Mesoporous silica nanoparticles as versatile platforms for pH responsive applications

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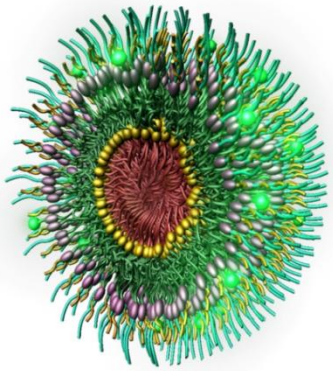
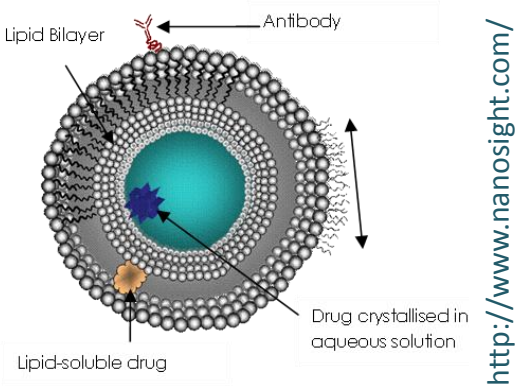
Drug delivery: from capsule to “nanocapsule”



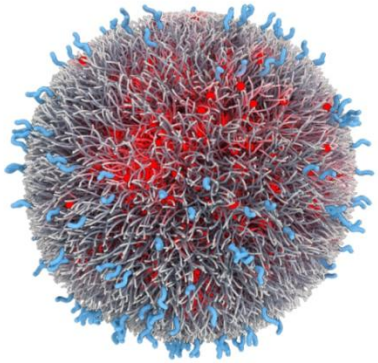
D. Peters, et al. PNAS, 2009.

Lipidic micelles



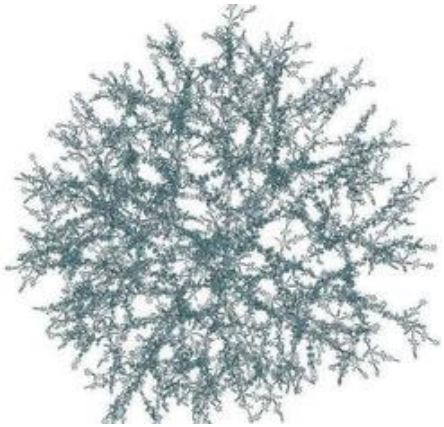
http://www.nanosight.com/

Liposomes



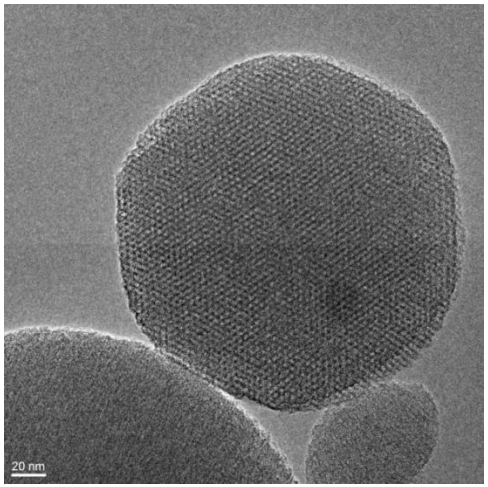
Polymeric nanoparticles

Image courtesy Digizyme



Dendrimers

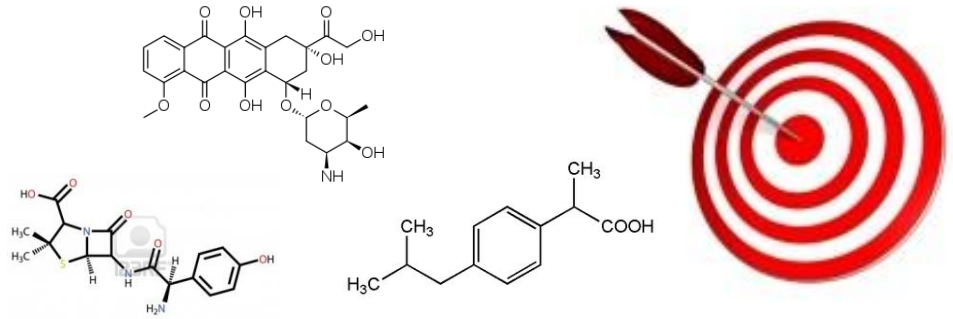
Prof. Dr. Hans-Jürgen Butt
Max Planck Institute for Polymer Research, Mainz



Mesoporous silica nanoparticles (MSN)

