Self-Rupturing Microcapsules

ARTICLE *in* ADVANCED MATERIALS · OCTOBER 2005

Impact Factor: 17.49 · DOI: 10.1002/adma.200401951

6 AUTHORS, INCLUDING:

Bruno G De Geest
Ghent University
146 PUBLICATIONS **3,897** CITATIONS
SEE PROFILE

Gleb Sukhorukov
Queen Mary, University of London
318 PUBLICATIONS **19,377** CITATIONS
SEE PROFILE

Kevin Braeckmans
Ghent University
174 PUBLICATIONS **3,940** CITATIONS
SEE PROFILE

Jo Demeester
Ghent University
240 PUBLICATIONS **8,724** CITATIONS
SEE PROFILE

[6] A. L. Rogach, D. Nagesha, J. W. Ostrander, M. Giersig, N. A. Kotov, *Chem. Mater.* **2000**, *12*, 2676.
[7] Y. Chan, J. P. Zimmer, M. Stroh, J. S. Steckel, R. K. Jain, M. G. Bawendi, *Adv. Mater.* **2004**, *16*, 2092.
[8] T. Mokari, H. Sertchook, A. Aharoni, Y. Ebenstein, D. Avnir, U. Banin, *Chem. Mater.* **2005**, *17*, 258.
[9] S. T. Selvan, C. Li, M. Ando, N. Murase, *Chem. Lett.* **2004**, *33*, 434.
[10] D. Gerion, F. Pinaud, S. C. Williams, W. J. Parak, D. Zanchet, S. Weiss, A. P. Alivisatos, *J. Phys. Chem. B* **2001**, *105*, 8861.
[11] T. Nann, P. Mulvaney, *Angew. Chem.* **2004**, *116*, 5511; *Angew. Chem. Int. Ed.* **2004**, *43*, 5393.
[12] S. Chang, L. Liu, S. A. Asher, *J. Am. Chem. Soc.* **1994**, *116*, 6739.
[13] X. Zhao, R. P. Bagwe, W. Tan, *Adv. Mater.* **2004**, *16*, 173.
[14] W. W. Yu, L. Qu, W. Guo, X. Peng, *Chem. Mater.* **2003**, *15*, 2854.
[15] a) S. Chen, P. Dong, G. Yang, J. Yang, *Ind. Eng. Chem. Res.* **1996**, *35*, 4487. b) M. L. Hair, W. Hertl, *J. Phys. Chem.* **1970**, *74*, 91.
[16] N. Hüsing, U. Schubert, R. Mezei, P. Fratzl, B. Riegel, W. Kiefer, D. Kohler, W. Mader, *Chem. Mater.* **1999**, *11*, 451.
[17] A. M. Derfus, W. C. W. Chan, S. N. Bhatia, *Nano Lett.* **2004**, *4*, 11.
[18] M. Y. Gao, S. Kirstein, H. Möhwald, A. L. Rogach, A. Kornowski, A. Eychmüller, H. Weller, *J. Phys. Chem. B* **1998**, *102*, 8360.
[19] N. Gaponik, D. V. Talapin, A. L. Rogach, K. Hoppe, E. V. Shevchenko, A. Kornowski, A. Eychmüller, H. Weller, *J. Phys. Chem. B* **2002**, *106*, 7177.
[20] H. Bao, Y. Gong, Z. Li, M. Y. Gao, *Chem. Mater.* **2004**, *16*, 3853.

Self-Rupturing Microcapsules**

By *Bruno G. De Geest*, *Christophe Déjugnat*, *Gleb B. Sukhorukov*, *Kevin Braeckmans*, *Stefaan C. De Smedt*,* and *Joseph Demeester*

Pharmaceutical research strives to design systems that deliver drugs according to therapeutic needs. For example, to avoid multiple dosing, scientists have designed controlled-drug-delivery tablets, pumps, implants, and patches that provide continuous drug release over a prolonged period of time. However, there are many applications in medicine where a non-uniform release profile could be more beneficial.[1] For example, for bioactive agents such as hormones, many have suggested that pulsed release may offer advantages over continuous release.[2] A pulsed-release pattern could also be advantageous for drugs that develop biological tolerance when they are constantly present at their target site. Additionally, a device that could release an initial dose and a booster dose of a vaccine at different times after a single injection ("single-shot vaccination") would be promising as it would reduce the number of injections required to generate immunity.[3]

