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INVITED REVIEW

Responsive hydrogel layers—from synthesis to applications

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Abstract Responsive polymer networks are interesting materials for a variety of different applications due to the fact that they can perform a large volume transition. However, the swelling transition is a diffusion limited process. Thus, the decrease of the feature size (e.g., in thin layers) is an appropriate way to create structures with reasonable response time. The possibility to pattern responsive polymer networks makes them useful for application in microsystem technology as well as in biomedicine. The transition behavior of these films showed similar trends to those of the corresponding linear polymers whereas confinement effects have been found for thin hydrogel layers. The ability to optimize the integration of these polymers is critical for the fabrication and development of platforms that harness the unique abilities of responsive polymer networks. Here, recent developments on chemically cross-linked hydrogel layers with respect to synthesis, characterization, and application are highlighted.

Keywords Hydrogel · Lithography · Stimuli-sensitive polymers · Swelling

Introduction

The volume phase transition in stimuli sensitive hydrogels is important for many applications, e.g., as (micro-) actuator and sensors materials [1] or in controlled cell attachment–detachment [2] and controlled drug delivery [3]. Most investigations focus on temperature or pH-sensitive polymers; however, a variety of other parameters (e.g., ionic strength, UV light, magnetic fields, etc.) has been studied [4, 5]. The majority of these applications require the use of hydrogels as thin layers at surfaces and interfaces. Therefore, the behavior of bulk hydrogel may not be necessarily extended to these types of geometries. Further decrease of the gel size led to the development of colloidal hydrogels with diameters down to 50 nm. Even complex structures like core–shell morphologies can be prepared [6, 7]. However, processing of such colloidal suspension is completely different as for hydrogel layers; thus, such structure are not included in this review. In order to enhance the performance of such hydrogels, different approaches have been investigated, e.g., templating processes by contact photonic crystals and noncontact colloidal arrays creating polymerized hydrogels for applications in chemical sensing and device fabrication [8]. The technological need for new and better soft materials has led to significant advances in the field of nanocomposite hydrogels, which have recently been reviewed [9].

Generally, (multi)layers of polymers are of interest due to their diverse applications, e.g., as biomaterials [10, 11]. Alternate coating of oppositely charged films produces polyelectrolyte multilayers [12]. Furthermore, temperature-responsive hydrogel films can also be prepared by the layer-by-layer (LbL) method. LbL-assembled films were prepared by the sequential chemical cross-linking between the amino and carboxyl groups on respective surfaces, swell and deswell in their aqueous media, thus, forming ultrathin hydrogels [13]. In such cases, application-relevant properties like switchability and patternability are rarely observed. A number of key parameters, such as responsiveness to external stimuli, directionality of response through alignment, transduction via surface stress, or

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changes in ionic conductivity, can be found in polymer brushes. Several examples of actuation and transduction in polymer brushes have been explored [14]. Heterogeneous-mixed polymer brushes (HPB) have the ability to respond in a controllable fashion to specific environmental stimuli. Recently, HPB of poly(styrene) and poly(2-vinylpyridine) have been reported. Using such technique, surface properties can be changed in presence of specific solvents [15, 16]. Switching mechanism of these brushes involves use of organic solvents, which are not suitable for bio-applications. Even though ultrathin films prepared by LbL technique and as polymer brushes are of great importance, such topics will not be covered in this review. Here, recent developments on chemically cross-linked hydrogels layers with respect to synthesis, characterization, and application are highlighted.

Synthesis and pattering

Recently, there has been considerable interest in the development of materials whose surface properties can be dynamically modulated. Stimuli-responsive polymers are one of the candidates used for surface modification because of their interesting characteristics. Dynamic control of the surface energy is of interest for controlling wettability, biomolecular adsorption, and cell adhesion. Several investigations were performed to create stimulus-responsive hydrogel structures on various substrates.

(Multi)layers of hydrogels with patternable properties can provide a surface with distinct behavior at different regions of the surface in presence of a stimulus. A number of microfabrication techniques have been developed to generate microscopic patterns on material surfaces. These include (1) photo lithography using photo masks, (2) soft lithography, which is a set of techniques that make use of an elastomeric “soft” material, commonly polydimethylsiloxane, (3) electron-beam patterning, and (4) direct printing (Fig. 1).

The stimuli-induced volume change usually arises from one of three major mechanisms: (1) changes in osmotic pressure or charge density (i.e., pH-responsive hydrogels); (2) changes in solvent affinity of the polymer backbone (i.e., temperature-sensitive hydrogels); or (3) changes in the polymer cross-link density. Recently, a method to fabricate microscopic hydrogel structures inside microchannels via a liquid-phase photo polymerization process has been developed [17]. The liquid-phase photo polymerization not only allows the construction of numerous hydrogel structures with varying properties quickly and easily but also provides the capabilities to make various shapes and sizes by simply choosing the proper photo mask during the polymerization process. Because these microscopic hydrogels are stationary inside microchannels, flowing a suitable buffer solution through the microchannel can control the chemical environment around the hydrogels without disrupting or moving the hydrogel. Dual pH-responsive core–shell hydrogels containing both a vinyl pyridine component and a 2-dimethylaminoethyl methacrylate component were prepared the same way. Complementary photo masks were utilized to prepare hydrogels with different core/shell volume ratios. Depending on the location of each polymer component, dramatically different swelling profiles were achieved. Selective swelling of the shell followed by the core components allowed the hydrogel to expand with the usual kinetics; however, by switching the location of each polymer component and swelling the core first, swelling rates decreased by over one order of magnitude and were dependent on the shell component′s volume [18]. Hydrogels of 2-hydroxyethyl methacrylate (HEMA) cross-linked with *N*,*N′*-cystaminebis-(acrylamide) (CBA) were prepared to study chemical-responsive gels. By chemically reducing disulfide bonds with dithiothreitol, the cross-link density of the hydrogel network decreased, leading to an observable swelling of the hydrogel. To maximize swelling response, acrylic acid (AA) was copolymerized with HEMA and CBA to afford a pH or chemically responsive hydrogel. The combination of a decrease in cross-link density and a driving force for swelling (deprotonation of AA) led to a fast swelling response (Fig. 1a) [19]. Intelligent hydrogels containing ionic groups (pH responsive) and poly(ethylene glycol) have been micropatterned onto gold surfaces using specific surface chemistry and free-radical polymerization. This novel method enables the microscale control and optimization of processes for the integration of polymeric systems with silicon, glass, and gold surfaces in devices (Fig. 1b) [20]. As a result of the microcontact printing of hydrophobic thiols, the monomer solutions remained only on the zones that were unmodified by stamping. These hydrophilic/hydrophobic interactions successfully created the micropattern regions containing hydrophilic monomer solution or hydrophobic thiol (air). Finally, a thermal-initiated polymerization reaction was carried out to create micropatterned hydrogel structures.