The “bow-and-arrow” concept

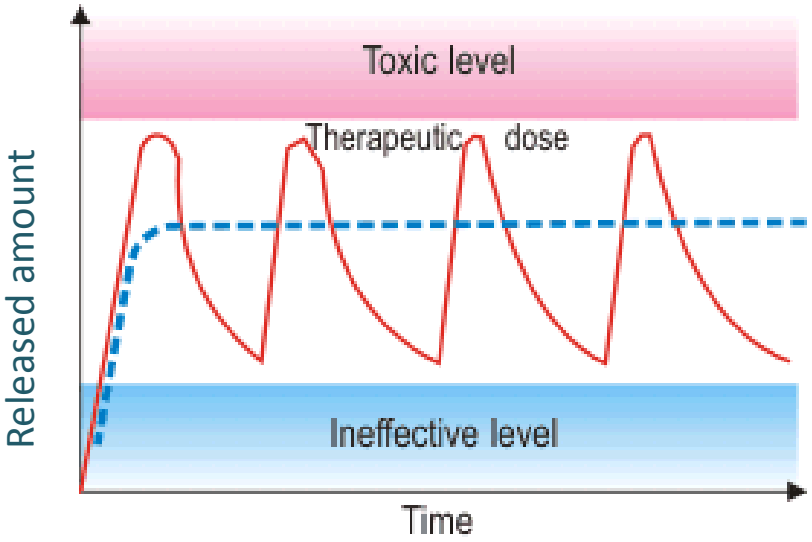
Nicolas Cage in The Weather Man



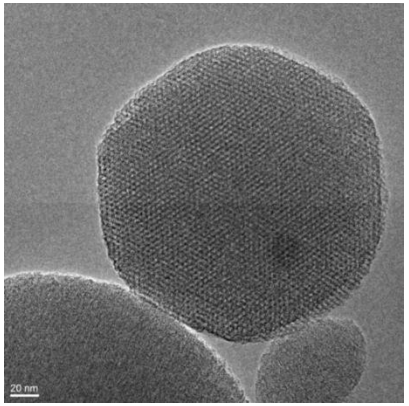
The best arrow (bioactive molecule) will not be effective without a good bow ..

To be able to deliver the drug **where and when** necessary

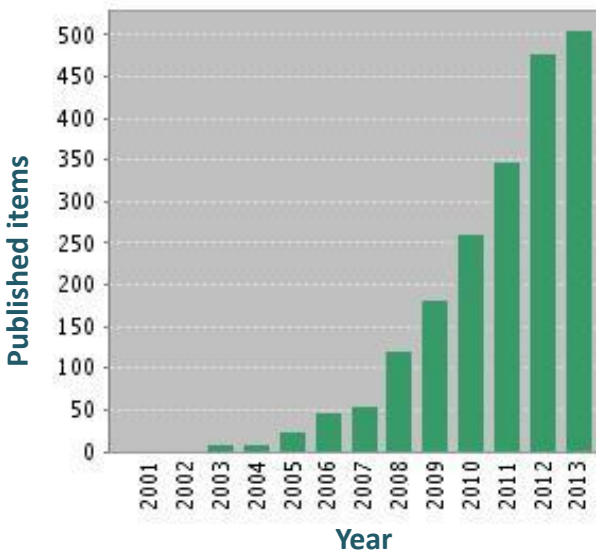
Issues related to drug release:
- Decrease of therapeutic dosage
- Control of release with time
- Reduction of side effects
- Targeting



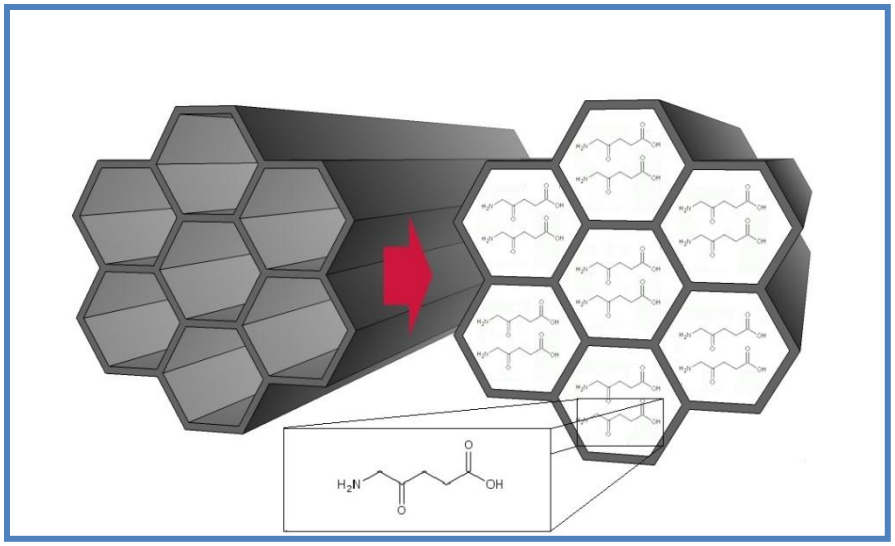
From “nanocarriers”…



Mesoporous silica nanoparticles (MSN)



