</td>
<td>0.04</td>
<td>85</td>
<td>3</td>
</tr>
<tr>
<td>SF3</td>
<td>0.2</td>
<td>0.45</td>
<td>60</td>
<td>0.4</td>
<td>0.04</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>SF4</td>
<td>0.2</td>
<td>0.45</td>
<td>90</td>
<td>0.1</td>
<td>0.01</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>SF5</td>
<td>0.06</td>
<td>0.9</td>
<td>120</td>
<td>0.06</td>
<td>0.03</td>
<td>85/50</td>
<td>6</td>
</tr>
</tbody>
</table>

*L. Vorweg, Elektrokinetische Untersuchungen an Modellkolloiden zur Beurteilung ihrer Stabilität, Dissertation 1997, Universität Potsdam*
Characterisation of the polystyrene latex particles

**Dynamic light scattering**
- Particle size distribution: $Q_0(d)$, $Q_3(d)$
- Particle size frequency distribution: $q_0(d)$, $q_3(d)$
- Median particle diameter: $d_{50,0}$, $d_{50,3}$
- Mean particle diameter: $d_{m,0}$, $d_{m,3}$
- Polydispersity index: $PDI = d_{50,3} / d_{50,0}$
- Non-uniformity index: $U = PDI - 1$
- Polydispersity index from autocorrelation function $g(\tau)$:
  \[
  \log g(\tau) = a + b \cdot \tau + c \cdot \tau^2 + \ldots
  \]
  \[
  PDI = 2 \cdot c / b^2 = \sigma^2
  \]

**Electrophoretic mobility**
- Zeta-potential: $\zeta$

**Streaming potential**
- Surface charge density: $\sigma$
**Principle of dynamic light scattering**

- Laser
- Optics
- Sample
- Photo multiplier
- Correlator

**Correlation function**

\[ g(\tau) = e^{-2D\cdot K^2 \cdot \tau} \]

- \( D \) diffusion constant
- \( K \) scattering light vector
- \( \tau \) delay time

**Stokes – Einstein – equation**

\[ d = \frac{k_B \cdot T}{3 \cdot \pi \cdot \eta \cdot D} \]

- \( d \) particle diameter
- \( k_B \) Boltzmann constant
- \( T \) absolute temperature
- \( \eta \) dynamical viscosity

**Optical unit of photon correlation spectroscopy**

- Scattering light intensity – time – function
- Auto correlation function
Determination of the zeta – potential for nanoparticle characterisation

Charge distribution around a moving particle in an electrical field

Helmholtz-Smoluchowski–equation

\[ \zeta = \frac{\vec{v} \cdot \eta}{E \cdot \varepsilon \cdot \varepsilon_0} \]

- \( \zeta \)  zeta - potential
- \( E \)  electrical intensity
- \( v \)  particle velocity
- \( \eta \)  viscosity
- \( \varepsilon \varepsilon_0 \)  dielectric constant

Detection of particle velocity in an interference pattern system of two lasers
Experimental results for polystyrene latex particles

mean particle diameter 75.7 nm (number), 98.8 nm (volume)
PDI = 0.124, zeta-potential -60.4 mV

mean particle diameter 194.4 nm (number), 242.1 nm (volume)
PDI = 0.084, zeta-potential -46.8 mV

Variation of particle sizes of polystyrene latex particles produced by emulsion polymerisation – from styrene, potassium peroxodisulphate, borax (stabilisation with sodium dodecyl sulphate)
Experimental results for polystyrene latex particles

Polystyrene latex nanoparticles stabilised with SDS and NaSS

Variation of particle sizes of polystyrene latex particles produced by emulsion polymerisation – from styrene, sodium styrene sulphonate, potassium peroxodisulphate, borax (stabilisation with sodium styrene sulphonate and dodecyl sulphate)
**Experimental results for polystyrene latex particles**

