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Controlled Double-Sensitivity of Microgels Applied to Electronically Adjustable Chemostats**

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Stimuli-sensitive hydrogels change their volume significantly in response to small alterations of certain environmental conditions.[1] The combination of both sensor and actuator properties probably allows the simplest realization of an active device for automatic concentration regulation of chemical substances. Because of its functionality, this apparatus is, ultimately, a chemical comparator or chemostat. Automatic flow control depending on ion and solvent concentrations in aqueous solutions has been demonstrated for the control of pH and the concentration of various alcohols.[2–5] Of particular interest are chemostats able to regulate biochemical substances, because case-sensitive drug-release systems or devices substituting body functions such as that of a pancreas could be realized.[6,7] However, the lack of adjustability of the operating conditions in order to regulate flow, for example, a critical concentration defined by the used hydrogel, inhibits the broad practical use of chemostats.

To achieve electronic adjustment of the device's operating conditions we use controlled double-sensitivity (CDS) of hydrogels. By controlling the temperature of a thermosensitive hydrogel, the phase-transition concentration is precisely adjustable to the required value.

The chemostat consists of a silicon-based upper and bottom plate and a circuit card for the PC-controlled operation (see Fig. 1a and b). The upper plate carries a platinum temperature sensor and contains a hydrogel chamber (600 μm × 600 μm × 350 μm) that is covered by a perforated membrane. The bottom plate has similar construction with an integrated platinum heating element.[8] Polymeric microgels based on poly(*N*-isopropylacrylamide) (PNIPAAm) have been inserted as a freeze-dried powder (average particle diameter 100 μm) into the hydrogel chamber. The temperature of the hydrogel chamber can be controlled by an integrated heating element and a temperature sensor.

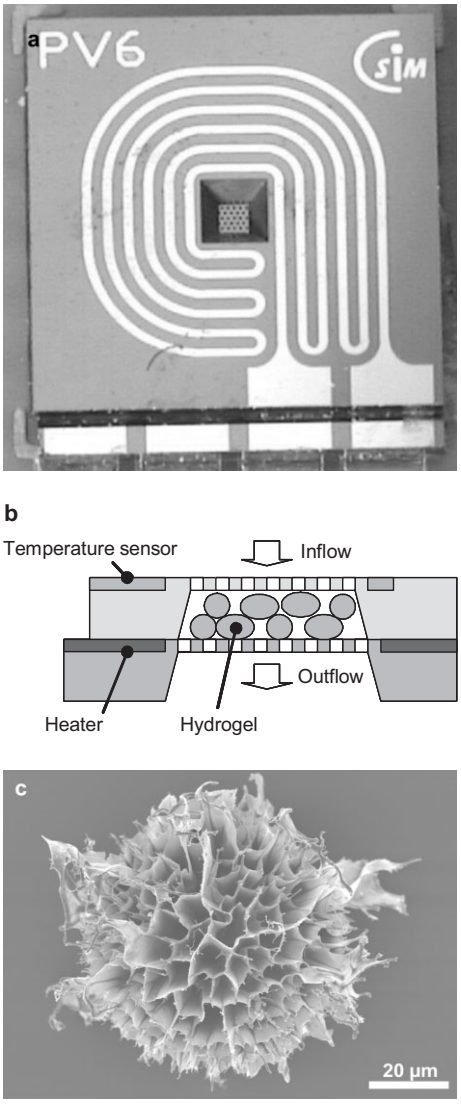

Figure 1. The chemostat design. a) The photograph of the chemostat shows the silicon-based upper plate, including the structure of the temperature sensor and the perforated membrane of the inflow. The dimension of the silicon chip is 5 mm × 5 mm. b) This schematic representation describes the internal structure of the chemostat. c) The microgel particles prepared by inverse-suspension polymerization are regular in shape and highly porous.