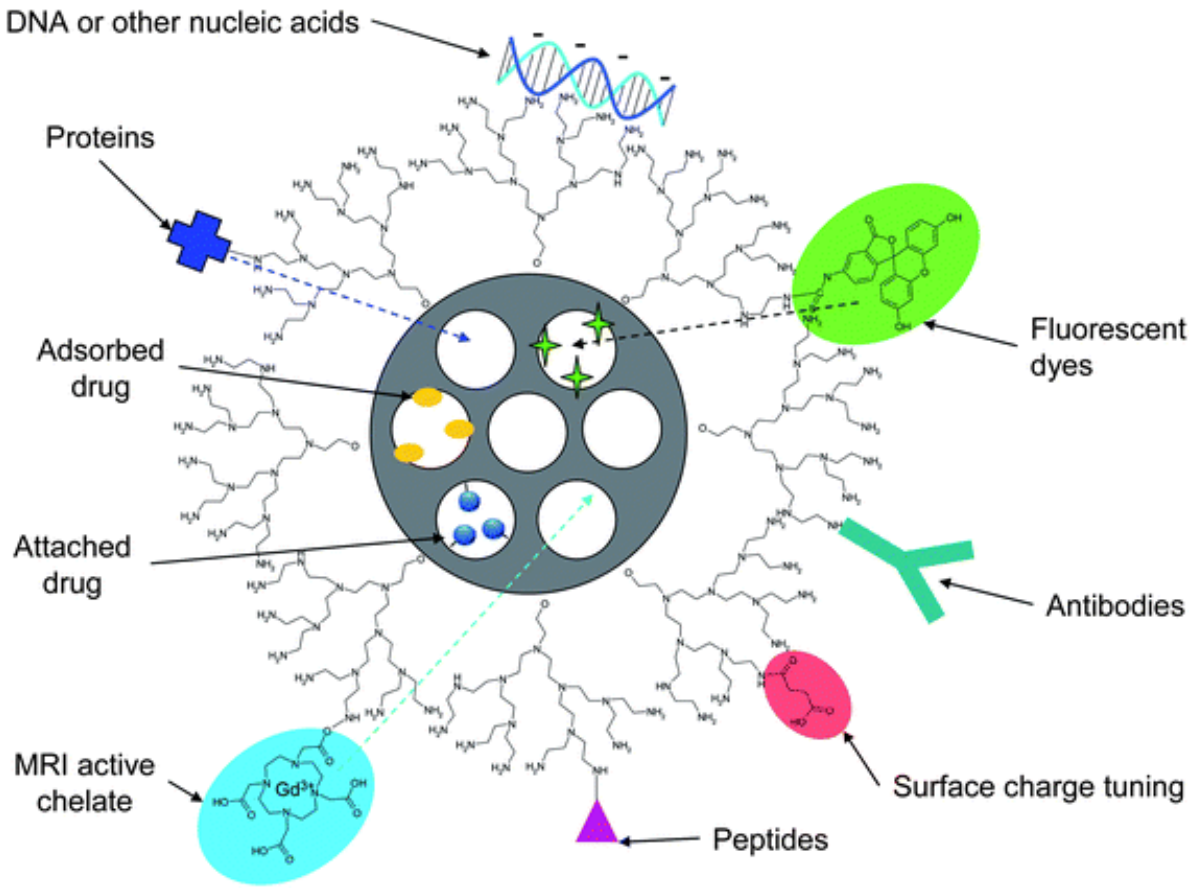
Search “mesoporous silica” and “drug delivery” (ISI WoS, 26/11/13)



- 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

M. Vallet-Regí et al. Angew. Chem. Int. Ed. 2007; S.-H. Wu et al. Chem. Commun. 2011; I.I . Slowing et al. Adv. Drug Deliv. Rev. 2008; M. W. Ambrogio et al. Acc. Chem. Res. 2011.

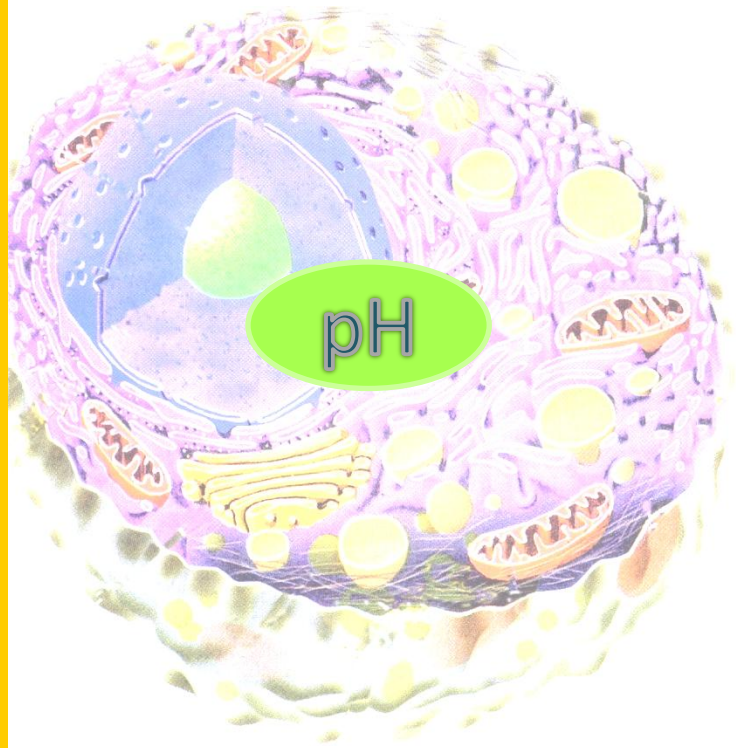
…to “nanoplatforms”



