Mesoporous silica nanoparticles as versatile platforms for pH responsive applications

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Drug delivery: from capsule to “nanocapsule”

Lipidic micelles

Polymeric nanoparticles

Image courtesy Digizyme

Liposomes

Dendrimers

Prof. Dr. Hans-Jürgen Butt
Max Planck Institute for Polymer Research, Mainz

Mesoporous silica nanoparticles (MSN)

http://www.nanosight.com/


NIS Colloquium “Advances in biomaterials” Torino 28-29 Nov 2013
The "bow-and-arrow" concept

The best arrow (bioactive molecule) will not be effective without a good bow..

To be able to deliver the drug where and when necessary

Issues related to drug release:
- Decrease of therapeutic dosage
- Control of release with time
- Reduction of side effects
- Targeting

Ian Sample, Materials World, 7 (10), 1999, 610-12.

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From “nanocarriers”...

Mesoporous silica nanoparticles (MSN)

- Ordered mesoporous structure allowing a controlled release
- High pore volume and specific surface area to host high drug loading
- Good chemical stability
- Biocompatibility and biodegradability
- Easy surface functionalization

Search “mesoporous silica” and “drug delivery” (ISI WoS, 26/11/13)

The MSN “container” can be decorated with drugs, proteins, nucleic acids, antibodies, receptors, diagnostic agents...

**pH as an internal (passive) stimuli**

Different pH values inside the cells:
Variations from slightly acidic environment (pH 6.2-6.5) in early endosomes to more pronounced acidity (pH ≈ 4.5 and 5.5) in late endosomes and lysosomes.

MSN as carrier for fluorescent dyes as intra and extracellular pH sensors

PhD work of G. Musso


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pH controlled drug release

Acid pH in tumors as compared to normal tissues

MSN “container” can be designed to release drugs only to the desired target

A simple approach is based on the employ of cationic polymers, able to electrostatically interact with negatively charged surface groups (COO⁻)


L. E. Gerweck, K. Seetharam, Cancer Res. 56, 1996, 1194
Rutin (quercetin-3-O-rutinoside), the glycoside of quercetin

- Flavonoid with **antioxidant** activity
- Antiallergic, anti-inflammatory and vasoactive, **antitumour**, antibacterial, antiviral and antiprotozoal properties
- Preventing properties: hypolipidaemic, **cytoprotective and anticarcinogenic**

- Poor solubility and photostability

**Outline of the work**

- Synthesis and functionalization of mesoporous silica nanoparticles: **COOH-MCM-41**
- Loading of the selected drug: **rutin**
- Decoration of COOH-MCM-41 with **polycations**
- Physico-chemical characterization
- Release tests at different pH

**PDDA**
Polydiallyldimethyl ammonium chloride

**PEI**
Polyethylenimine (branched)
**pK_a** around 8-10


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COOH-MCM-41/polycation systems: general properties

<table>
<thead>
<tr>
<th>Sample</th>
<th>SSA (m²·g⁻¹)</th>
<th>Pore diameter (Å)</th>
<th>Pore volume (cm³·g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCM-41</td>
<td>1239</td>
<td>37</td>
<td>1.18</td>
</tr>
<tr>
<td>COOH-MCM-41</td>
<td>843</td>
<td>33</td>
<td>0.89</td>
</tr>
<tr>
<td>COOH-MCM-41/PDDA</td>
<td>152</td>
<td>-</td>
<td>0.15</td>
</tr>
<tr>
<td>COOH-MCM-41/PEI</td>
<td>519</td>
<td>26</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Mesoporous materials (type IV isotherm)
Specific surface area, pore volume and size decrease when PDDA and PEI are added: blocking of the pores

Thermogravimetric analysis

PDDA = 8.4 wt%
PEI = 17 wt%

HRTEM

In both systems an amorphous layer (5-10 nm thick) surrounds the mesoporous nanoparticles
COOH-MCM-41/polycation systems: surface properties

$\xi$-potential measurements as a function of pH: effect of surface functionalization

In both samples isolated Si-OH are consumed forming hydrogen-bonding adducts

In both regions new vibrational modes are observed, which can be assigned to the two polycations


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COOH-MCM-41/polycation/rutin complexes

Two different solvents employed for the impregnation of the silica, followed by interaction with polycations:

- MCM-41/PEI/RU
- MCM-41/PDDA/RU

Ethanol
Water buffer at pH 7.6

XRD

A large fraction of rutin is present as crystals, probably located on the external surface of the nanoparticles.

Infrared spectroscopy

IR spectra of the complexes are dominated by the vibrational features of rutin. In the case of MCM-41/PEI/RU changes are observed in the rutin aromatic ring modes, suggesting a direct interaction with PEI.

HRTEM

HRTEM image of MCM-41/PDDA/RU showing that the mesoporous structure is preserved.

### Table: Rutin wt% (TGA) and Rutin wt% (UV-Vis)

<table>
<thead>
<tr>
<th>Samples</th>
<th>Rutin wt% (TGA)</th>
<th>Rutin wt% (UV-Vis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCM-41/RU</td>
<td>38,3</td>
<td>40,8</td>
</tr>
<tr>
<td>MCM-41/PDDA/RU</td>
<td>29,1</td>
<td>39,2</td>
</tr>
<tr>
<td>MCM-41/PEI/RU</td>
<td>13,0</td>
<td>14,3</td>
</tr>
</tbody>
</table>
Release tests: MCM-41/PDDA/RU

A difference in the release profile of rutin is observed with respect to MCM-41/RU complex at pH 6.6 and particularly at pH 7.6. This is in agreement with an optimum of the electrostatic interaction COO⁻/PDDA at higher pH.

A dependence of rutin release on pH is observed also without PDDA.

Rutin solubility increases with pH.

Possible negative effect of the buffer ionic strength on the stability of MSN.
Release tests: MCM-41/PEI/RU

In the case of PEI the comparison with MCM-41/RU is not possible, due to the different loading of the samples

Comparison of release profiles at different pH

Different pH dependence of rutin release in the two complexes

In case of MCM-41/PEI/RU the highest and fastest release is observed at pH 4.6 (lowest rutin solubility)

Higher release inhibition at pH 6.6

Equilibrium between protonation of PEI, deprotonation of COOH and solubility
Conclusions and future perspectives

The interaction of two different polycations with a nanosized COOH-MCM-41 material was explored

The materials were characterized with different techniques to assess the effect of polycations and rutin on porosity, structure, morphology and surface

Both PDDA and PEI form an amorphous layer around the silica nanoparticles (5-10 nm) and affects their surface charge

Differences were observed in the rutin loading (prepared in different solvents) and in the case of PEI infrared spectroscopy showed a direct interaction with rutin

The two polycations show a different pH dependence in controlling rutin release

Work in progress

Optimization of rutin impregnation procedure to reduce the amount of crystalline precipitate on the external surface of nanoparticles

Further studies on the release performance of PEI (comparison with COOH/MCM-41 sample with comparable loading)
Acknowledgements

Development of polymeric and oxidic materials for stimuli responsive applications
OXIPOLISTI
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