Photo chemical cross-linking of dimethylmaleimide (DMI)-functionalized polymers provides an efficient way to synthesize hydrogels in a selective and controlled manner. By the use of DMI as the chromophore, photo cross-linkable copolymers based on *N*-isopropyl acrylamide (NIPAAm) and other monomers could easily be synthesized by free-radical polymerization. Phase transition temperatures of the soluble PNIPAAm copolymers between 24.7 and 58.5 °C were obtained by changing the amount of chromophore bearing monomer (more hydrophobic) and/or a hydrophilic comonomer [21]. Photo cross-linkable co- and terpolymers were prepared by free-radical polymeriza-

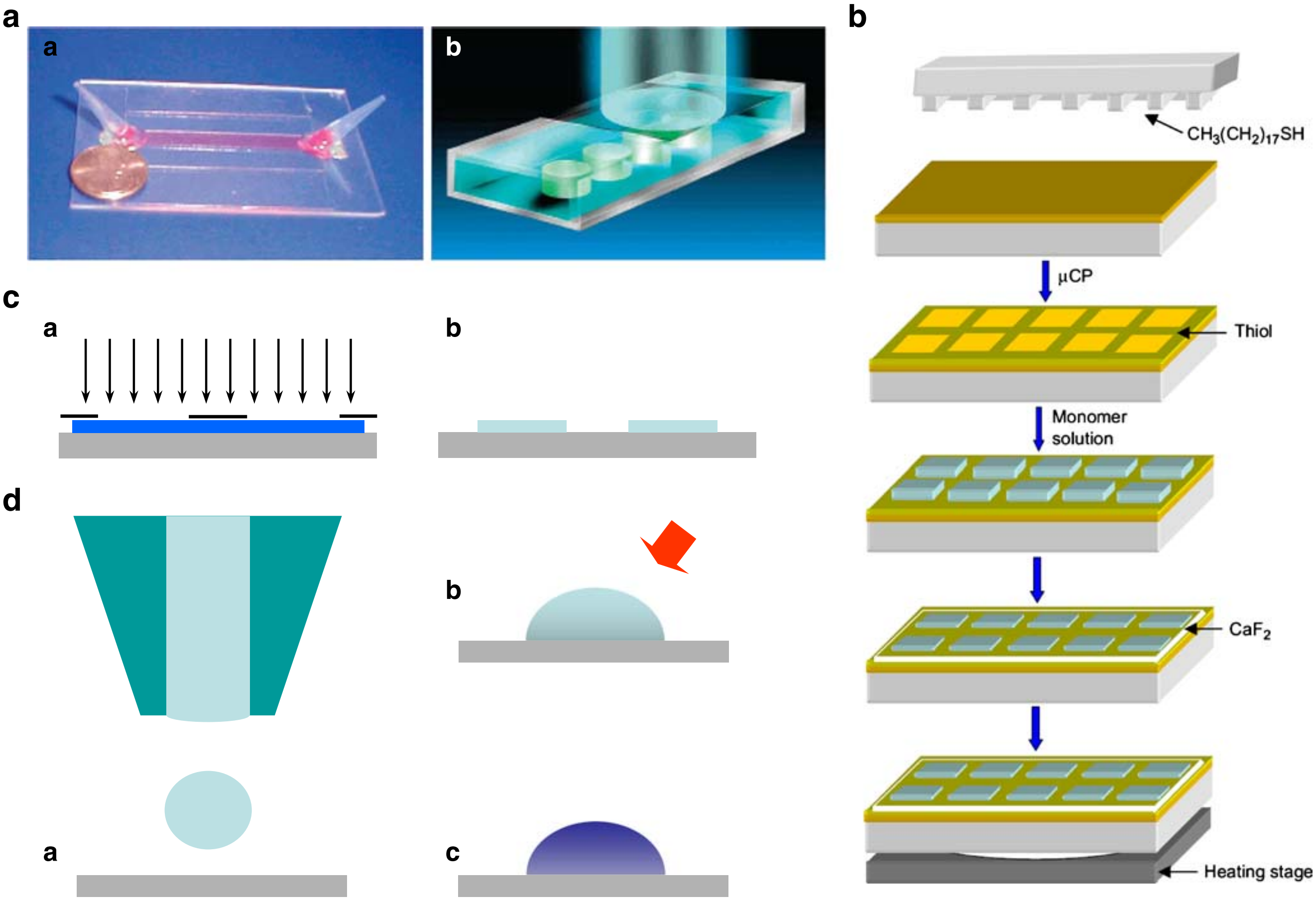

Fig. 1 **a** Preparation of hydrogels. Hydrogels were prepared by first introducing a prepolymer mixture (monomers, cross-linker, and a photo initiator) into a micro-channel (*a*). Exposure to UV light through a photo mask resulted in the desired hydrogel structures (*b*). (Reprinted with permission from [19]. Copyright 2003 American Chemical Society.) **b** A schematic diagram of pattern thiol monolayer formation and reaction setup. As a result of the micro contact printing of the hydrophobic thiols, the monomer solutions remained only on the square zones that were unmodified by stamping. These hydrophilic/hydrophobic interactions successfully created the micro pattern regions containing hydrophilic monomer solution or hydrophobic thiol (air). Then, a thermal initiated polymerization reaction was carried out to create micro patterned hydrogel structures. (Reprinted from [20], Copyright 2006, with permission from Elsevier.) **c** Principle of photo lithographic patterning of PNIPAAm photo polymers. *a* Dry layers of photo cross-linkable copolymers could be efficiently converted into gel networks by UV irradiation. *b* Pattern with lateral dimensions down to 4 µm at reasonable film thickness of this highly swellable material could be obtained [28]. **d** Approach for inkjetting hydrogel microarrays. *a* Deposition of nanoliter volume of reactants. *b* Gelation of the mixture by redox initiation or radiation curing. *c* The size of the features can be controlled by changing the number of drops printed per spot [55]