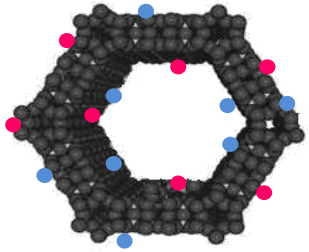
The MSN “container” can be decorated with drugs, proteins, nucleic acids, antibodies, receptors, diagnostic agents…

J. M. Rosenholm, C. Sahlgren and M. Lindén, Nanoscale, 2010, 2, 1870–1883
H. Meng, M. Xue, J.I. Zink, A. E. Nel, J. Phys. Chem Lett. 2012, 3, 358-359

pH as an internal (passive) stimuli

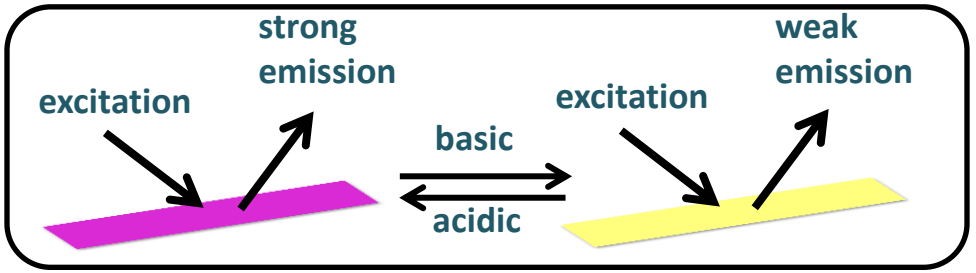


Different pH values inside the cells:
Variations from slightly acidic environment (pH 6.2-6.5) in early endosomes to more pronounced acidity (pH ≅ 4.5 and 5.5) in late endosomes and lysosomes.



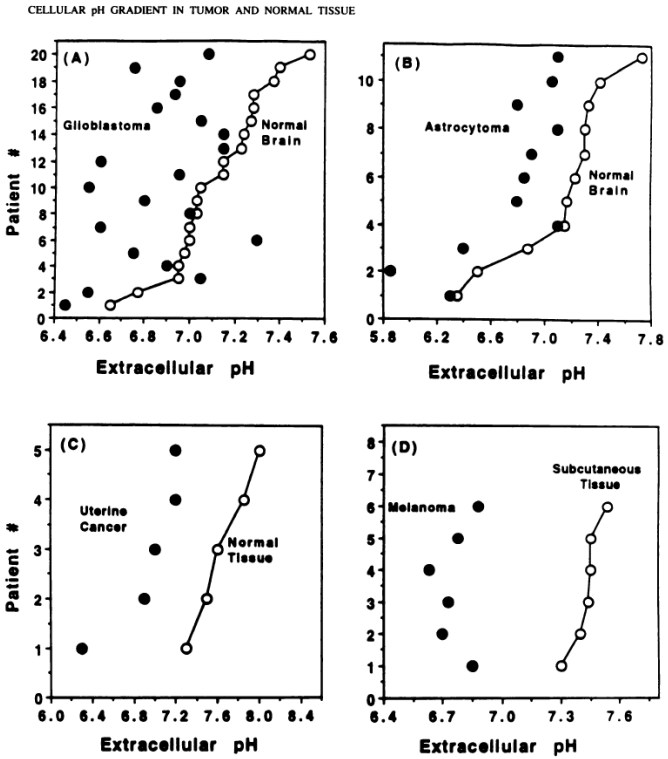
MSN as carrier for fluorescent dyes as intra and extracellular pH sensors

PhD work of
G. Musso



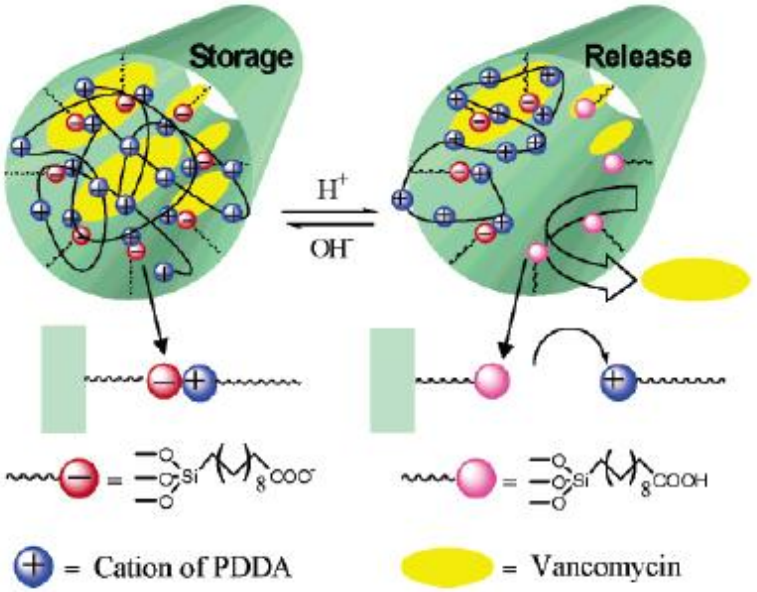
R.V. Benjaminsen, H. Sun, J.R. Henriksen, N.M. Christensen, K. Almdal, T.L. Andresen, ACSNano 5 (2011) 5864–5873