To achieve pulsed delivery we tried to design "self-rupturing microcapsules". As Figure 1 shows, we envision (bio)degradable microgels surrounded by a membrane that is permeable to water but impermeable to both the microgels' degradation products and the entrapped drugs. As the microgels degrade, their swelling pressure will increase which should rupture the membrane. Rupture is followed by a sudden release of the entrapped drug. The release time of the drug will therefore be governed by the degradation kinetics of the microgels, as this will determine the increase in swelling pressure and thus the time of rupture of the microcapsules. This paper aims to investigate whether we can experimentally achieve such self-rupturing microcapsules. Microcapsules which rupture upon applying an external trigger such as an electric field,[4] IR light,[5] pH,[6] etc., have been reported before. However, the requirement of an external trigger greatly limits the in-vivo applicability. To the best of our knowledge, self-rupturing microcapsules, in which an internal mechanism governs the rupture, have never been reported.

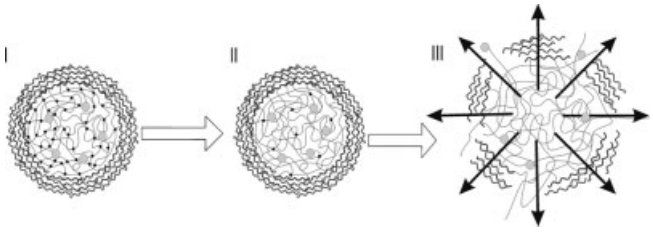

Figure 1. Schematic representation of self-rupturing microcapsules. I) Before degradation the polymer chains in the microgels are connected in a three-dimensional network by chemical crosslinks (●). The grey disks represent the encapsulated drugs. The microgels are surrounded by a polyelectrolyte membrane. II) The microgels degrade by hydrolysis of the crosslinkers. As degradation proceeds, the crosslink density decreases and free polymer chains are produced. III) At the end of the degradation process, the core of the capsule has become a polymer solution and the corresponding swelling pressure causes the membrane to rupture.

Biodegradable dextran-based microgels, with an average diameter of 7 μm, were prepared from dextran–hydroxyethyl methacrylate (dex-HEMA) as described by the Hennink group.[7] Radical polymerization of the methacrylate groups crosslinks the dextran chains. Because these methacrylate groups are connected to the dextran backbone by a carbonate ester, the degradation of the microgels occurs by hydrolysis of the crosslinks, yielding both the original dextran chains and HEMA oligomers as degradation products.[8] The degradation

[*] Prof. S. C. De Smedt, B. G. De Geest, Dr. K. Braeckmans, Prof. J. Demeester
Laboratory of General Biochemistry and Physical Pharmacy
Department of Pharmaceutics, Ghent University
Harelbekestraat 72, BE-9000 Ghent (Belgium)
E-mail: Stefaan.Desmedt@ugent.be
Dr. C. Déjugnat, Dr. G. B. Sukhorukov
Max Planck Institute of Colloids & Interfaces
Am Muehlenberg 1, D-14476 Potsdam (Germany)

[**] Ghent University is thanked for a scholarship BOF 01112403. Wim Hennink, Mies van Steenbergen, and Sophie Van Tomme are gratefully thanked for helpful discussions. Chris Vervaet and Eveline Pringels are thanked for lyophilization. Christophe Déjugnat thanks the European project "Nanocapsules" for funding. Prof. H. Möhwald helped tremendously by reading the manuscript. Supporting Information is available online from Wiley InterScience or from the author.

 DOI: 10.1002/adma.200401951

ADVANCED MATERIALS

of dex-HEMA gels can be tailored from days to months by changing the crosslink density.[8] To obtain positively charged microgels, we copolymerized dex-HEMA with dimethylaminoethyl methacrylate (DMAEMA; $pK_a = 8.3$).[9] These microgels are hereafter referred to as dex-HEMA-DMAEMA microgels.