**Tab. 1: Results of the emulsion polymerisation process with SDS**

<table>
<thead>
<tr>
<th>charges</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
</tr>
<tr>
<td>S2</td>
</tr>
<tr>
<td>S3</td>
</tr>
<tr>
<td>S4</td>
</tr>
<tr>
<td>S5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>charges</th>
<th>$d_{10,0}$ in nm</th>
<th>$d_{50,0}$ in nm</th>
<th>$d_{90,0}$ in nm</th>
<th>$d_{m,0}$ in nm</th>
<th>$d_{m,3}$ in nm</th>
<th>PDI</th>
<th>zeta-potential in mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>53.2</td>
<td>71.3</td>
<td>104</td>
<td>75.7</td>
<td>98.8</td>
<td>0.124</td>
<td>- 60.4</td>
</tr>
<tr>
<td>S2</td>
<td>132</td>
<td>184</td>
<td>275</td>
<td>194.4</td>
<td>242.1</td>
<td>0.084</td>
<td>- 46.8</td>
</tr>
<tr>
<td>S3</td>
<td>84.3</td>
<td>110</td>
<td>151</td>
<td>113.7</td>
<td>128.1</td>
<td>0.006</td>
<td>- 42.2</td>
</tr>
<tr>
<td>S4</td>
<td>82.5</td>
<td>109</td>
<td>153</td>
<td>113.2</td>
<td>130.7</td>
<td>0.007</td>
<td>- 42.4</td>
</tr>
<tr>
<td>S5</td>
<td>123</td>
<td>172</td>
<td>263</td>
<td>183.6</td>
<td>237.6</td>
<td>0.076</td>
<td>(- 1.4)</td>
</tr>
</tbody>
</table>

**Tab. 2: Results of the emulsion polymerisation process with SDS/NaSS**

<table>
<thead>
<tr>
<th>charges</th>
<th>$d_{10,0}$ in nm</th>
<th>$d_{50,0}$ in nm</th>
<th>$d_{90,0}$ in nm</th>
<th>$d_{m,0}$ in nm</th>
<th>$d_{m,3}$ in nm</th>
<th>PDI</th>
<th>zeta-potential in mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF1</td>
<td>13.2</td>
<td>17.7</td>
<td>25.7</td>
<td>18.68</td>
<td>26.97</td>
<td>0.329</td>
<td>- 54.9</td>
</tr>
<tr>
<td>SF2</td>
<td>40.4</td>
<td>52.4</td>
<td>72.1</td>
<td>54.41</td>
<td>61.72</td>
<td>0.021</td>
<td>- 86.4</td>
</tr>
<tr>
<td>SF2a</td>
<td>20.6</td>
<td>27.3</td>
<td>38.6</td>
<td>28.60</td>
<td>34.60</td>
<td>0.129</td>
<td>- 80.8</td>
</tr>
<tr>
<td>SF2b</td>
<td>73.7</td>
<td>97.4</td>
<td>138</td>
<td>102.2</td>
<td>121.6</td>
<td>0.044</td>
<td>(0.0)</td>
</tr>
<tr>
<td>SF3</td>
<td>37.0</td>
<td>48.3</td>
<td>66.2</td>
<td>49.90</td>
<td>56.60</td>
<td>0.007</td>
<td>- 72.8</td>
</tr>
<tr>
<td>SF4</td>
<td>39.4</td>
<td>51.9</td>
<td>72.9</td>
<td>54.13</td>
<td>63.38</td>
<td>0.055</td>
<td>- 58.1</td>
</tr>
<tr>
<td>SF5</td>
<td>67.8</td>
<td>89.3</td>
<td>127</td>
<td>93.64</td>
<td>111.2</td>
<td>0.035</td>
<td>- 71.3</td>
</tr>
</tbody>
</table>
Results and discussion

- **Monodisperse polystyrene latex nanoparticles** with mean diameters $d_{m,0}$ from 75 nm to 185 nm can be produced with an emulsion polymerisation process using styrene, potassium peroxodisulphate, borax, and sodium dodecylsulphate.

- The nanoparticles are stabilised by sodium dodecylsulphate (sterically/electrostatically), the zeta-potential ranges from -42.6 to -60.4 mV.