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



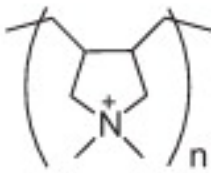
A simple approach is based on the employ of cationic polymers, able to electrostatically interact with negatively charged surface groups (COO^-)

Q. Yang, S. Wang, P. Fan, L. Wang, Y. Di, K. Lin, F.S. Xiao, Chem. Mater. 2005, 17, 5999-6003;

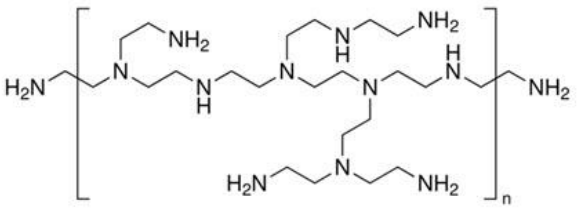
I.F. Tannock, D. Rotin, Cancer Res. 49, 1989, 4373.
L. E. Gerweck, K. Seetharam, Cancer Res. 56, 1996, 1194

Outline of the work

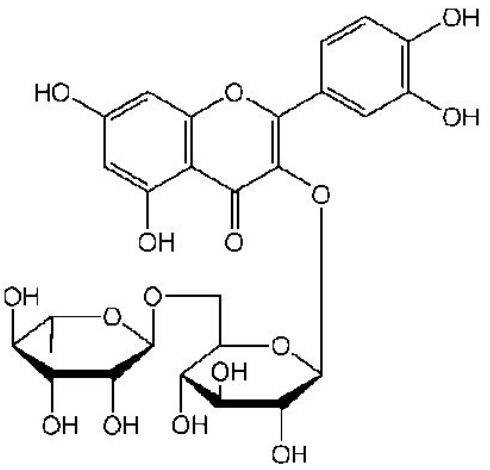
- Synthesis and functionalization of mesoporous silica nanoparticles: **COOH-MCM-41**
- Loading of the selected drug: **rutin**
- Decoration of COOH-MCM-41 with **polycations**
- Physico-chemical characterization
- Release tests at different pH



PDDA
Polydiallyldimethyl ammonium chloride



PEI
Polyethylenimine (branched)
pK_a around 8-10



Rutin (quercetin-3-O-rutinoside), the glycoside of quercetin

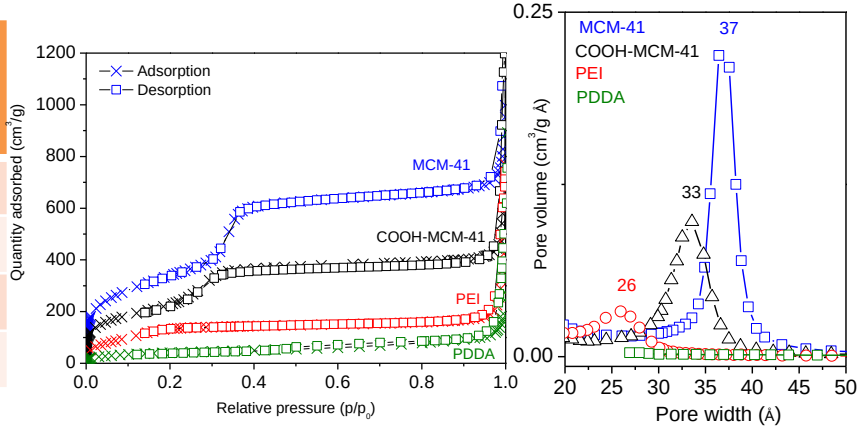
- Flavonoid with **antioxidant** activity
- Antiallergic, antiinflammatory and vasoactive, **antitumour,** antibacterial, antiviral and antiprotozoal properties
- Preventing properties: hypolipidaemic, **cytoprotective and anticarcinogenic**

- **Poor solubility and photostability**

G. Berlier, L. Gastaldi, S. Sapino, I. Miletto, E. Bottinelli, D. Chirio, E. Ugazio, Int. J. Pharm. 457 (2013) 177– 186

COOH-MCM-41/polycation systems: general properties

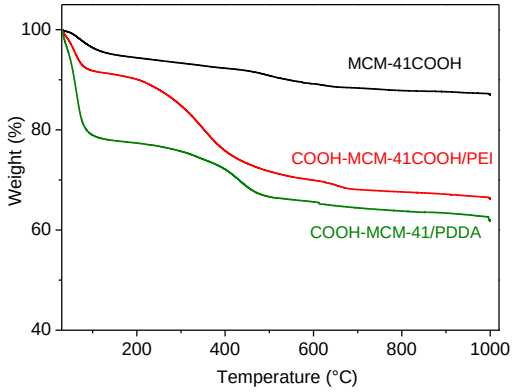
Sample	SSA ($m^2 \cdot g^{-1}$)	Pore diameter (Å)	Pore volume ($cm^3 \cdot g^{-1}$)
MCM-41	1239	37	1.18
COOH-MCM-41	843	33	0.89
COOH-MCM-41/PDDA	152	-	0.15
COOH-MCM-41/PEI	519	26	0.55



