Responsive polymersomes and nanocapsules as robust and tunable carrier systems

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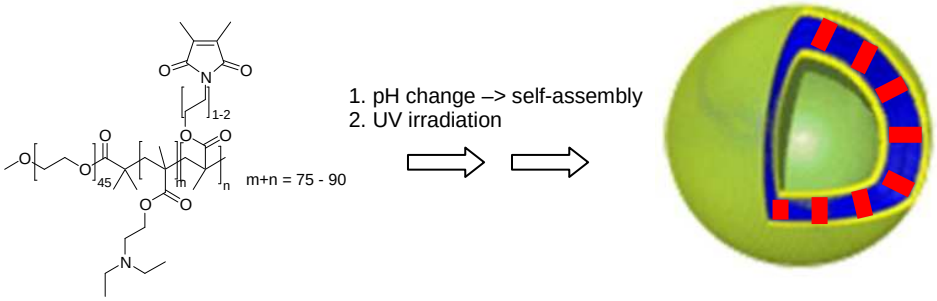
Abstract
In the recent years organic nanoparticles based on synthetic macromolecules have found significant interest especially in the area of biotechnology, biomedicine and synthetic biology as various carrier molecules. This comprises core-shell and hydrogel nanoparticles, dendritic structures, defined aggregates as well as polymersomes and polymeric (hollow) nanocapsules.[1-4] For defined up-take and release as well as for use as bionanoreactors, responsiveness has to be introduced into the various nanocarriers. Here we would like to present different synthetic strategies for the preparation of responsive nanocarriers. Synthetic details can be found in the references.[5-7]
We prepared in one strategy UV-crosslinkable polymersomes based on the self-assembly of amphiphilic block copolymers. We combined this cross-linking with a well-known pH sensitive polymer to give a highly stable polymersome with strictly controlled trans-membrane diffusion by reversible pH switches. Polyethylenglycole (PEG) was used as a biostable hydrophilic block, which is combined with the pH sensitive polydiethylaminoethyl-methacrylate (PDEAM) and photocross-linkable poly-dimethyl-maleic imidobutyl methacrylate (PDMIBM) as hydrophobic components (Scheme 1)[5]. The content of the PDMIBM is high enough to provide effective cross-linking after 30 s of UV irradiation, while the pH sensitivity remains. While pH sensitive polymersomes usually disassemble upon acidification, ours show a definite swelling, since the cross-linked membrane remains intact. This swelling is reversible as well as reproducible, indicating a highly stable cross-linking. These vesicles provide a very good basis for a synthetic bionanoreactor. While the membrane is not open for diffusion traffic in the basic state, small molecules are able to diffuse inside in an acidic state. Thus, cascade enzyme reactions could be carried out under pH control using polymersome-encapsulated enzymes in a one-pot arrangement (Scheme 2).

Furthermore, we used surface-initiated RAFT polymerization to synthesize narrowly distributed hollow nanocapsules (PtBMA-*co*-PDMIPM-*b*-PHPMA) employing silica nanoparticles as sacrificial templates and 2,3-dimethyl maleic imidopropyl methacrylate as a photo cross-linker. [7] This method was also used to synthesize an intelligent polymer nanocapsule with an ultrathin membrane [8]. The key concept is to use pH-responsive polydiethylaminoethylmethacrylate (PDEAEMA) as main membrane-generating component and a degradable disulfide bond to cross-link the membrane. The permeability of membrane, tuned by adjusting pH and using different lengths of the cross-linkers, was proven by showing a dramatic swelling behavior of the nanocapsules with the longest cross-linker from 560 nm at pH 8.0 to 780 nm at pH 4.0. Also, due to the disulfide cross-linker, degradation of the capsules using GSH as reducing agent was achieved which is further significantly promoted at pH 4.0. Using a rather long-chain dithiol cross-linker (C3), the synthesized nanocapsules demonstrated a good permeability allowing an enzyme myoglobin can be post-encapsulated, where the pH controlled enzyme activity by switching membrane permeability was also shown.