- The polydispersity index goes from 0.007 to 0.124 (nearly monodisperse nanoparticle system).

- **Monodisperse polystyrene latex nanoparticles** with mean diameters $d_{m,0}$ from 18 nm to 185 nm can be produced with an emulsion polymerisation process using styrene, potassium peroxodisulphate, sodium styrene sulphonate, borax, and sodium dodecylsulphate.

- The nanoparticles are stabilised by sodium polystyrene sulphonate and sodium dodecylsulphate (sterically/electrostatically), the zeta-potential ranges from -54.9 to -80.8 mV (higher by NaSS).

- The polydispersity index goes from 0.007 to 0.329 (nearly monodisperse nanoparticle system).

- With increasing process temperature, the polystyrene nanoparticles get smaller (S2 - S4), and the surface charge density get higher (NaSS) - potassium peroxodisulphate disintegration rate higher.

- The nanoparticle sizes are influenced e.g. by the surfactant, initiator and co-polymer concentration.
What to need for a perfect nano carrier?

Ref.:
A. Musyanovych, K. Landfester, Formation of smart nanocapsules for defined slow or sudden release, Max-Planck-Institut für Polymerforschung, lecture
Transportation of nanoparticles through the blood-brain barrier (BBB)

Blood-brain barrier: separation of circulating blood and cerebrospinal fluid (CSF) in the central nervous system (CNS).

Problem: Endothelial cells restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophilic molecules into the CSF, cells of the barrier actively transport metabolic products such as glucose across the barrier.

Surface modification (coating) of nanoparticles is necessary!

dextrane (polysaccharide)
α-1.6-glucopyranose polymer with α-1.2, α-1.3, and α-1.4 side chains
molar mass $M_W = 70,000 \text{ g/mol}$

chitosane (polysaccharide)
β-1,4 - 2-Acetamido-2-desoxy-β-D-glucopyranose polymer,
2,000 monomer units, linear linked

derivatives of polyoxyethylenes
poloxamer polymers (from POE and POP chains)
poloxamine polymers (from POE, POP, ethylenediamine chains)
polyoxyethyleneglycole (from POE)
polsorbate (POE sorbitan monostearate) e.g. Tween 80
Emulsion polymerisation process

I Period of particle formation (Nucleation)
Inside the O/W emulsion, there are micelles (5-10 nm), surfactant stabilized monomer droplets (1-10 µm), and initiator (e.g. hydrochloric acid, OH). Monomer is (a) solubilised inside micelles, and sparingly dissolved in water. Initiator forms monomer ions, with the in water sparingly soluble monomer (N-butyl-2-cyanoacrylate) oligo-ions. These oligo-ions are stabilized by surfactant (swollen micelles), or solubilised in monomer containing micelles. Polymerisation starts, formation of small latex particle.

II Period of growth
Latex particles grow until monomer droplets in emulsion are gone. Increasing surface area of the latex particle adsorbs more surfactant molecules, no micelles. Disappearance of droplets.

III Period of final polymerisation
Rest of monomers in the latex particles (50-300 nm) are polymerized.

Couvreur,P.; Kante,B.; Grislain,L; Roland,M.; Speiser,P.: Toxicology of polyalkylcyanoacrylate nanoparticles II. Doxorubicin-loaded nanoparticles, J. Pharm. 71 (1982) 790-792
Polymerisation process in miniemulsions

**Phase I:**
- Water
- Surfactant
- Initiator

**Phase II:**
- Oil
- Monomer

**Nano-droplets:**
- Kinetically stable
- Small (100 - 500 nm)
- Homogeneous in size

**Nano-reactors:**
- 100 - 500 nm
- Polymer particle is 1:1 copy of nanodroplets

**Physical characteristics of emulsion droplets**

<table>
<thead>
<tr>
<th>Radius (in nm)</th>
<th>Laplace Pressure (in MPa)</th>
<th>Shear Rate to Rupture (in s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2.0</td>
<td>10⁹</td>
</tr>
<tr>
<td>100</td>
<td>0.2</td>
<td>10⁸</td>
</tr>
<tr>
<td>1,000</td>
<td>0.02</td>
<td>10⁷</td>
</tr>
<tr>
<td>10,000</td>
<td>0.002</td>
<td>10⁶</td>
</tr>
</tbody>
</table>