tion, and the resulting linear polymers and cross-linked gel films were shown to be both pH- and temperature-responsive. The transition temperatures of the films showed similar trends to those of the corresponding linear polymers, and this could be explained in terms of a balance between hydrophobic and hydrophilic side groups in the polymer gel and the osmotic contribution of ionizable comonomers [22]. These polymers could be efficiently converted into gel networks by UV irradiation in the presence of thioxanthone as the photo sensitizer. Cross-linking was achieved by [2+2] cyclodimerization of the DMI moiety present in the polymer chains [23, 24]. Investigation of the swelling properties of thick films showed that the critical temperature (T_c) was only slightly influenced by the cross-linking reaction. However, by decreasing the film thickness, T_c shifted towards higher temperatures, which was attributed to the confinement effect of the substrate. This effect also caused a highly anisotropic gel swelling. Lateral swelling amounted to only a few percent of the swelling perpendicular to the surface [25]. The formation of surface bound hydrogels has been visualized by cryo-transmission electron microscopy [26].

The photo lithographic patterning of PNIPAAm photo polymers is a suitable way to prepare microfabricated thermo-responsive hydrogels. Pattern with lateral dimensions down to 4 µm at reasonable film thickness of this highly swellable material could be obtained. The patterning results obtained on a hydrophobically pretreated Si-wafer were, thus, sufficient for the proposed applications. For advanced applications, the resolution properties and the adhesion of the gels were increased by the use of a specially designed adhesion promoter [27]. This provided a cross-linked insoluble networks, which could be used as a solid substrate for coating a second layer. The swelling properties of the resulting pattern could be adjusted either by the chromophore content of the photo polymer or by the irradiation time. The investigated gels showed response times faster than 2 s. This was much faster than expected taking into account the sizes of the pattern only. It has been shown that this behavior is attributed to the sponge-like nanostructure of the hydrogels having characteristic dimensions of three orders of magnitude smaller than the gel pattern. Based on these polymers, tailor-made and cheap microvalves and micro-pumps can be developed and applied as yet unrivaled in different fields of microtechnology (Fig. 1c) [28].

Due to the presence of the photo cross-linker, such multilayer films can be patterned to develop surfaces with different properties at different regions [28, 29]. Patterned thin layers were obtained by irradiating a polymer film with UV light through a common chromium mask on both Au and Si wafers. The photo patterning turned out as a negative photo lithographic process. Hydrogel was formed at the UV-exposed areas, leaving uncross-linked polymer at unexposed areas. It was observed that the cross-link density significantly affects the resolution properties of the patterned surfaces. This implies that a loosely cross-linked network obtained by irradiating the film for 1–5 min contains a low cross-link density and, therefore, results in highly swollen hydrogel. As a result of this behavior, the hydrogel films were prone to detach from the substrate producing patterns with some defects.

In order to study bilayer assembly, photo cross-linkable PNIPAAm was chosen as a stimulus-sensitive component and poly(dimethyl acrylamide) as a hydrophilic component. Film thickness of both layers could be controlled either by polymer solution concentration or spin speed in coating. Synthesized polymers have predefined properties like molecular weight and photo cross-linker content, which result in the uniform cross-linking of the thin film. In order to achieve linkage of the two hydrogel layers, it is important to choose a solvent for spin coating of the top layer that is a good solvent for the first gel as well. During film formation, a thin interpenetrating network is formed and afterwards fixed by UV irradiation. Selection of a poor solvent did not yield in entanglement and, thus, in bilayer formation. Within the multilayer hydrogel assembly, chemically different hydrogel layers retained their swelling properties in response to temperature changes. Different photo cross-linked hydrogels in a multilayer assembly have shown high resolution patterns and uniform film formation [30].

The photo cross-linking technique has been used for multiresponsive hydrogel layers based on poly(2-*N*,*N*-dimethylamino)ethyl methacrylate as well [31]. Polymer networks can be fabricated by cross-linking thin films of statistical copolymers composed of different monomers and a photo-reactive benzophenone derivative monomer [32–34]. Covalent attachment of the film to the surface is achieved by means of a benzophenone-based silane monolayer. UV illumination simultaneously cross-links and chemically links the layer to the surface, forming stable networks that do not delaminate upon swelling. It is observed that the surface-attached networks swell less than the non-attached bulk networks at the same cross-link density; however, the swelling of surface-attached networks is larger than that suggested by simple geometric considerations for swelling in one dimension. The results are in qualitative agreement with Flory–Rehner theory extended to 1D swelling predicting that the volumetric degree of swelling on the surface-attached network should be approximately the square root of the degree of swelling in the unconstrained network [32]. Cyclic voltammetry using potassium ferricyanide revealed that ions could permeate the photo-cross-linked ultrathin polymer films. The permeability of the ultrathin hydrogel films can dramatically be changed by varying the pH and temperature of the aqueous media [35]. The benzophenone technique has also been used to link other hydrogel particles to surfaces [36]. Photo reactions have been used to prepare micrometer-scale microreliefs with a high aspect ratio being formed instantly on a thin hydrogel layer composed of thermoresponsive PNIPAAm and photo-responsive spirobenzopyran, just by irradiating with blue light [37]. Another chemical cross-linking reaction forming thin hydrogel layers involved the preparation of reactive isocyanate prepolymers followed by simple heat curing [38]. Fibrous membranes and monolithic films were prepared from aqueous mixture of poly(vinyl alcohol) and poly(acrylic acid) at 3.5 COOH/OH molar composition via electrospinning and solution cast, respectively, then cross-linked by heat-induced esterification. Both forms of hydrogels exhibited increasing swelling with increasing pH. For hydrogel fibrous membranes, planar expansion was immediate without the time lag observed on the films [39].

