Tayloring functions in microcapsules: Responsiveness and remote controlling

Gleb Sukhorukov

Department of Materials, Queen Mary University of London, UK

Coating colloids and Hollow capsules
Responsive capsules
Composite capsules - Remote activation
Two compartmental capsules
Capsules delivery in living systems
Intracellular sensing
Conclusions and Perspectives
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Hollow Capsule Fabrication

Organic and inorganic colloidal particles, dye or drug nanocrystals, emulsion droplets, gas bubbles, biological cells, protein aggregates. Size 50nm – 50 µm.

Cores

Hollow Polyelectrolyte Capsule
Core removal (decomposition)

Layer-by-layer Capsules

- Size and shape are determined by templating colloid particle.
- Layer constituents:
  - synthetic polyelectrolytes and biopolymers
  - inorganic nanoparticles
- The Capsule Wall is tunable in **Nanometer** range
  Thickness, composition and functionality are controlled by constituents and the layer number
- 1 layer of polyelectrolyte ➔ 1-2 nm

- Encapsulation ➔ micro- and nanoreactor engineering
- Controlling permeability for wide class of molecules
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**External stimulus**
(ions, pH, temperature, ...)

Sharp physical or chemical modifications
Temperature induced capsule shrinkage

Capsule diameter depends on incubation temperature

Dr. Karen Köhler
Morphology of (PDADMAC/PSS)$_4$ capsules

SEM

Temperature induced transition from a hollow shell to a full sphere

TEM
**pH-sensitive hollow capsules**

Sodium Poly (Styrene Sulfonate) (PSS)

\[ \text{SO}_3^- , \text{Na}^+ \]

Poly (Allylamine Hydrochloride) (PAH)

\[ \text{NH}_3^+ , \text{Cl}^- \]

SWOLLEN STATE (18 \( \mu \)m)

\[ \text{pH} \quad \xrightarrow{\text{HCl 0.1 M}} \quad \xrightarrow{\text{NaOH 0.1 M}} \quad \text{pH} \]

SHRUNK STATE (8 \( \mu \)m)

Christophe Dejugnat
Encapsulation and release

Confocal fluorescence Laser Scanning Microscopy

ΔT, pH

Permeable „Open gate“

Impermeable „Closed gate“

pH, salt

Encapsulated

Release
Weak polyelectrolytes

Tuning of electrostatic interactions by pH

Poly(acrylic acid) (PAA)
Poly(methacrylic acid) (PMA)
Poly(allylamine hydrochloride) (PAH)
Poly(4-vinylpyridine hydrochloride) (PVP)

Increasing hydrophobicity
(PAH/PMA)$_5$ capsules templated on SiO$_2$

<table>
<thead>
<tr>
<th>PAH</th>
<th>PMA</th>
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<tbody>
<tr>
<td>[CH$_3$]$_n$</td>
<td>[CH$_3$C]$_p$</td>
</tr>
<tr>
<td>NH$_3^+$</td>
<td>HO</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td></td>
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</table>

- thin shells
- $d_{2L} = (3 \pm 0.2)$ nm
- smooth surface

Tatjana Mauser
Influence of pH on \((\text{PAH/PMA})_5\) capsules

- Capsule dissolution
- Capsule dissolution

- Addition of HCl: pH < 2
- Swelling: t ~ 1 sec
- Dissolution: t ~ 2 sec

Tatjana Mauser
Optically driven Encapsulation

Matthieu Bedard – Optically addressable microcapsules
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Magnetite nanoparticles assembled in capsule wall

Targeted capsule delivery via magnetic field to tissues
Capsules with Composite Shell are Susceptible to Remote Activation

Ag-nanoparticles doped capsules can be ruptured by Infrared Laser 830nm

→ Optically activated release;
→ Infrared window for biomedical application
Fluorescence Imaging

A. Skirtach et al., Nanoletters, 2005
Ultrasound stimulated release.

Before - encapsulated

After – released

– Power of Ultrasound for capsule rupture is compared to medical use without damage of tissues
– Higher depth of operation inside the body

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1. Encapsulation of macromolecules after incorporation into calcium carbonate microparticles ("coprecipitation method")

\[ \text{CaCl}_2 + \text{Na}_2\text{CO}_3 \rightarrow \text{Coprecipitation} \rightarrow \text{LbL-coating} \rightarrow \text{Core-dissolution} \rightarrow \text{encapsulated biopolymer} \]

Porous calcium carbonate microparticles (Ø 5µm)

2. Fabrication of multicompartment "ball-in-ball" particles calcium carbonate microparticles

\[ \text{CaCO}_3 \text{ prec. 1} \rightarrow \text{CaCO}_3 \text{ prec. 2} \]
Fabrication of two-compartment calcium carbonate particles

**Ball-in-ball**

Particle (type III)

**Ball-in-ball**

Particle (type IV)

SEM-images
Step 1: Coprecipitation
- Rhodamin-HSA
- Magnetite
- CaCO3
- Alexa 488-HSA

Step 2: LbL-coating
- Initial core
- PEM

Step 3: Coprecipitation
- Initial core-shell-particle
- Coproduct
- Ball-in-ball particle (type I)
- Ball-in-ball particle (type II)

Step 4: Magnetic separation
- Ball-in-ball particles after magnetic separation

Step 5: LbL-coating
- Ball-in-ball particle (type III)
- Ball-in-ball particle (type IV)

CaCO3-extraction
- Single-shell-capsule (mixed components)
- Shell-in-shell-capsule (separated components)

Magnetic separation

Unpurified raw-product

Product purification by an external magnetic field.