**Laplace Pressure:**

\[ \Pi_L = \frac{2 \cdot \sigma}{r} \]

**Shear Rate to Rupture:**

\[ \gamma = \frac{\sigma}{r \cdot \eta_C} \]

**Micro-emulsion:** Thermodynamically stable emulsion (oil, water, surfactant, co-surfactant)

**Only kinetically stable emulsion:**
- Nano-emulsion (1 - 100 nm)
- Mini-emulsion (100 - 1,000 nm)
- Macro-emulsion > 1.0 μm
Growth of miniemulsion droplets

Ostwald ripening

coalescence

diffusion of oil through the water phase

collision and fusion of oil droplets

suppression of Ostwald ripening

hydrophobic solvents with a very low solubility in the continuous phase have to be used

suppression of coalescence

effective surfactants

Sodium dodecyl sulphate
Lutrol F68

Forces: same chemical potential in each droplet - osmotic pressure vs. Laplace pressure

Schematic representation of poly(alkylcyanoacrylate) formation

initiation

(a) \[ \text{initiation} \quad \text{HO}^- \]

propagation

(b) \[ \text{propagation} \quad \text{HO}^- + \text{CN} \parallel \text{CN} \rightarrow \text{HO}^- \text{CN} \parallel \text{CN} \]

termination

(c) \[ \text{termination} \quad \text{H}^+ \quad \text{HO}^- \text{CN} \parallel \text{CN} \rightarrow \text{HO}^- \text{CN} \parallel \text{CN} \]

Poly(alkylcyanoacrylate) formation via a stepwise anionic polymerisation by anionic initiation, reversible propagation, and reversible termination

Initiation and propagation of an alkylcyanoacrylate polymerisation process

Initiation and propagation steps involved during a polymerisation process to PACA initiated by a base ($B^-$), a nucleophile ($Nu$), and a radical ($P^*$).

Experimental set-up for the PBCA mini-emulsion polymerisation process

**Oil phase (temperature 4 °C)**
- n-butyl-2-cyanoacrylate (monomer)
- soybean oil

**Water phase (pH 1.0)**
- 0.1 M phosphoric acid $H_3PO_4$
- sodium dodecylsulfate (surfactant)
- Lutrol F68 (Poloxamer 188)
  (surface modification, surfactant)
- rhodamine 123 (fluorescence marker)

**Process parameter (polymerisation process)**
- sonofication
  - temperature 0°C, 4 min, Sonoplus HD70, power 70 %
- polymerization
  - 30 seconds after sonofication
  - 0.1 M ammonia $NH_3$
- duration of polymerization process

**Characterisation:**
- particle size distribution
- zeta-potential

**Reactants**
- HO-[CH$_2$-CH$_2$-O]$_{80}$-
- [CH$_2$-CH(CH$_3$)-O]$_{27}$-
- [CH$_2$-CH$_2$-O]$_{80}$-H
- Lutrol F68, Pluronic F68

**Surfactants**
- Na C$_{12}$ H$_{25}$ SO$_4$
  - sodium dodecylsulfate
- Lutrol F68 (Poloxamer 188)
  - (surface modification, surfactant)
- rhodamine 123

**O/W mini-emulsion**

**Poly-(n-butyl-2-cyanoacrylate)-NP**
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

Particle size distribution $Q_p(d)$ in %

- $Q_0(d)$
- $Q_3(d)$

Mean particle diameter: 51.3 nm (number)
167.6 nm (volume)

PDI = 0.210 (light scattering), PDI = 3.27 (PSD)