The formation of hydrogel layers on conducting substrates via an electrochemical route can be achieved by free-radical polymerization initiated by an electron transfer from the substrate to a redox-active initiator. Such gels adhere well to the substrates [40]. Moreover, the use of plasma immobilization and electron-beam irradiation has been investigated for the preparation of stimulus-responsive hydrogel films [41–44]. A patterned thermo-responsive hydrogel was immobilized on a polymer substrate by low-pressure argon plasma treatment using a masking technique [41].

Patterned hydrogel structures have potential application in microfluidics, tissue engineering, and other soft matter technologies. Photo patterning of *thick* cross-linked poly(2-hydroxyethyl methacrylate) hydrogels can be obtained through spatial manipulation of polymerization kinetics. Specifically, patterned hydrogels were fabricated by creating an inverse photo mask in which the mask allows the initiating light to pass through all areas but at different intensities [45]. A novel high-resolution technique for fabricating hydrogel microstructures using photo resist lithography and dry etching have been introduced recently. This method alleviates the need for photo initiators used in conventional approaches and is applicable to a broad range of hydrogels. This technique is also compatible with traditional microfabrication methods, thus, allowing the integration of hydrogels with microelectronics and micro-electromechanical system microstructures. Environmentally sensitive hydrogels of different shapes and sizes were patterned in a batch scale (wafer level) with resolutions down to 2.5 µm. The patterned pH-sensitive hydrogels with micron-sized dimensions exhibit volume responses within seconds of change in pH. Deposited aluminum thin films on top of hydrogel microstructures were used to fabricate environmentally sensitive free-standing micromirrors [46]. In order to overcome limitations of photo lithography, a new patterning technique based on hydrogels has been developed, i.e., a variant of the top–down approach for the miniaturization of an existing 3D or 2D object or pattern, where the starting pattern to be replicated is much bigger than the final desired size. Thus, engineering of patterns in the size range of hundreds of nanometers becomes possible by starting with a mask or mold that contains micrometer-sized features, fabricated easily by photo lithography. The patterns were generated in stages, from large to small, by the process of pattern miniaturization using hydrogels [47]. Other patterning techniques involve the use of an elastic stamp. Microgel rings have been fabricated on a glass surface by a micro-transfer technique. The polymer melt is transferred to the substrate surface in a confined space with a picoliter volume along the boundary of the polymeric stamp. The surface of the polymer features is smoothened by surface tension in an annealing cycle, which results in isotropic rings. After cross-linking, the hydrogels respond swiftly when immersed in water. Asymmetric rings are also obtained by tilting the substrate [48]. When a flat rigid stamp contacts the surface of a soft hydrogel film, a competition between the adhesive and elastic forces engenders an isotropic, labyrinth pattern on the length scale of the film thickness. Many complex structures such as an array of femtoliter beakers and doubly periodic channels are generated from a simple stamp. The elastic nature of the patterns allows in situ tuning, manipulation, and reconfiguration of structures [49]. Fabrication of thermo-sensitive hydrogel thin films also was possible by the use of a cross-linkable organic/inorganic hybrid copolymer [50] as well as polymers end capped with hydrophobic groups forming physical cross-links [51, 52].

The adaptation of inkjet printing technology to the complex fields of tissue engineering and biomaterial development based on hydrogels presents the potential to increase progress in these emerging technologies through the implementation of this high-throughput capability via automated processes to enable precise control and repeatability [53]. For example, mammalian cell-seeded hydrogel microarrays were created using two different commercial microarrayers with four different pin types. The hydrogel was formed by photo-initiation method [54]. By inkjet printing of monomers and initiator polymer, hydrogel microarrays can be fabricated, allowing up to 1,800 individual polymer features to be printed on a single glass slide (Fig. 1d) [55].

Characterization

The volume phase transition of constrained hydrogel layers can be studied by a combination of surface plasmon resonance spectroscopy (SPR) and optical waveguide spectroscopy (OWS) [56] to determine the refractive index, film thickness, and swelling behavior of thin photo cross-linked hydrogel films [25]. The principle is based on the detection of refractive index changes in a thin dielectric layer on top of a metal surface and probed by the evanescent field of a laser beam. The reflected intensity of the beam is recorded as a function of incident angle, and it decreases dramatically as the light couples into the plasmon mode of the metal or the waveguide of the dielectric. The evanescent wave of the plasmon decays exponentially into the dielectric; therefore, it makes SPR as a surface sensitive technique. For the dielectric with known refractive index, this technique provides information about the film thickness or vice versa.

The same setup was used for the determination of film thickness in case of thick films (dry thickness>500 nm) by OWS. For thicker films, the position of the plasmon minima is sensitive only to the refractive index while the position of waveguide modes depends on both film thickness and refractive index. OWS provides more accurate results, as film thickness and refractive index could be determined independently.

SPR and OWS were used to obtain information about the volume phase transition of the corresponding photo cross-linked PNIPAAm hydrogel films showing highly anisotropic swelling behavior. The agreement between the swelling discontinuity in the surface-tethered network and the two-phase region on uncross-linked PNIPAAm suggests that confinement does not alter the miscibility gap of PNIPAAn [34]. The swelling behavior of these films was also studied as a function of dry film thickness in the range of 9 nm to 2.3 μm. The swelling behavior of the films fell into two distinct regimes separated by a critical thickness, which ranged from 280 to 500 nm for all samples with DMI chromophore content around 5%. The transition temperature was found to vary with film thickness in the thick-film regime, and the ionizable groups were found to have little effect on the swelling ratio, which is determined primarily by cross-linking density in the swollen state and by film thickness in the collapsed state [22]. A refractive index gradient, perpendicular to the swollen hydrogel film surface, could be analyzed in detail by application of the reversed Wentzel–Kramers–Brillouin (WKB) approximation to the optical data. This novel approach to analyzing thin-film gradients with the WKB method presents a powerful tool for the characterization of inhomogeneous hydrogels, which would otherwise be very difficult to capture experimentally [33].