The microgel particles have been prepared by an inverse-suspension polymerization process. This technique allows the synthesis of particles with a regular shape, and variation of the microgel diameter (from 100 nm to 100 μm), crosslinking

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ADVANCED MATERIALS

degree, porosity, mechanical properties, as well as the chemical composition. The porosity influences both the mechanical stability and the time behavior of the microgels. Highly porous particles (see Fig. 1c) possess a very short response time while less porous microgels are mechanically more stable. The porosity depends strongly on the crosslinking degree, which can be controlled by the concentration of the crosslinking agent in the reaction mixture.

The PNIPAAm microgels possess lower critical solution temperature (LCST) behavior in aqueous media. Below the volume phase transition temperature T_t the microgel is in the swollen state. If T_t (in pure water T_t is close to 34 °C) is exceeded, PNIPAAm de-swells. The presence of certain substances can shift the T_t of the hydrogel.[9,10]

The volume phase transition temperature of PNIPAAm microgels was studied by differential scanning calorimetry (DSC) (Mettler-Toledo DSC 308, heating rate 10 K min^{-1}) in the presence of different alcohols (see Fig. 2a). The volume phase transition of the PNIPAAm is an endothermic effect and results in the appearance of a peak in the DSC thermographs, which can be used for the precise determination of T_t. This critical temperature depends on the alcohol concentration in a nonlinear relationship. With increase of the hydrophobic part in the alcohol structure T_t is shifted to lower alcohol concentrations. At a certain alcohol concentration (c_{limit}) PNIPAAm loses its temperature-sensitive character because of the good solubility of the polymer chains provided by the effective solvation of the alcohol molecules. This critical alcohol concentration is 11.7 mol L^{-1} for methanol, 4.1 mol L^{-1} for ethanol, and 1.75 mol L^{-1} for 1-propanol.

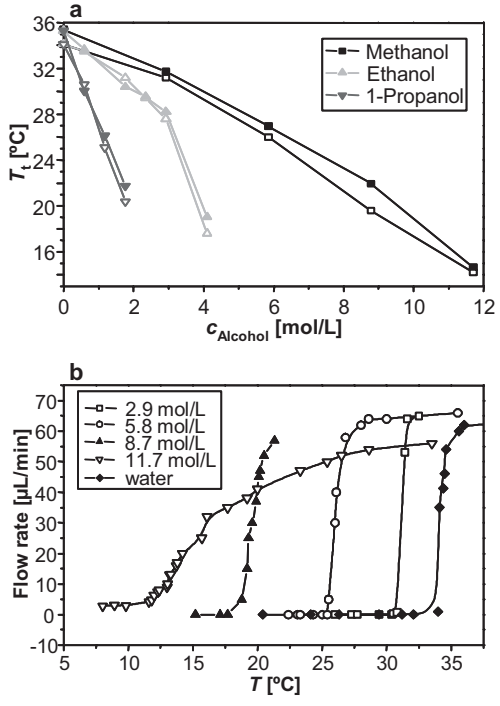

Figure 2. The volume phase transition concentration of PNIPAAm microgels in alcohol solutions depends on the temperature of the system. a) This diagram shows the volume phase transition temperature of a microgel determined by DSC measurements (solid symbols) as well as the operating point of the chemostat device (open symbols) for different alcohol concentrations in water. The switching temperature of the chemostat correlates with DSC data. b) As shown here for different methanol concentrations in water, the chemostat can be used up to the critical alcohol concentration c_{limit} = 11.7 mol L^{-1}. When this concentration is exceeded the device loses its regulation function.