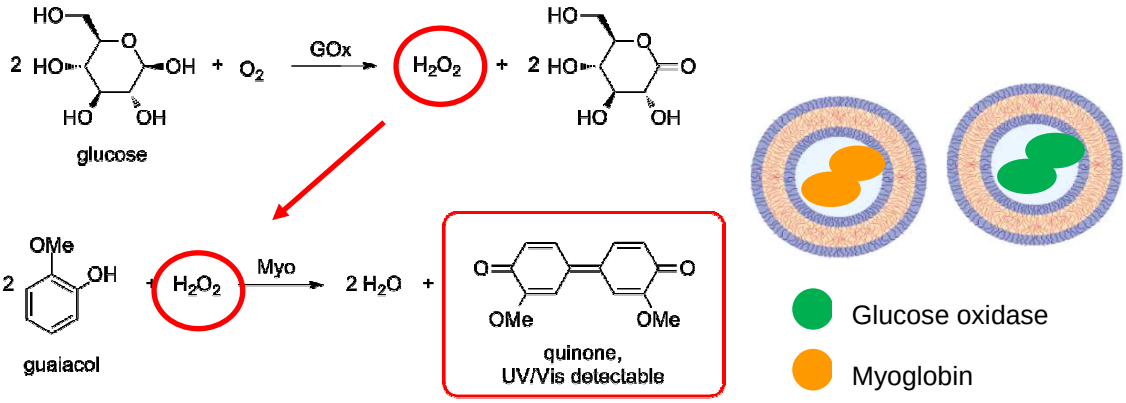
References

[1] Blanazs, A.; Armes, S.P.; Ryan, A.J. *Macromol. Rapid Commun.* **2009**, *30*, 267.
[2] Hendrickson, G.R.; Smith, M.H.; South, A.B.; Lyon, L.A. *Adv. Funct. Mater.* **2010**, *20*, 1697.
[3] Wang, Y.; Angelatos, A.S.; Caruso, F. *Chemistry of Materials* **2007,** *20*, 848-858. C.
[4] van Hest, J.C.M.; Kim, K.T.; Zhu, J.H.; Meeuwissen, S.A.; Cornelissen, J.J.L.M.; Pochan, D.J.; Nolte, R.J.M. *J. Am. Chem. Soc.* **2010**, *132*, 12522.
[5] Gaitzsch, J.; Appelhans, D.; Grafe, D.; Schwille, P.; Voit, B. *Chem. Commun.* **2011**, *47*, 3466.
[6] Gaitzsch, J.; Appelhans, D.; Wang, L.; Battaglia, G.; Voit, B. Angew. Chem. **2012**, *51*, 4448.
[7] Huang, X.; Appelhans, D.; Formanek, P.; Simon, F.; Voit, B. *Macromolecules* **2011**, *44*, 8351. [8] Huang, X.; Appelhans, D.; Formanek, P.; Voit, B*,* ACS Nano **2012***, 6*, 9718.

Schemes and Figures



Scheme 1: Block copolymer structure forming photo-crosslinkable polymersomes



Scheme 2: pH controlled cascade enzyme reaction carried out by polymersome enclosed enzymes glucose oxidase and myoglobin

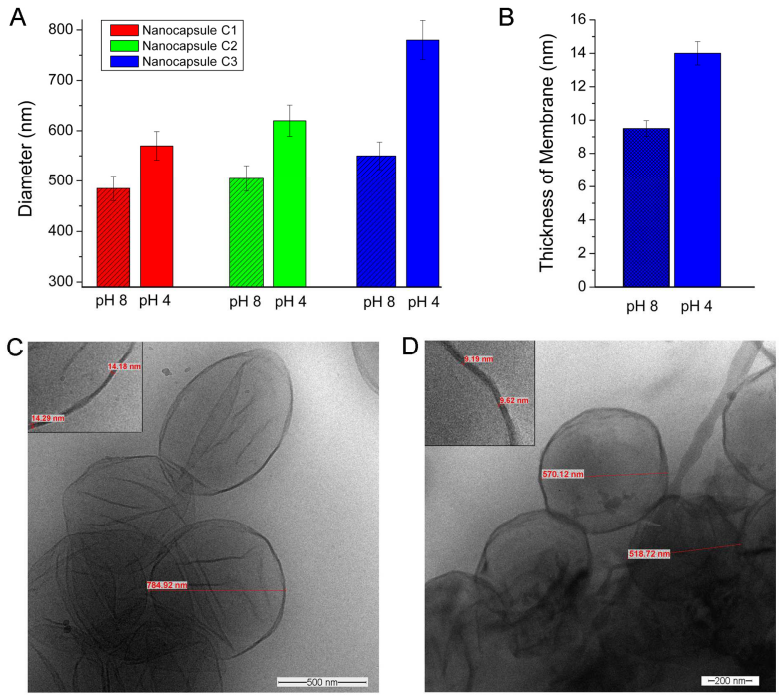


Figure 1: (A) diameter of nanocapsules C1 to C3 (by the template method using three different crosslinker) in pH 4.0 and 8.0 buffer solution, respectively, measured by DLS, (B) thickness of the membrane of nanocapsules C3 at pH 4.0 and pH 8.0, (C) and (D) Cryo-TEM images of nanocapsules C3 in pH 4.0 and pH 8.0 solution.