Mesoporous materials (type IV isotherm)

Specific surface area, pore volume and size decrease when PDDA and PEI are added: **blocking of the pores**

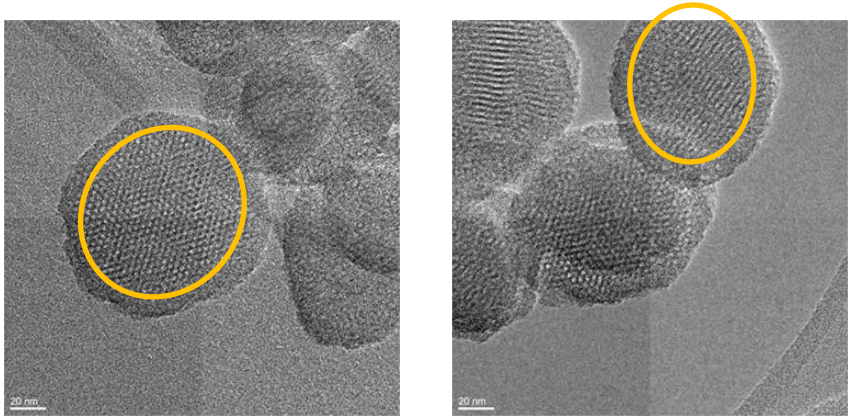
Thermogravimetric analysis



PDDA = 8.4 wt%

PEI = 17 wt%

HRTEM

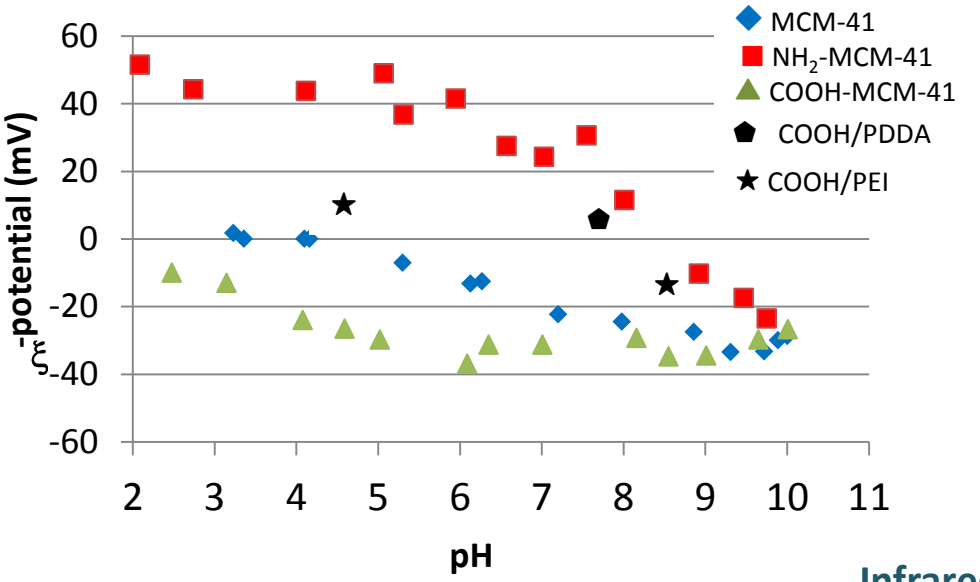


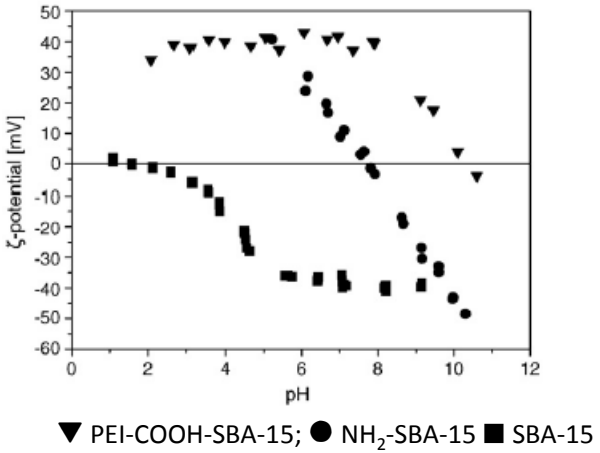
COOH-MCM-41/PDDA COOH-MCM-41/PEI

In both systems an amorphous layer (5-10 nm thick) surrounds the mesoporous nanoparticles

COOH-MCM-41/polycation systems: surface properties

ξ-potential measurements as a function of pH: effect of surface functionalization