The SPR/OWS technique has been applied to gain additional insight to the mechanism of the anisotropic swelling of responsive hydrogels. The swelling behavior is affected by the non-equilibrium chain conformations resulting from the spin-coating process as well as the stress distribution in the gel layer. This varies as a function of both the gel modulus measured by AFM force–distance curves and the gel reference state, which can be varied by the method of preparation. The swelling behavior and mechanical properties of the photo cross-linked hydrogel layers can be compared to previous reports of free-radical polymerized hydrogels by considering the effects of the different reference states. Finally, these measurements can be compared to theoretical models for hydrogel swelling, and this can be used to describe the hydrogel morphology and to explain the trends seen as a function of film thickness [27]. In order to obtain special information of hydrogel swelling, imaging techniques have been applied [41, 57]. Micropatterned, thermoresponsive hydrogel film can be characterized with imaging ellipsometry. The characterization was carried out on the dry film as well as on a swollen sample in water. Through imaging ellipsometry, it was possible to distinguish the different regions of interest on a micrometer scale and to follow the swelling of the hydrogel part as a function of the temperature.

AFM was used to characterize photo cross-linked hydrogel layers based on NIPAAm. The degree of swelling could be directly observed with AFM imaging, and the temperature-dependent elastic modulus was measured using force–distance curves. By choosing cantilevers with the appropriate spring constants, standard AFM cantilevers could be used with minimal damage to the swollen hydrogel layers. A colloid-modified cantilever was also used for modulus measurements, and the improved resolution is likely due to the inhomogeneous network structure relative to the size of the tip. The modulus increased with increasing polymer volume fraction. These results were compared to rubber elasticity theory for a swollen network, which was used to study the hydrogel morphology. The network appears to have a high concentration of dangling chain ends, which is to be expected from the photo cross-linking of linear polymers, and hydrophobic aggregation makes a significant contribution to the mechanical properties of the collapsed gel network [58].

Similar spin-cast films of cross-linked PNIPAAm have been prepared and investigated with respect to their use as transducers for sensing. The swelling transition (which can be induced by parameters other than temperature, as well) was probed by combination of an acoustic and optical technique, namely the quartz crystal microbalance (QCM) and plasmon resonance SPR spectroscopy. This combination provides a number of different parameters, which—in conjunction—allow for the use of thick layers for sensing. The SPR coupling angle is mostly sensitive to the refractive index inside the film. The frequency shift and the bandwidth, on the other hand, strongly depend on the film thickness. For certain, particularly interesting cases, there exists an intermediate situation where the film thickness equals a quarter of the wavelength of sound, inducing a film resonance. Around this condition, the sensitivity of the QCM is resonantly enhanced. The sharpness of the film resonance can be adjusted by the cross-linker content. For higher cross-link density, the film resonance is less pronounced, which decreases sensitivity but, on the other hand, increases reproducibility and reliability [59]. A quartz crystal microbalance with dissipation monitoring (QCM-D) was used to assess water and moisture uptake characteristics of plasma polymerized PNIPAAm hydrogel films [42] as well as the physical properties of interpenetrating polymer networks (IPNs). The IPNs, based on acrylamide (AAm) and poly (ethylene glycol), swell from thin, rigid films when dry to expanded, viscoelastic films when hydrated. The dry IPNs could be analyzed using the Sauerbrey relationship, but for the hydrated films, it was necessary to interpret QCM-D data with a Kelvin–Voigt viscoelastic model [60].

The macroscopic determination cross-linking efficiency of photo-cross-linked polymers is supported by multiple-quantum NMR experiments yielding information on the fraction of monomer units present in elastically effective network chains. Quantification of these gave values comparable to the ones obtained by rheology. Furthermore, the NMR experiments indicate that the average length of active network chains is just slightly dependent on cross-linking efficiency or concentration, a fact that can be traced back to the importance of the spacing of functional groups along the initial polymer chains [23].

Applications

Hydrogels are soft materials and shows a large volume change in dependence of various environmental parameters. Therefore, hydrogel-based valves have four main advantages compared to common valves. Highly miniaturized valves still showing a distinctive pressure resistance without a leakage flow can be realized. Furthermore, the valves are highly particle-tolerant. Due to the manifold sensitivities of hydrogels, a number of automatic sensor-actuator functions can be realized [17, 61]. However, such functions can only be realized successfully, if cross-sensitivities caused by the composition of the process media or environmental parameters are considered (Fig. 2).

Hydrogel-based actuators can generate manifold developments in microfluidics, biotechnology, chemical, and medical engineering (Fig. 2a) [61–63]. Microvalves can be used in microfluidic processors due to their capability of miniaturization combined with other advantages like a small dead volume, a simple setup, and an integrability