Figure 2b shows the dependence of the flow rate on the temperature in the chemostat actuator chamber for different methanol concentrations. The experimental data indicates that temperature control allows a shift of the operating point, but the shape of the flow rate–temperature curves remain unaltered. If the methanol concentration reaches the critical value c_{limit} = 11.7 mol L^{-1} there is no sharp change of the flow rate with temperature. The switching temperature of the chemostat correlates with the experimentally determined DSC data (see Fig. 2a) for different alcohol types. The operating points of the chemostat are somewhat smaller compared with the calorimetry data (e.g., the switching temperature of the chemostat is lower than the volume phase transition temperature determined by DSC). This effect can be explained by the mechanical design. At a certain swelling degree of the hydrogel actuator in the chemostat chamber the liquid flow is terminated. For example, within the same actuator chamber, a large hydrogel actuator will close a valve and stop the liquid flow at a lower swelling degree than a smaller actuator of the same chemical composition.

This device can be adjusted in an operating range between pure water and the c_{limit} with a calculative precision of 60 mmol L^{-1} (methanol), 25 mmol L^{-1} (ethanol), and 15 mmol L^{-1} (1-propanol) by temperature change of 0.1 K. The average deviation obtained by repeated alcohol variation measurements is 80 mmol L^{-1} (methanol), 50 mmol L^{-1} (ethanol), and 40 mmol L^{-1} (1-propanol).

The volume phase transition temperature of the PNIPAAm microgel as a function of NaCl concentration is presented in Figure 3a. The DSC measurements indicate a linear dependency of the volume phase transition temperature on salt concentration:

$$T_t(c_{NaCl}) = T_t(H_2O) + A \cdot c_{NaCl} \quad (1)$$

where $(0 \le c_{NaCl} \le 1 \text{ mol L}^{-1})$, $T_t(H_2O) = 34.42$ °C, and $A = -13.4$ K mol^{-1}.

Analogous to alcohol mixtures, switching the concentration of salt can be adjusted by controlling the temperature within the device. Figure 3a shows that the difference between the chemostat and the DSC data is in the range of 0.75 K. Contrary to the alcohol solutions PNIPAAm microgels do not loose their temperature sensitivity at high salt concentrations (see Fig. 3b). It is difficult to adjust the salt concentrations lower then 20 mmol L^{-1} because of the bad reproducibility of the experimental data.

The average deviation of the salt concentrations investigated by repeated variations is 25 mmol L^{-1}. However, it has

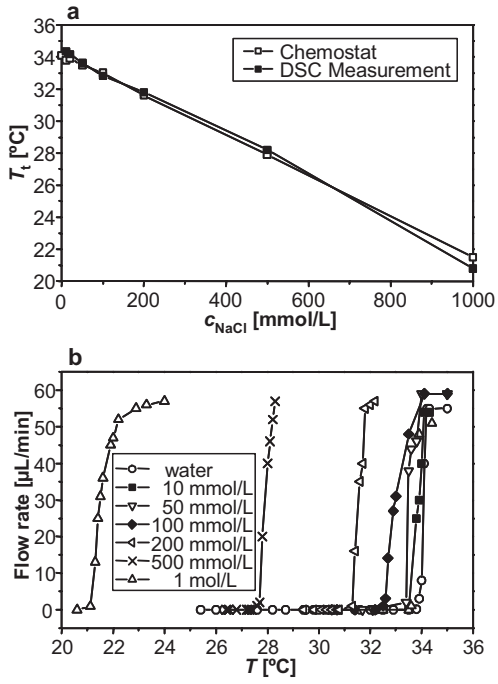

Figure 3. The critical salt concentration initiating the volume phase transition of PNIPAAm microgels depends on the system temperature. a) The volume phase transition temperature determined for different NaCl concentrations in water (solid symbols: DSC measurements) is in good agreement with the operating point of the chemostat (open symbols). b) The chemostat keeps the regulation function by high salt concentrations.

been observed that PNIPAAm microgels lose their actuator properties if they are exposed to aqueous solutions containing high salt concentrations for a long time. It is suggested that ions can be accumulated within microgel particles, providing an effective electrostatic repulsion force and material enrichment, which prevents the collapse of the polymer chains upon heating. This effect can be avoided by systematic rinsing of the chemostat with deionized water.