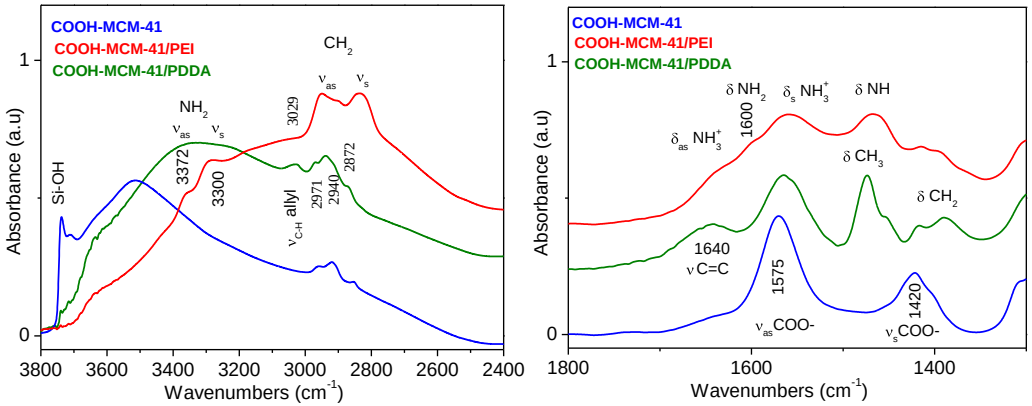




Infrared spectroscopy

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



J.M. Rosenholm, M. Lindén, J. Contr. Rel. 128 (2008) 157

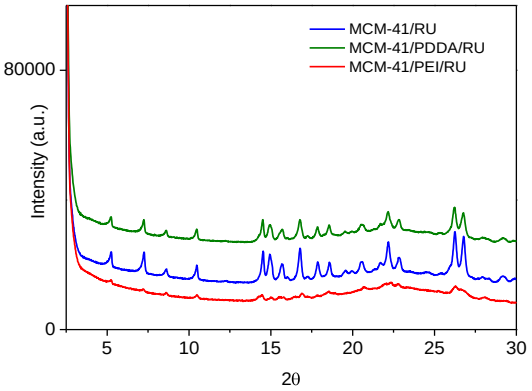
COOH-MCM-41/polycation/rutin complexes

Samples	Rutin wt% (TGA)	Rutin wt% (UV-Vis)
MCM-41/RU	38,3	40,8
MCM-41/PDDA/RU	29,1	39,2
MCM-41/PEI/RU	13,0	14,3

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

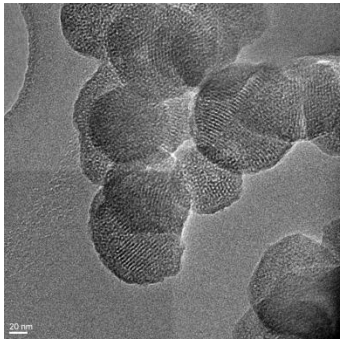
- MCM-41/PEI/RU — EtOH
- MCM-41/PDDA/RU — water
  buffer at pH 7.6

XRD



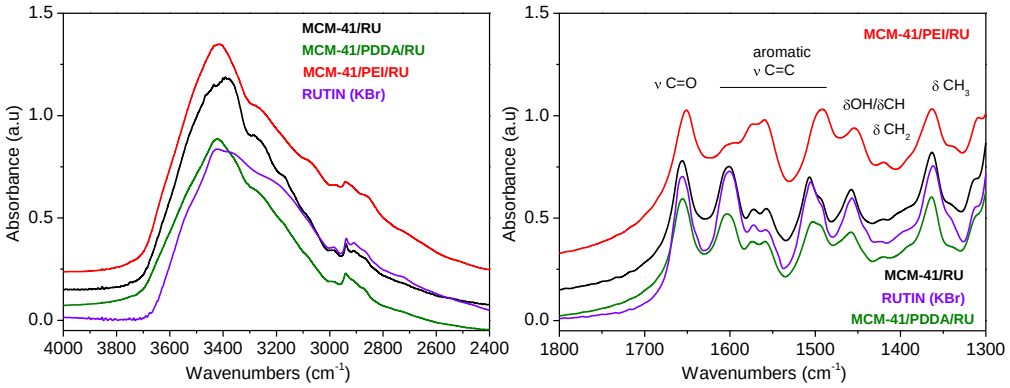
A large fraction of rutin is present as crystals, probably located on the external surface of the nanoparticles