The dex-HEMA-DMAEMA microgels were coated with polyelectrolytes using layer-by-layer (LbL) deposition.[10] Briefly, this technique is based on the sequential adsorption of oppositely charged polyelectrolytes on a charged substrate. The major advantage of this technique is that the dimensions of the obtained membrane can be controlled to within nanometers. To the best of our knowledge, LbL coating of micrometer-sized hydrogel particles has not been reported yet. Poly(sodium 4-styrenesulfonate) (PSS) served as polyanions while poly(allylamine hydrochloride) (PAH) served as polycations. This polyelectrolyte pair has been thoroughly studied and has proved to be ideally suited to coat colloids.[11] The adsorption procedure was monitored by measuring the electrophoretic mobility after each adsorption step. The initial ζ-potential of the dex-HEMA-DMAEMA microgels was +29 mV and oscillated steadily between –50 and +50 mV upon alternating adsorption of PSS and PAH, well in agreement with published data on PSS/PAH coating of other types of particles.[11b] To visualize the coating, rhodamine-labeled PAH (PAH tetramethylrhodamine isothiocyanate, PAH_{TRITC}) was used. Figure 2 shows a confocal laser scanning microscopy (CLSM) image of $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels; a clear fluorescent ring can be observed, which indicates the formation of a polyelectrolyte membrane surrounding the microgels.

As outlined above, to obtain self-rupturing microcapsules the membrane should be impermeable to the degradation products of the microgels. As the microgels degrade by hydrolysis of the HEMA crosslinks, the major degradation product is dextran (being the chains used to synthesize the dex-HEMA, which had an average molecular weight of 19 kDa; 1 Da = 1 g mol^{-1}). By using CLSM we investigated the permeability of the $(PSS/PAH)_3$ coating to fluorescein isothiocyanate (FITC) dextrans (FDs) of two molecular weights (4 and 20 kDa) at pH 7 and 9, respectively. Uncoated and $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels were immersed in FD-solutions. Figure 3 shows that the uncoated dex-HEMA-DMAEMA microgels were permeable to both FD 4 and 20 kDa, independent of the pH; the results are summarized in Table 1. The permeability of the $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels was, however, pH dependent: at pH 7 the coated microgels were permeable to both 4 and 20 kDa FDs, while at pH 9 they were impermeable. Similar findings on the pH-dependent permeability of $(PSS/PAH)_3$ coatings were reported by Antipov et al.[12] These permeability observations allowed us to suggest that at pH 9 the polyelectrolyte membrane should be impermeable to the degradation products of the microgels, being 19 kDa dextran chains. This should allow a build-up of the osmotic pressure upon degradation of the gel in the microcapsules. To the contrary, at pH 7 the $(PSS/PAH)_3$ coating is expected to be permeable to the degradation products and, consequently, a rise in osmotic pressure is not expected.

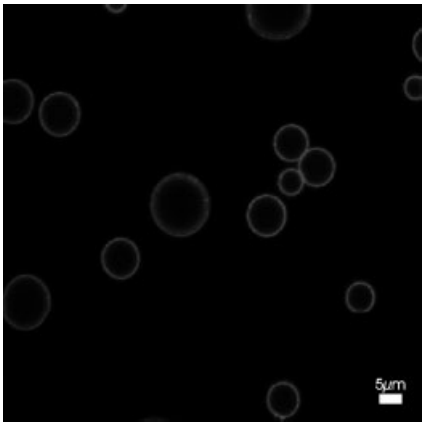

Figure 2. CLSM images of $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA-microgels. PAH was fluorescently labeled with TRITC.

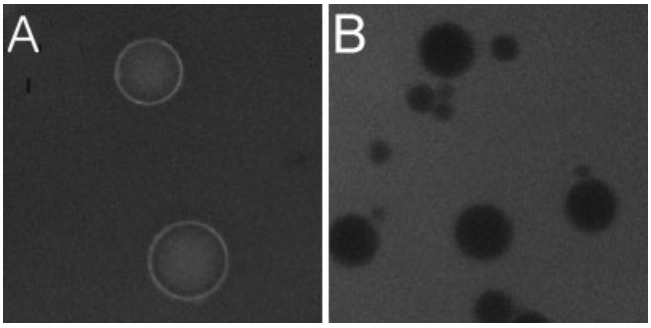

Figure 3. The $(PSS/PAH)_3$-coated microgels immersed in a 20 kDa FD solution at A) pH 7 and B) pH 9.

Table 1. Permeability of uncoated and $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels to FDs.