The presented chemostat device can resist an applied pressure drop of up to 6 bar (600 kPa) between the inlet and the outlet without any leakage. When this limit is exceeded the device is damaged. In general, by increasing the effective filling of the hydrogel chamber with a microgel, the pressure resistance of the device as well as the back pressure increase. The effective filling is determined by the filling weight and the size of the particles of the microgel.[5] Small particles, which result in a large packing density, increase the effective filling. Furthermore, to avoid clogging side-effects, the particle size should not under-run a threshold of two to three times the size of the membrane perforation holes. For prevention of critical conditions, an emergency-stop function (shut-off or fully open) can be integrated due to the electronic control of this device.

Besides the control of sensor and actuator properties, CDS is suitable for the adjustment of all properties based on changes in density or activity of the hydrogel functionalities. CDS can also be applied to hydrogels functionalized by their chemical composition as well as for gels filled with functional materials. We believe that stimuli-responsive materials with adjustable properties, for example, catalytic, promotion, initiation, and inhibition functionalities, will provide advanced features in chemistry, biochemistry, and biology.

The extremely flexible microgel preparation technology offers variation of the particle size and the crosslinking degree as well as the incorporation of reactive groups or functional materials in nanoparticle form. The principle of the electronically adjustable chemostat opens broad possibilities for the application of hydrogel-based systems in chemical and biotechnological processes as well as in medical treatment. The electronic device-control allows combination with both integrated data processing based on micro processors and transponder-based connection with central data processing. Therefore, monitoring and supervising functions can be integrated in control devices, for example, acting as case-sensitive drug-release systems. Furthermore, the principle can be applied in sensing devices, fluidic drives, etc.

Experimental

Span80 and *N,N*-methylene-bis-acrylamide were received from Aldrich. Tween80, *n*-heptane, *N,N,N′,N′*-tetramethylethylenediamine, and ammonium peroxydisulphate were obtained from Merck. *N*-Isopropylacrylamide was received from Acros Organics and recrystallized in *n*-hexane before use. Alcohols (> 99.5 %) were obtained from AppliChem. 4 inch Si wafers (orientation <100>, n-type, specific conductance = 250 Ω cm, 500 µm thickness) were obtained from SICO Wafer GmbH Heiningen.

Device Fabrication: Perforated diaphragms and chambers were generated by a two-side process (wet etching with 30 wt % KOH at 80 °C; plasma etching, ASE-Bosch process). Applied materials were silicon wafers. Heating elements (110 nm thickness, resistance 70 Ω) and temperature sensors (110 nm thickness, resistance 200 Ω), both prepared by a platinum-thin-film system (plated by GeSiM mbH with MSBA-400SP from Malz & Schmidt) with lift-off patterning, were located on top of the silicon parts. Freeze-dried microgel particles were filled with a filling degree of 90 vol % into the actuator chamber. The upper and bottom parts, and the circuit card were coupled by a combination of flip-chip and gluing technology. Electrical connection was realised by gold wire bonding.

Microgel Synthesis: The synthesis of the PNIPAAm microgels was performed by means of inverse-suspension polymerization. The continuous phase consisted of *n*-heptane (200 g) with dissolved Span80 (2 g) and Tween80 (0.4 g). The aqueous solution containing water (12 g), monomer *N*-isopropylacrylamide (2.4 g), crosslinker *N,N*-methylene-bis-acrylamide (0.12 g), and initiator ammonium peroxydisulphate (0.432 g) was prepared in a separate flask. The aqueous solution was redispersed in *n*-heptane forming microscopic droplets. The polymerization in aqueous droplets containing monomer was initiated by addition of a catalyst *N,N,N′,N′*-tetramethylethylenediamine (0.1 g) at $T = 25$ °C. After 3 h, PNIPAAm microgels were washed three times with acetone and three times with water by precipitation and redispersion procedure. In this synthetic procedure, by varying the stabilizer or crosslinker concentration, an effective control of the microgel dimensions and swelling properties was provided.

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