Zeta-potential - not measurable

Particle size distributions $Q_0(d)$ and $Q_3(d)$ of poly-(butylcyanoacrylate) nanoparticles, particles without addition of the fluorescence marker rhodamine 123
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

sample 2: mean particle diameter 69.2 nm (number), PDI = 0.214 (light scattering)
184.3 nm (volume), PDI = 2.66 (PSD)

Reproducibility of the mini-emulsion process

Particle size distributions $Q_0(d)$ and $Q_3(d)$ of poly-(butylcyanoacrylate) nanoparticles, without the fluorescence marker rhodamine 123, reproducibility of the mini-emulsion process
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

Particle size distribution $Q_p(d)$ in %

mean particle diameter 68.9 nm (number)
149.8 nm (volume)
PDI = 0.190 (light scattering), PDI = 2.17 (PSD)
zeta-potential: -47.5 mV

Particle size distributions $Q_0(d)$ and $Q_3(d)$ of poly-(butylcyanoacrylate) nanoparticles, particle surface is coated with the fluorescence marker rhodamine 123
Experimental results for poly-(butylcyanoacyrlate) - nanoparticles

sample 4: mean particle diameter 42.3 nm (number), PDI = 0.178 (light scattering)
148.5 nm (volume), PDI = 3.51 (PSD)
zeta-potential: -42.5 mV

Reproducibility of the mini-emulsion process

sample 3

mean particle diameter 68.9 nm (number)
149.8 nm (volume)
PDI = 0.190 (light scattering), PDI = 2.17 (PSD)
zeta-potential: -47.5 mV

Particle size distributions $Q_0(d)$ and $Q_3(d)$ of poly-(butylcyanoacyrlate) nanoparticles, coated with the fluorescence marker rhodamine 123, reproducibility of the mini-emulsion process.
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

Sample 3: mean particle diameter 68.9 nm (number), PDI = 0.190 (light scattering)
149.8 nm (volume), PDI = 2.17 (PSD)

Influence of the fluorescence marker rhodamine 123 on the particle size distributions $Q_0(d)$ and $Q_3(d)$ of poly-(butylcyanoacrylate) nanoparticles
**More poly-(butylcyanoacrylate) - nanoparticles:**

<table>
<thead>
<tr>
<th>Surfactants</th>
<th>Surface modifier masking PBCA NP surface for crossing BBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium dodecylsulfate, SDS</td>
<td>Lutrol F68, HLB 29, CMC 1.14·10⁻³ mol L⁻¹, no zeta potential (also surfactant!)</td>
</tr>
<tr>
<td>HLB 40, CMC 8.14·10⁻³ mol L⁻¹, negative zeta potential</td>
<td>Tween 80, HLB 15.0, CMC 1.2·10⁻³ mol L⁻¹, no zeta potential (also surfactant!)</td>
</tr>
</tbody>
</table>

![Surfactant structures](image)

<table>
<thead>
<tr>
<th>Surface modifier masking PBCA NP surface for crossing BBB</th>
<th>Fluorescence marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextran 70,000</td>
<td>Rhodamine 123</td>
</tr>
</tbody>
</table>

![Dextran and Rhodamine structures](image)

**Miniemulsion polymerization process:**
- Rhodamine 123 Lutrol F68-SDS-PBCA NP
- Rhodamine 123 Tween 80-PBCA NP
- Rhodamine 123 Dextran 70,000-Lutrol F68-PBCA NP
- Rhodamine 123 DEAE-Dextran-Lutrol F68-PBCA NP

**Anionic emulsion polymerization:**
- Rhodamine 123 Dextran 70,000-PBCA NP
- Rhodamine 123 Lutrol F68-PBCA NP
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

Mean particle diameter (Z-average mean) vs. ultrasound homogenization time for rhodamine 123 labeled Tween 80 and Lutrol F68-SDS-PBCA nanoparticles

Mean particle diameter (Z-average mean) vs. mass ratio surfactant/monomer (S) for rhodamine 123 labeled Tween 80, Lutrol F68 SDS, DEAE-dextran Lutrol F68 and Lutrol F68-SDS-Dextran 70.000-PBCA nanoparticles
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