	Uncoated microgels		Coated microgels	
	FD 4 kDa	FD 20 kDa	FD 4 kDa	FD 20 kDa
pH 7	Permeable	Permeable	Permeable	Impermeable
pH 9	Permeable	Permeable	Impermeable	Permeable

To verify this we studied the behavior of uncoated and $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels during degradation. Both microgel types were incubated at 37 °C at pH 7 as well as pH 9. Microscopy experiments on uncoated microgels revealed that at pH 7 the microgels were completely degraded after 5 days, while at pH 9, they were completely degraded in 1 day, due to accelerated hydrolysis at an alkaline pH. Figure 4A shows a CLSM image of $(PSS/PAH)_3$-coated

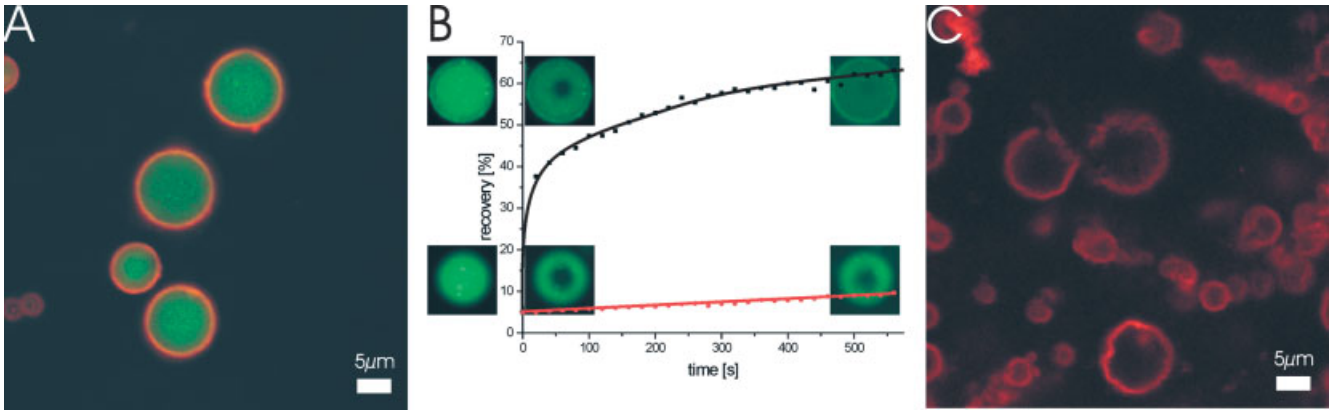

Figure 4. A) CLSM image of $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels 5 days after degradation at pH 7. 150 kDa FD was encapsulated in the microgels. B) Fluorescence recovery curves after bleaching a spot inside the capsules. The red curve corresponds to non-degraded capsules (lower images) while the black curve corresponds to capsules degraded at pH 7 (upper images). C) CLSM image of $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels 1 day after degradation at pH 9. Only remnants of broken capsules are present.

dex-HEMA-DMAEMA microgels 5 days after degradation at pH 7. To prove that at pH 7 degradation of the microgels had indeed occurred, we studied the mobility of encapsulated 150 kDa FD by fluorescence recovery after photobleaching (FRAP) before and after incubating the $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels for 10 days in buffer at pH 7. Figure 4B clearly shows that in non-degraded microgels the fluorescence does not really recover after the bleaching step, indicating that the FD chains are (sterically) immobilized in the microgel network. In $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels incubated for 10 days at pH 7, the fluorescence significantly recovered, indicating that the FD chains became mobile due to degradation of the network in the microgels. Nevertheless, the microgels were degraded, and clearly rupture did not occur.

Consequently, we studied the behavior of the $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels at pH 9. As shown in Figure 4C, only remnants of broken polyelectrolyte shells were visible after degradation of the dex-HEMA-DMAEMA microgels. To prove the self-rupturing of the particles, we tried to witness the rupturing of the membrane. In this experiment, $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels with encapsulated 150 kDa FD were placed at 80 °C for 4 min (to accelerate the degradation) in buffer at pH 9. The particles were subsequently examined by CLSM (at 40 °C) and followed over time. Figures 5A1–A4 show four snapshots of the particles taken after 60, 75, 90, and 105 min: rupturing of the coating occurs and the encapsulated 150 kDa FD is suddenly released from the particles.[13] In accordance with Laplace's law, larger capsules rupture earlier than smaller capsules. However, the time interval during which all the capsules ruptured is less than 10 % of the total time required for the degradation of the microgel core. As a negative control we also followed the behavior of non-coated dex-HEMA-DMAEMA microgels. As shown in Figures 5B1–B4, the microgels dissolved gradually in the alkaline solution.[13]