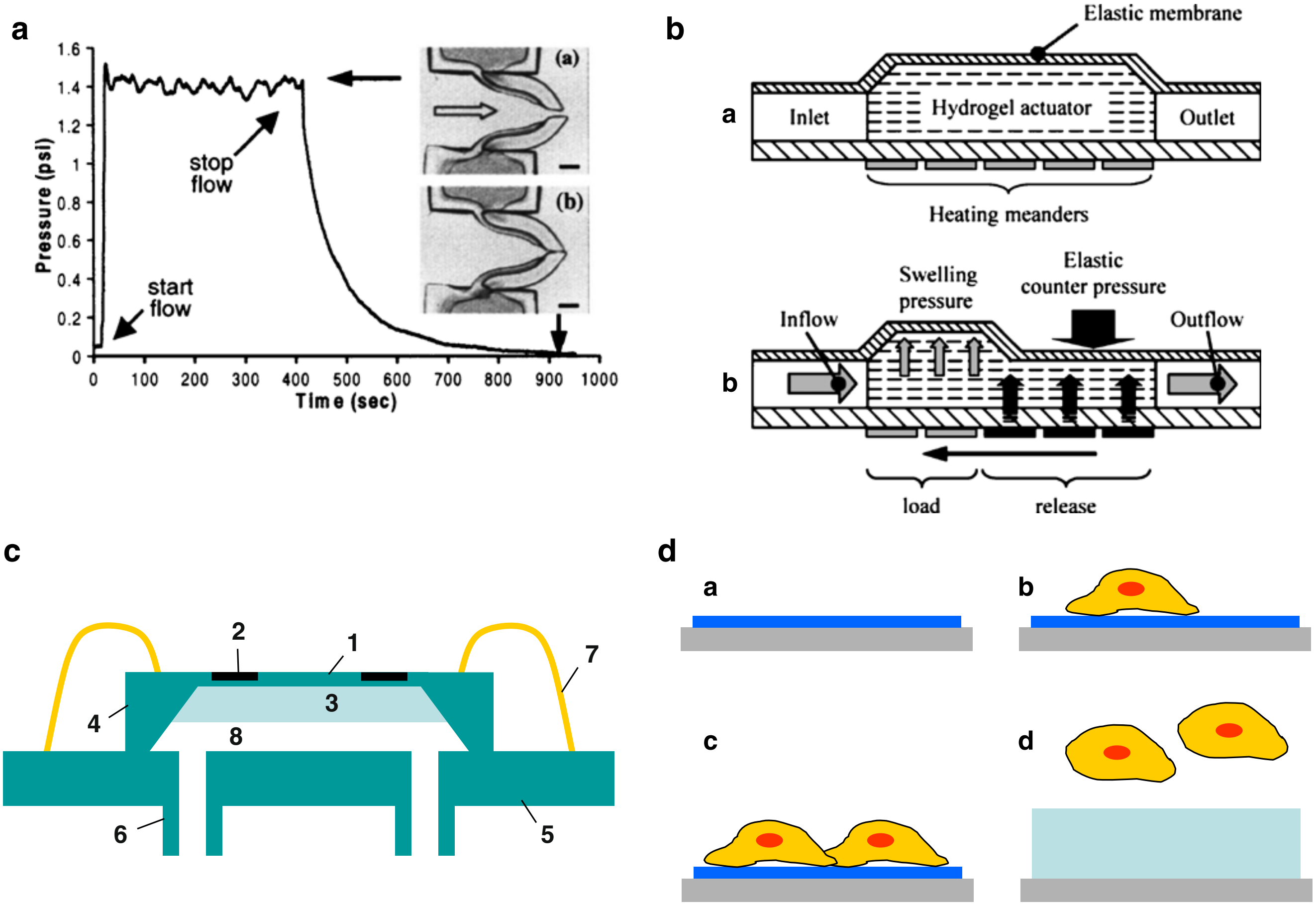

Fig. 2 **a** Pressure profile of a biomimetic hydrogel valve during forward flow. After starting fluid flow at 1.0 mL/min, the pressure increases rapidly, and the valve opens at 1.5 psi. The pressure then stabilizes at around 1.4 psi. Upon stopping the flow, the valve gradually closes as the pressure gradient across the valve decreases. Micrograph (*a*) shows the valve in its open state upon forward flow (the arrow indicates the direction of the flow). Micrograph (*b*) shows the valve in its normally closed state after the flow is stopped. *Scale bars* are 500 mm. (Reprinted with permission from [61]. Copyright 2001, American Institute of Physics.) **b** Schematic setup (*a*) and operating principle (*b*) of a diffusion micro pump. The hydrogel actuator uses its swelling pressure to tense an elastic membrane acting as a pressure accumulator. If the swollen PNIPAAm actuator is sequentially heated by the heating meanders above its phase transition temperature (starting with the outlet-side), then the actuator shrinks releasing the swelling agent. The released solution is immediately pushed to the outlet by the pressure of the elastic membrane because the inlet is sealed by a swollen actuator segment. To reload the pump, the heating meander has to be switched off incipient inlet-sided so that the PNIPAAm cools down below the phase transition temperature and swells by absorbing the liquid. ([68] Reproduction by permission of The Royal Society of Chemitry) **c** Operational principle of hydrogel-based sensors with hydrogel layer, deposited onto the bending plate: *1* bending plate; (*2*) mechanoelectrical transducer (piezoresistive bridge); (*3*) swellable hydrogel; (*4*) Si chip (5×5×0.3 mm); (*5*) socket; (*6*) tube; (*7*) interconnect; (*8*) solution. Swelling of the hydrogel causes a bending of plate (*1*) resulting in a change of its resistance. This change can be read out by the mechanoelectrical transducer [75, 76]. **d** Principle for gentle cell expansion and harvesting. A temperature responsive polymer, e.g., PNIPAAm, is fixed to the cell culturing plastic plate (*a*). The surface becomes hydrophobic over 32 °C which enables cells to attach to the surface (*b*) and grow (*c*). At room temperature, cells cultured on PNIPAAm spontaneously detach as a confluent sheet (*d*) [81]

into microsystems. The used hydrogel actuators show a good chemical and long-term resistance. The application potential of the valves is limited by two special circumstances. The switch behavior of the hydrogel actuators is a diffusion-controlled process. Thus, switch frequencies of >10 Hz are difficult to realize. Hence, hydrogel-based microvalves cannot be used in highly dynamic applications. The second limitation results from the fact that hydrogels need the direct contact with the process medium as the swelling agent. The development of hydrogel based microvalves will, hence, go into two directions [29]. In automatic microvalves, the hydrogel can act as integrated actuator-sensor. In this kind of application, a critical concentration, e.g., nutrient broth for cell cultivation can be kept constant by opening or shutoff while reacting a threshold value. Secondly, electronically controllable microvalves as toggle elements for microfluidic processors can be developed. By appropriate combination of these microvalves, different operations can be realized. Due to their properties, hydrogel-based microvalves are supposed for the handling of small liquid volumes as well as liquids containing particles.