Mean particle diameter (Z-average mean) vs. pH for rhodamine 123 labeled Tween 80 PBCA nanoparticles

Zeta potential vs. pH for rhodamine 123 labeled Tween 80 PBCA nanoparticles
Experimental results for poly-(butylcyanoacrylate) - nanoparticles

Mean particle diameter (Z-average mean) vs. mass fraction of monomer for rhodamine 123 labeled Tween 80 - Lutrol F68 SDS, DEAE-dextran Lutrol F68 and Lutrol F68 SDS dextran 70,000 PBCA nanoparticles

Mean particle diameter (Z-average mean) vs. mass fraction of stabilizer (dextran 70,000 and DEAE-dextran) for rhodamine 123 labeled Lutrol F68 SDS dextran 70,000, Tween 80-dextran 70,000 and DEAE dextran Lutrol F68-PBCA nanoparticles
Comparison of the poly-(butylcyanoacrylate) - nanoparticles:
Particle size, polydispersity index, Zeta potential

Average particle diameter (Z-average) of the manufactured PBCA nanoparticles

PDI polydispersity index of manufactured PBCA nanoparticles
Comparison of the poly-(butylcyanoacrylate) - nanoparticles: Particle size, polydispersity index, Zeta potential

**Average particle diameter (Z-average) of the manufactured PBCA nanoparticles**

**Zeta potential of the manufactured PBCA nanoparticles**
Scanning electron microscopy images of poly-(butylcyanoacrylate) - nanoparticles

Nonmodified (without dextran 70,000) PBCA nanoparticles:
Tween 80-PBCA-NP (a), Lutrol F68 SDS-PBCA-NP (b)

Dextran-modified PBCA NPs:
Tween 80-dextran 70.000 (a), DEAE-dextran-Lutrol F68 (b) and Lutrol F68-SDS-dextran 70.000-PBCA-NPs (c)
In vivo testing of PBCA NPs with In Vivo Confocal Neuroimaging (ICON)

Model: Blood-retina barrier - selectively permeable barrier between the retina and the retinal supplying vessels - very similar to the blood-brain barrier

In vivo testing of PBCA NPs with In Vivo Confocal Neuroimaging (ICON): Injection of 0.3 mL NP suspension in anesthetized rat via the tail vein, study of the rat under the ICON
ICON recordings at different time points

ICON recordings at different time points for Tween 80-PBCA nanoparticles
ICON recordings of different PBCA nanoparticles

- Lutrol-SDS: 87nm, neg. zeta potential
- DEAEDextran-Lutrol: 464nm, pos. zeta potential
- Dextran-Lutrol: 420nm, neg. zeta potential
- Tween: 143nm, neg. zeta potential
- Tween-Dextran: 130nm, pos. zeta potential
- Tween abs.: 128nm, neg. zeta potential
**Summery**

**Aim:** to control size and zeta-potential of PBCA nanoparticle
small, narrow distributed NPs with negative zeta potential

**Influence of process parameter on PBCA nanoparticles during production:**
short ultrasonic duration gives small particles (2 minutes)
pH value has no influence on particle size, zeta potential is pH dependent
amount of surfactant has no definite influence on particle size, but a ratio
surfactant/monomer of 0.2 seems to be reasonable
a monomer mass fraction of 12 wt-% seems to offer the smallest size
*Rhodamine 123 Lutrol F68 SDS PBCA NPs* seems to be the most promising
(smiest particle size, most negative zeta-potential)

**In vivo Confocal Neuroimaging testing of PBCA nanoparticles:**
*Rhodamine 123 Lutrol F68 SDS PBCA particles* have no good transition
over BBB, but *Rhodamine 123 DEAE-Dextran Lutrol F68 PBCA NPs*: biggest size
and positive ZP, but still go well over BBB
*Rhodamine 123 Tween 80 PBCA nanoparticles* cross the BBB at the best
Surface properties of the particles have more influence than zeta-potential and size
for overcoming the blood-brain barrier!