As outlined above, when completely degraded a dex-HEMA gel turns into a solution of dextran and HEMA oligomers. In case the LbL membrane is permeable to the HEMA oligomers, one can assume that, when the dex-HEMA-DMAEMA microgel is totally degraded, the swelling pressure of the microcapsule becomes the osmotic pressure of the corresponding dextran solution, which is estimated to be 150 kPa for the dex-HEMA-DMAEMA microgels used in this study.[14] Therefore, assuming a particle mean diameter of 7 μm and using Laplace's law ($\tau = \Delta\pi r2$, where τ is the tensile strength [$N\,m^{-1}$], $\Delta\pi$ is the osmotic pressure gradient [$N\,m^{-2}$], and r is the radius [m]), an upper limit of the tensile strength

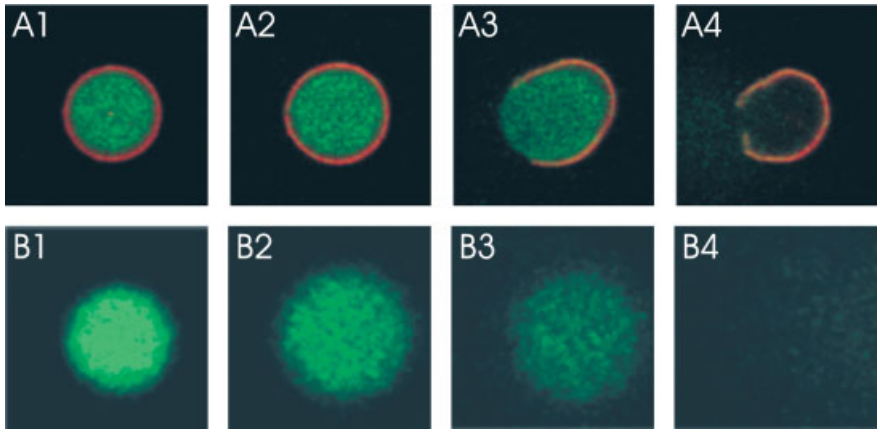

Figure 5. Snapshots of A1–4) $(PSS/PAH)_3$-coated dex-HEMA-DMAEMA microgels during the rupturing of the membrane and B1–4) uncoated dex-HEMA-DMAEMA microgels. The time interval between the snapshots is 15 min.

ADVANCED MATERIALS

of the $(PSS/PAH)_3$ membrane is estimated to be 0.26 $N\,m^{-1}$. The osmotic pressure of 150 kPa, which is able to rupture the capsules, is in accordance with the reported data on the osmotic pressure required to induce severe deformations in hollow polyelectrolyte capsules.[15]

In conclusion, this study shows that charged dex-HEMA microgels can be coated with polyelectrolytes using electrostatic interactions: CLSM and ζ-potential measurements proved that sequential adsorption of PSS and PAH at the surface of the dex-HEMA-DMAEMA microgels could be achieved. We observed that the permeability of the $(PSS/PAH)_3$ coating was pH dependent: while it was permeable to 20 kDa FITC-dextran at pH 7, it was impermeable at pH 9. Consequently, as the major degradation product of dex-HEMA-DMAEMA microgels is 19 kDa dextran, we expected that at pH 9 the $(PSS/PAH)_3$ coating should be impermeable to the degradation products. This should increase the (inner) swelling pressure of the microcapsules upon degradation of the entrapped gel, which could lead to a rupturing of the surrounding membrane. Indeed, sudden rupturing of the coating due to the degrading gel could be experimentally confirmed. In this way, self-rupturing microcapsules are obtained as they rupture without the need of an external trigger: the time of rupture is completely governed by the degradation kinetics of the entrapped gel, which governs how the swelling pressure of the microcapsules increases as a function of time.

The dextran-based microgels described above are promising for biomedical applications based upon reports that dex-HEMA is biocompatible[16] and because proteins can be easily incorporated inside dex-HEMA microgels with encapsulation efficiencies up to 90 %.[17] Our ongoing research is focusing on the development of monodisperse microgels which should significantly enhance the simultaneous rupture of the microcapsules, and we will further evaluate the potential of the self-rupturing microcapsules for pulsed drug delivery.