Hydrogel actuators can transform a chemical signal (e.g., change in pH of the local environment) into a mechanical response (swelling) generating pressure, e.g., to drive an infusion. The hydrogel actuators can be separated from the drug reservoir by an elastomeric-impermeable membrane. As the hydrogel actuators expand, the expansion deflects the flexible membrane down and reduces the volume of the drug reservoir causing the infusion of drug through the needle that is the only outlet for the reservoir [64]. Another possibility to generate a drug delivery device is to use responsive hydrogels as barriers to use as a gate to control drug release [65]. The use of hydrogels itself for drug delivery has recently been summarized [66]. Using pH- and temperature-sensitive hydrogels as clutches, autonomous micromixers and micropumps have been fabricated and tested that they perform as closed-loop microsystems [67]. Polymeric micropumps based on the temperature-sensitive hydrogel PNIPAAm can be designed in two ways. The diffusion-based micropump contains a photo-patterned monolithic actuator, which is placed within the pump chamber and provides a valveless single-layer setup. The diffusion micropump is intended for low performance applications and can operate in two modes: peristaltic or pulsatile. The second type, a displacement pump, provides a higher performance. The pump comprises a microgel-based actuator, which is placed within a separate actuator layer and active microvalves (Fig. 2b) [68]. This approach can be extended to polymeric large-scale integrated MEMS based on a stimulus-responsive polymer. These devices provide a simple single-layer setup and allow simultaneous but individual control of a large number of random elements [69]. Multifunctional responsive gel membranes present a new and promising platform for the development of "smart" devices for bioseparation, biosensors, and "smart" drug release. These membranes combine functions of stimulus-responsive control and regulation of the mass transport with a range of properties such as storage, catalysis of chemical reactions, antimicrobial activity, and optical-signal transduction. Recent developments have been highlighted [70].

Based on hydrogel technology using simple wet-chemical methods, a high-density microlens array have been fabricated that can be tuned or switched by an external laser source. The fabrication technology is inexpensive, scalable, and rapid, in contrast to traditional micromolding or photo lithographic approaches [71, 72]. More complex structures have been designed for dynamic actuation systems by integrating high-aspect ratio silicon nanocolumns, either free-standing or substrate-attached, with a hydrogel layer. The nanocolumns were put in motion by the "muscle" of the hydrogel, which swells or contracts depending on the humidity level. This actuation resulted in a fast reversible reorientation of the nanocolumns from tilted to perpendicular to the surface. By further controlling the stress field in the hydrogel, the formation of a variety of elaborate reversibly actuated micropatterns was demonstrated [73]. Such structures show a reversible wetting behavior switching from hydrophilic to superhydrophobic and vice versa [74].

Temperature responsive hydrogels show a strong ability to change their swelling degree in dependence on organic solvent or salt concentration in aqueous solutions. This behavior can be used for appropriate sensors if a suitable transducer transforms the volume change into an electrical output signal. Piezoresistive sensors were used where the hydrogel led to a deflection of a silicon membrane within the sensor chip. This principle allows for a strict separation of the fluid from the piezoresistors as well as from other electronic components at the front side of the sensor chip. Photo cross-linkable PNIPAAm copolymers have been applied and investigated for organic solvent concentration sensors and salt concentration sensors. The sensor′s output voltage was measured during the swelling of the hydrogel under influence of water solutions with different organic and inorganic solute concentrations at different temperatures. The change in the gel volume phase transition temperature depends on the solution viscosity and the concentration of the additive affecting the stiffness of the polymer chain in the surrounding solution. The influence of an initial gel conditioning procedure on the signal value and the sensitivity of the proposed chemical sensors was investigated and the measurement conditions necessary for high signal reproducibility and long-term stability were determined (Fig. 2c) [75].

Based on such results, a new type of online analytics system for biomedical and environmental monitoring was developed. In order to provide the specific analyte detection, a chemical sensor with a functionalized hydrogel coating has been integrated together with a viscosity sensor in a miniaturized biocompatible rheochemical microsystem. The sensor has been calibrated and tested in aqueous solutions of alcohol and salts of different concentration. The selective sensitivity of the polyelectrolyte block-copolymer coating to toxic transition-metal ions has been demonstrated [76]. Silicon-on-insulator wafers were used to fabricate cantilevers on which a polymer consisting of poly(methacrylic acid) with poly(ehylene glycol) dimethacrylate was patterned using free-radical UV polymerization. As the pH around the cantilever was increased above the *pKa* of PMAA, the polymer network expanded and resulted in a reversible change in surface stress causing the microcantilever to bend [77]. Recently, the progress on pH hydrogel sensors has been summarized. The review introduces the physical background of the special properties of stimulus-responsive hydrogels. Following, transducers are described which are able to convert the non-electrical changes of the physical properties of stimulus-responsive hydrogels into an electrical signal. Finally, the specific sensor properties, design rules, and general conditions for sensor applications are discussed [78].

A number of researchers have recognized that 3D hydrogels may provide a viable alternative to 2D surfaces for biomedical applications involving proteins and whole cells. The ideal hydrogel material for biochip applications would (1) be easily micropatterned, (2) contain a high density of functional groups to allow incorporation of biomolecules, (3) provide a passive background, thus, preventing nonspecific protein adsorption, (4) be highly hydrated (semiwet or gel-like), thus, mimicking the natural environment of cells and proteins, and (5) be optically transparent, allowing for unimpaired optical assessment of results [79]. Thus, the described hydrogels would be excellent candidates.