HRTEM



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

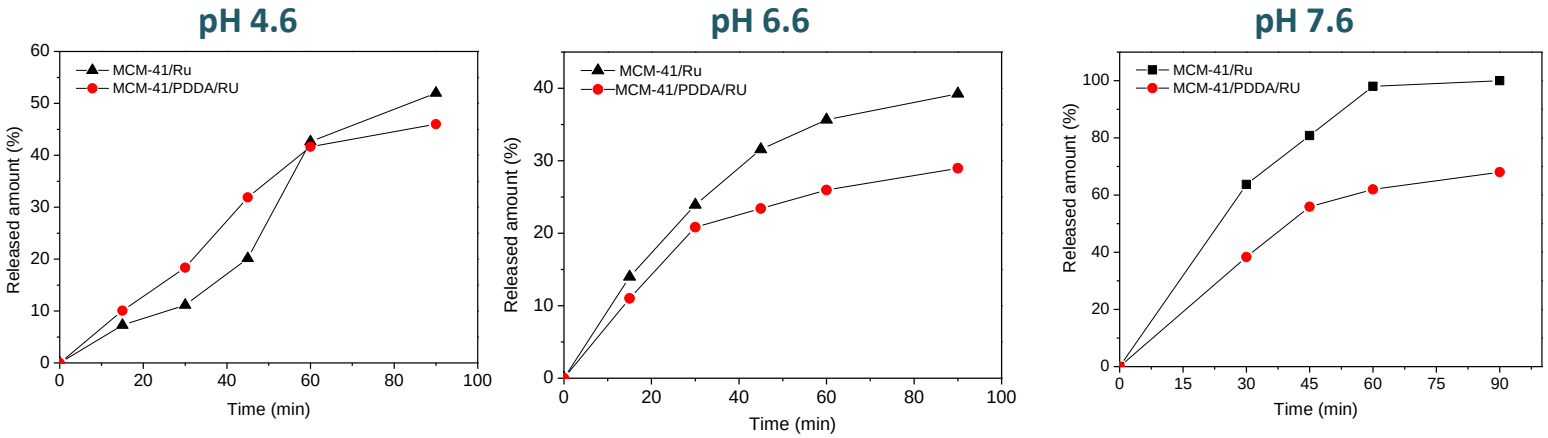
Infrared spectroscopy



IR spectra of the complexes are dominated by the vibrational features of rutin

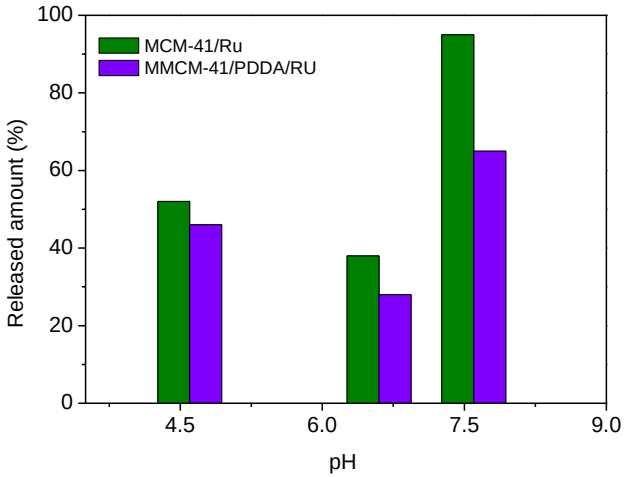
In the case of MCM-41/PEI/RU changes are observed in the rutin aromatic ring modes, suggesting a direct interaction with PEI

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

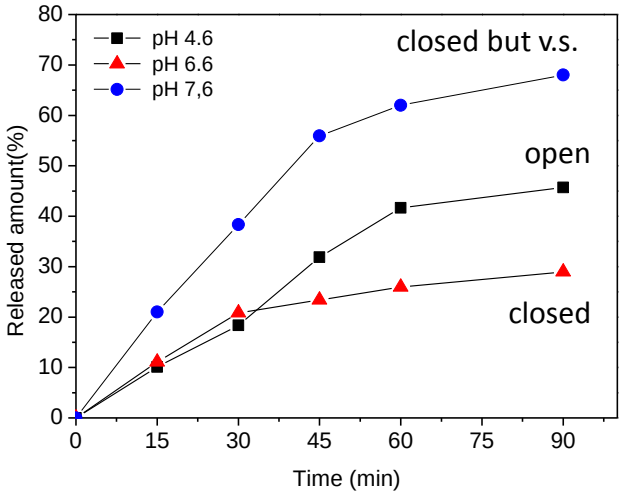
Rutin solubility increases with pH

Possible negative effect of the buffer ionic strength on the stability of MSN

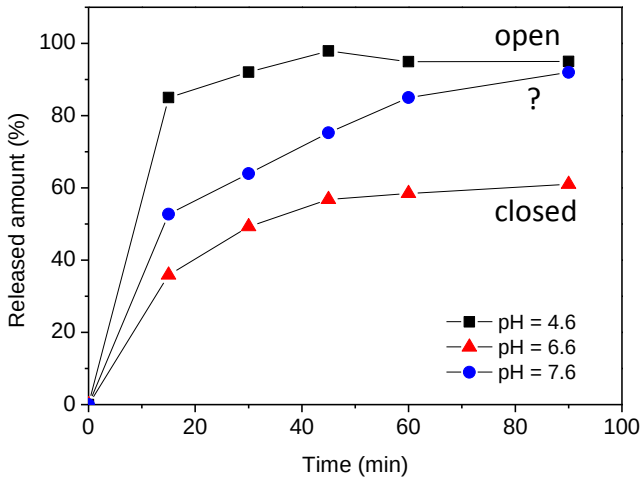
Release tests: MCM-41/PEI/RU

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



MCM-41/PDDA/RU



MCM-41/PEI/RU

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 controling 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 perfomance of PEI (comparison with COOH/MCM-41 sample with comparable loading)

Acknowledgements

Development of polymeric and oxidic materials for stimuli responsive applications

OXIPOLISTI

Progetto di Ateneo – CSP 2011

Compagnia di San Paolo

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You for kind attention