Experimental

Materials: *N*,*N*,*N*′,*N*′-tetramethylenediamine (TEMED), DMAEMA, tetramethyl rhodamine B isothiocyanate (TRITC), PSS (70 kDa), PAH (70 kDa), and FD (4 kDa, 20 kDa, and 150 kDa) were purchased from Aldrich. Potassium peroxodisulfate (KPS) and polyethylene glycol (PEG; 20 kDa) were purchased from Merck. Dextran (19 kDa) was obtained from Fluka. TRITC-labeled PAH was prepared as reported in the literature [18]. Dex-HEMA was prepared and characterized according to a method described elsewhere [8]. Dextran with a number-average molecular weight of 19 kDa was used. The degree of substitution (DS; the number of HEMA groups per 100 glucopyranose units in dextran) of the dex-HEMA used in this study was 2.5 as determined by ^{1}H NMR [8].

Preparation of Dex-HEMA-DMAEMA Microgels: Dex-HEMA-DMAEMA microgels with an initial water content of 70 wt.-% were prepared according to Franssen et al. [7]. In detail, 71 mg dex-HEMA, 20 μL FITC-dextran solution (50 mg mL^{-1}), and 35 μL DMAEMA were dissolved in 1.577 mL water and subsequently emulsified with a 3.35 mL 24 vol.-% aqueous PEG solution. Radical polymerization of the aqueous dex-HEMA emulsion droplets was initiated by adding TEMED (100 μL, pH neutralized with 4 N HCl) and KPS (9 mg). The reaction was carried out at room temperature for 1 h. Afterwards the obtained microgels were washed three times with pure water to remove PEG, KPS, and TEMED. Finally the microgels were suspended in 5 mL and stored at –20 °C.

LbL Coating of the Dex-HEMA: 500 μL (15 mg mL^{-1}) microgels were dispersed in 1 mL polyelectrolyte solution (2 mg mL^{-1} in 0.5 M NaCl) and shaken for 15 min. The excess polyelectrolyte was removed by two centrifugation steps. This procedure was repeated until three polyelectrolyte bilayers were obtained.

Confocal Microscopy: CLSM experiments were performed using a MRC1024 Bio-Rad scanning system equipped with a 60× water-immersion objective. Permeability experiments were preformed in 96-well plates by mixing a 50 μL FD (1 mg mL^{-1}) solution with 50 μL microgel dispersion, both in 0.1 M carbonate buffer at pH 9 or in a 0.1 M phosphate buffer at pH 7. FRAP experiments were performed by bleaching a circular region inside the capsules. The fluorescence recovery was quantified by calculating the ratio of the fluorescence intensity of the recovering region to the fluorescence intensity of a non-bleached region in the same capsule.

Received: November 29, 2004
Final version: June 9, 2005
Published online: August 16, 2005

[1] a) B. Lemmer, *Ann. Biol. Clin.* **1994**, *52*, 179. b) J. T. Santini, M. J. Cima, R. Langer, *Nature* **1999**, *397*, 335. c) A. C. R. Grayson, I. S. Choi, B. M. Tyler, P. P. Wang, H. Brem, M. J. Cima, R. Langer, *Nat. Mater.* **2003**, *2*, 767.

[2] a) G. W. Creasy, M. E. Jaffe, *Ann. N. Y. Acad. Sci.* **1991**, *618*, 548. b) T. F. Nielsen, P. Ravn, Y. Z. Bagger, L. Warming, V. Christiansen, *Osteoporosis Int.* **2004**, *15*, 168. c) P. E. Lazzereni, P. L. Capecchi, S. Bisogno, M. Galeazzi, R. Marcolongo, F. L. Pasini, *Ann. Rheum. Dis.* **2003**, *62*, 694.

[3] J. Hanes, J. L. Cleland, R. Langer, *Adv. Drug Delivery Rev.* **1997**, *28*, 97.

[4] P. F. Kiser, G. Wilson, D. Needham, *Nature* **1998**, *394*, 459.

[5] a) A. G. Skirtach, A. A. Antipov, D. G. Shchukin, G. B. Sukhorukov, *Langmuir* **2004**, *20*, 6988. b) B. Radt, T. A. Smith, F. Caruso, *Adv. Mater.* **2004**, *16*, 2184. c) A. S. Angelatos, B. Radt, F. Caruso, *J. Phys. Chem. B* **2005**, *109*, 3071.