Oliver Kreft
Controlled Mixing or Separation of Biomolecules

<table>
<thead>
<tr>
<th>Ball-in-ball-particle IV</th>
<th>Core dissolution</th>
<th>Shell-in-shell capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>B + EDTA</td>
<td>1 sec</td>
<td>2 sec</td>
</tr>
<tr>
<td></td>
<td>3 sec</td>
<td>4 sec</td>
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<tr>
<td></td>
<td>5 sec</td>
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</table>

Oliver Kreft
Principle of a coupled assay using the Amplex Red reagent. Oxidation of glucose (GOD) by glucose oxidase results in generation of H2O2, which is coupled to conversion of the Amplex Red reagent to fluorescent resorufin by peroxidase (POD).
Example for prospective applications:
Coupled enzyme assay with glucose oxidase (GOD) and peroxidase (POD)

H$_2$O$_2$ formation  Resorufin formation

<table>
<thead>
<tr>
<th>Time</th>
<th>Image</th>
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<tr>
<td>0 sec</td>
<td><img src="image1.png" alt="Image" /></td>
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<td>10 sec</td>
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GOD: $\beta$-D-glucose + H$_2$O + O$_2$ $\rightarrow$ D-gluconic acid-$\delta$-lactone + H$_2$O$_2$

POD: H$_2$O$_2$ + Amplex Red® + H$^+$ $\rightarrow$ H$_2$O + resorufin + CH$_3$COOH

CLSM image of a shell-in-shell capsule containing GOD and POD, after adding glucose and Amplex Red. Resorufin formation results in red fluorescence of the capsule interior.

Separate compartments for biochemical reactions

Mixing of reaction partners by physical triggers:

Shell doped with NP

Release of inner capsules by external trigger:

Shell doped with NPs
Shell-in-Shell Microcapsules/Outlook:

AFM & SEM images of shell-in-shell microcapsules

O. Kreft et al, Advanced Materials, 2007, 19, 3142
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Capsules in cells - Artificial organelles
Reporting on cell interior

Capsules Uptake by Breast cancer cells

Small 2005 1(2), 194-200
Targeted drug delivery - Use of polymer capsules as multifunctional (magnetic, labeled) carrier systems

Capsules in cells - Artificial organelles
Remote activation in the cells

In cooperation with Dr. Wolfgang Parak, (LM Uni-München) Dr. Andre Skirtach
In-house developed optical setup for remote release experiments

Various sources, CCD, real-time imaging, portable, easy transferable to new location

Andre Skirtach
Optically induced release inside cells

Towards Intracellular Capsule Delivery to Neurons

PSS/PAH capsules filled with labelled BSA

In cooperation with Prof. Jo Martin and Dr. D. Davidson
(Queen Mary, Neuroscience Center)
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**Intracellular Sensing Systems**
Conclusions and perspectives

![Diagram showing pH responsiveness in microcapsules](image-url)
Polymer Microcapsules as Mobile Local pH-Sensor

SNARF dye
*Ratiometric pH measurement. The dye shifts the maximum of the fluorescence emission from green to red color upon increasing the pH.*
SNARF-loaded capsules change from red to green fluorescence upon internalization by MDA-MB435S breast cancer cells.

(A) SNARF-fluorescence 30 min after adding the capsules to the cell culture.
(B) The same cells after another 30 min of incubation.

Intracellular Sensors

Encapsulated pH – sensor, SNARF-based dye

Before Uptake

After Uptake

Green – low pH
Emission 580nm
Inside cell endosome

Red – high pH
Emission 650 nm
Outside cell

Kreft, O., Muñoz Javier, A., Sukhorukov, G.B., Parak, W.J.
J. Mater. Chem., 2007, 42, 4471-4476
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Research strategies

- Design of Nano-engineered shell on colloidal particles/capsules inc. Emulsion, micro- and nanocrystals, bubbles
  Tuning release, delivery systems into cells and tissues,
- Stimuli-responsive capsules Remote (IR-, US, MW) activated release
- Diagnostics/Sensing using encapsulated material
Multifunctionality to Microcapsules

- Macromolecule encapsulation
- Targeting
- Sensors
- Controled release
- Magnetism
- Protection
- Remote activation
- Visualization, Sensors
- Cell-/Tissue-Targeting

Microreactors
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