[6] a) T. Mauser, C. Dejugnat, G. B. Sukhorukov, *Macromol. Rapid Commun.* **2004**, *25*, 1781. b) C. Dejugnat, G. B. Sukhorukov, *Langmuir* **2004**, *20*, 7265.

[7] O. Franssen, W. E. Hennink, *Int. J. Pharm.* **1998**, *168*, 1.

[8] a) W. N. E. van Dijk-Wolthuis, J. A. M. Hoogeboom, M. J. van Steenbergen, S. K. Y. Tsang, W. E. Hennink, *Macromolecules* **1997**, *30*, 4639. b) W. N. E. van Dijk-Wolthuis, S. K. Y. Tsang, J. J. Kettenes-van den Bosch, W. E. Hennink, *Polymer* **1997**, *38*, 6235.

[9] S. R. Van Tomme, M. J. van Steenbergen, S. C. De Smedt, C. F. van Nostrum, W. E. Hennink, *Biomaterials* **2005**, *26*, 2129.

[10] a) G. Decher, *Science* **1997**, *277*, 1232. b) G. B. Sukhorukov, E. Donath, H. Lichtenfeld, E. Knippel, M. Knippel, A. Budde, H. Mohwald, *Colloids Surf., A* **1998**, *137*, 253. c) E. Donath, G. B. Sukhorukov, F. Caruso, S. A. Davis, H. Mohwald, *Angew. Chem. Int. Ed.* **1998**, *37*, 2202.

[11] a) A. A. Antipov, G. B. Sukhorukov, E. Donath, H. Mohwald, *J. Phys. Chem. B* **2001**, *105*, 2281. b) I. L. Radtchenko, G. B. Sukhorukov, S. Leporatti, G. B. Khomutov, E. Donath, H. Mohwald, *J. Colloid Interface Sci.* **2000**, *230*, 272. c) A. I. Petrov, A. A. Antipov, G. B. Sukhorukov, *Macromolecules* **2003**, *36*, 10 079.

[12] A. A. Antipov, G. B. Sukhorukov, S. Leporatti, I. L. Radtchenko, E. Donath, H. Möhwald, *Colloids Surf., A* **2002**, *198*, 535.

[13] Movies are available on http://www.ugent.be/fw/biofys/en/staff/degeest

[14] B. G. Stubbe, F. Horkay, B. Amsden, W. E. Hennink, S. C. De Smedt, J. Demeester, *Biomacromolecules* **2003**, *4*, 691.

[15] a) C. Y. Gao, S. Leporatti, S. Moya, E. Donath, H. Möhwald, *Langmuir* **2001**, *17*, 3491. b) C. Gao, E. Donath, S. Moya, V. Dudnik, H. Möhwald, *Eur. Phys. J. E* **2001**, *5*, 21.
[16] a) J. A. Cadee, M. J. A. van Luyn, L. A. Brouwer, J. A. Plantinga, P. B. van Wachem, C. J. de Groot, W. den Otter, W. E. Hennink, *J. Biomed. Mater. Res.* **2000**, *50*, 397. b) C. J. De Groot, M. J. A. VanLuyn, W. N. E. Van Dijk-Wolthuis, J. A. Cadee, J. A. Plantinga, W. Den Otter, W. E. Hennink, *Biomaterials* **2001**, *22*, 1197.
[17] O. Franssen, R. J. H. Stenekes, W. E. Hennink, *J. Controlled Release* **1999**, *59*, 219.
[18] H. Jeffery, S. S. Davis, D. T. Ohagan, *Int. J. Pharm.* **1991**, *77*, 169.

Large-Scale "Surface-Programmed Assembly" of Pristine Vanadium Oxide Nanowire-Based Devices**

By *Sung Myung, Minbaek Lee, Gyu Tae Kim, Jeong Sook Ha*, and *Seunghun Hong**

Nanowires and nanotubes are drawing a tremendous amount of attention due to their potential applications in various nanoscale devices, such as field-effect transistors (FETs),[1–4] chemical and biological sensors,[5–8] nanoprobes,[9] and nanocables.[10] Divanadium pentoxide (V_2O_5) nanowires or nanotubes have been utilized in FETs,[11] sensors,[12,13] spintronic devices,[14] and nanolithography templates.[15,16] However, previous reports have only shown the fabrication of a few devices, so the lack of a mass-production method is holding back their practical applications. Since nanowires are usually synthesized in a solution or powder form, individual nanowires have to be picked up and assembled onto the substrate to build functional devices, which cannot be achieved by conventional microfabrication strategies. Previous techniques used for nanowire assembly include flow-cell methods,[17] electromagnetic-field alignment,[18] biomolecular methods,[19] etc.[20–23] However, since these methods often rely on external forces to precisely align nanowires, it can be a time-consuming task to produce a large number of nanowire circuits with arbitrary orientations. In addition, the surface functionalization of nanowires in some techniques may even change the properties of the nanowires. Herein, we report a simple but efficient method named "surface-programmed assembly" for high-precision assembly and alignment of a large number of pristine V_2O_5 nanowires on solid substrates. In this strategy, positively charged surface molecular patterns are utilized to assemble and align millions of V_2O_5 nanowires over a large surface area, while neutral surface molecular patterns are utilized to avoid any unwanted adsorption of nanowires. This method does not rely on any external force for nanowire alignment, and it is compatible with conventional microfabrication processes. Significantly, we demonstrate precision assembly and alignment of V_2O_5 nanowire arrays and nanowire-based devices over a large surface area (~1 cm × 1 cm). This method may pave the way toward industrial-level production of V_2O_5 nanowire-based devices for practical applications.

Figure 1 shows the schematic diagram of our strategy. First, we patterned the substrates with a self-assembled monolayer (SAM) of molecules with positively charged and neutral terminal groups. For example, on Au surfaces, we utilized cysteamine or 2-mercaptoimidazole (2-MI) as a positively charged SAM molecule, while 1-octadecanethiol (ODT) was utilized as a neutral molecular species. On SiO_2 surfaces, aminopropylethoxysilane (APTES) and 1-octadecyltrichlorosilane (OTS) were utilized as positively charged and neutral SAM molecular species, respectively. The molecular patterning process was carried out by patterning the first molecular species via dip-pen nanolithography (DPN),[24–26] microcontact print-

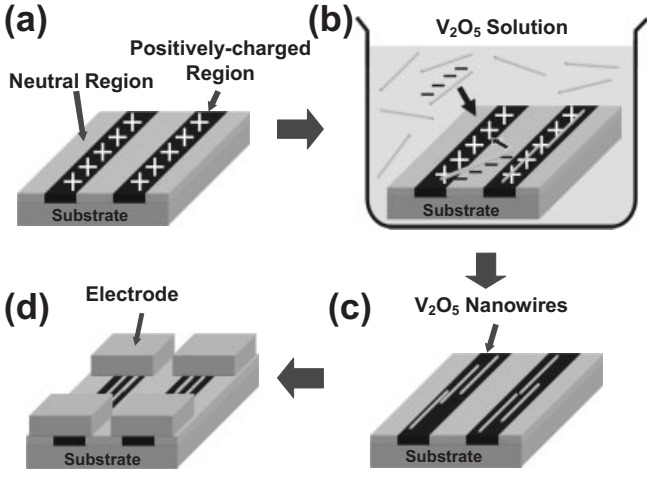

Figure 1. Schematic diagram depicting "surface-programmed assembly" of V_2O_5 nanowires on solid substrates. a) Patterning a self-assembled monolayer with positively charged and neutral terminal groups. b) Assembly and alignment of nanowires directed by surface molecular patterns. c) Rinsing with de-ionized water leaves aligned nanowire patterns. d) Additional microfabrication process (e.g. lift-off) to fabricate electrodes.

[*] Prof. S. Hong, S. Myung, M. Lee
Physics and Nano-Systems Institute, Seoul National University NS50
Shilim-Dong, Kwanak-Gu, Seoul 151-742 (Korea)
E-mail: shong@phya.snu.ac.kr
Prof. G. T. Kim
Department of Electrical Engineering, Korea University
Anam-Dong, Sungbuk-Gu, Seoul 136-701 (Korea)
Prof. J. S. Ha
Department of Chemical and Biological Engineering, Korea University
Anam-Dong, Sungbuk-Gu, Seoul 136-701 (Korea)

[**] The work in this paper was supported by the Ministry of Science and Technology through the National Research Laboratory (NRL) program and, in part, the 21st Century Frontier R & D Program. S. H. acknowledges equipment support from the Nano-Systems Institute National Core Research Center program of Korea Science and Engineering Foundation. Supporting Information is available online at Wiley InterScience or from the author.

 DOI: 10.1002/adma.200500682