In the last decade, responsive hydrogel layers have been used to develop methods for gentle cell expansion and harvesting. When the temperature-responsive polymer, e.g., PNIPAAm, is fixed to the cell-culturing plastic plate, the surface of the plate changes reversibly hydrophilic–hydrophobic in response to temperature change across the lower critical solution temperature of 32 °C. The surface becomes hydrophobic over 32 °C which enables cells to attach to the surface and grow [80]. At culture temperatures, cells behave similarly to those on tissue culture polystyrene (TCPS); while at room temperature, cells cultured on PNIPAAm spontaneously detach as a confluent sheet. In comparison, cells grown on TCPS remain attached indefinitely after the temperature drop, requiring enzymatic or mechanical removal (Fig. 2d) [81]. Since then, different approaches have been made to enhance the response behavior, e.g., by incorporating pH [82] or light [83] sensitive compounds as well as poly(ethylene glycol) graft arms [84]. Degradable hydrogels have been prepared by a combination of step growth polymerization and photo cross-linking [85]. Based on those results, a rapidly regenerable cell culture system in which the cell culture substrate detects cell death and selectively releases the dead cells has been developed. This culture material was achieved by combining a detector that responds to the signal from the dead cells and an actuator to release the dead cells [86]. Further progress in the use of hydrogels in biology and medicine has been highlighted recently [87]. Of particular interest for tissue engineering is the combination of special hydrogel properties with possibilities to tailor-made their structures. In order to control cell migration a method of fabricating photo cross-linked hydrogels with gradients of immobilized molecules and cross-linking densities is introduced. Two macromer/initiator solutions are injected into a unique poly(dimethylsiloxane) channel system that produces a prepolymer gradient that is subsequently polymerized into a water-swollen hydrogel with ultraviolet light exposure. The gradient is controlled by the injection flow rate [88]. Thermo-responsive coatings of PNIPAAm can be prepared by radio frequency plasma on addressable microheaters. The use of photo lithographically fabricated microheater array allows the PNIPAAm transition to occur spatially under the control of individual heaters. This localized change in the surface behavior is used to direct site-specific cell attachment [89]. Another approach for guiding cell behavior is to directly pattern the hydrogels [90]. Internally complex materials via controlled 3D patterning within existing photo active scaffolds rather than via conventional layer-by-layer techniques has been validated using single-photon absorption and two-photon absorption photo lithography to internally immobilize mono- and diacrylate-derivatized moieties into preformed PEGDA hydrogels [91].

Conclusion

The current work describes general strategies to apply smart hydrogels for actuator-sensor systems. In order to meet the requirements for hydrogel application, tailor-made polymers were developed. Smart hydrogels with defined degree of swelling and transition temperature were synthesized. Multisensitive gels were prepared by random and graft copolymerization with special comonomers to incorporate sensitivities towards temperature, pH value, solvent composition, ion concentration, etc. Consistent downscaling of the gel size resulted in fast smart gels with sufficient response times. The experiments have shown that it is possible to use sensitive polymer gels as material for flow control in microvalves, automatic valves, flow sorters, or pumps, which can be switched by temperature, pH, different cosolvents, salts, etc.

The limits for further miniaturization of such microdevices are set by the limits of the patterning technology for hydrogels. The resolution of the hydrogel pattern made from a photo cross-linkable sensitive polymer is in the range of 2–10 µm. This limit can be overcome by the use of colloidal nano-hydrogels, which have a gel size in the range of 100 nm.

The utilization of hydrogels is not limited to their actuatoric properties only. While undergoing a phase transition, drastic changes in the material properties occurs. Changes in the elastic modulus are applicable in sensors. Transducers can be based on different principles like QCM or piezoresistive devices. Such devices have great potential as hydrogel based sensors in liquid analysis. Another important property of smart hydrogels is their transition from a hydrophilic to a hydrophobic (and vice versa) material. Since absorption of biomolecules is sensitive to the nature of the substrate, applying a stimulus might alter the absorption. The synthesized polymers can be used for switchable and patternable supports for protein absorption and cell growth.

References

1. Arndt KF, Kuckling D, Richter A (2000) Polym Adv Technol 11:496–505
2. Hoffman AS (2002) Adv Drug Deliv Rev 43:3–12
3. Brahim S, Narinesingh D, Guiseppi-Elie A (2003) Biomacromolecules 4:1224–1231
4. Hoffman AS (2000) Clin Chem 46:1478–1486
5. Liu R, Fraylich M, Saunders BR (2009) Colloid Polym Sci 287:627–643
6. Blackburn WH, Lyon LA (2008) Colloid Polym Sci 286:563–569
7. Berndt I, Pedersen JS, Lindner P, Richtering W (2006) Langmuir 22:459–468
8. Texter J (2009) Colloid Polym Sci 287:313–321
9. Schexnailder P, Schmidt G (2009) Colloid and Polymer Science 287:1–11
10. Salloum DS, Schlenoff JB (2004) Biomacromolecules 5:1089–1096
11. Mendelsohn JD, Yang SY, Hiller JA, Hochbaum AI, Rubner MF (2003) Biomacromolecules 4:96–106
12. Jaber JA, Schlenoff JB (2006) Curr Opin Colloid Interface Sci 11:324–329
13. Serizawa T, Matsukuma D, Akashi M (2005) Langmuir 21:7739–7742
14. Comrie JE, Huck WTS (2008) Macromol Rapid Commun 29:539–546
15. Draper J, Luzinov I, Minko S, Tokarev I, Stamm M (2004) Langmuir 20:4064–4075
16. Goodman D, Kizhakkedathu JN, Brooks DE (2004) Langmuir 20:3297–3303
17. Beebe DJ, Moore JS, Bauer JM, Yu Q, Liu RH, Devadoss C, Jo BH (2000) Nature 404:588–590
18. Plunkett KN, Moore JS (2004) Langmuir 20:6535–6537
19. Plunkett KN, Kraft ML, Yu Q, Moore JS (2003) Macromolecules 36:3960–3966
20. Biswal D, Hilt JZ (2006) Polymer 47:7355–7360
21. Pareek P, Adler HJ, Kuckling D (2006) Prog Colloid Polym Sci 132:145–151
22. Harmon ME, Kuckling D, Frank CW (2003) Macromolecules 36:162–172
23. Seiffert S, Oppermann W, Saalwächter K (2007) Polymer 48:5599–5611
24. Xiuling Y, Corten C, Görner H, Wolff T, Kuckling D (2008) J Photochem Photobiol A: Chem 198:34–44
25. Kuckling D, Harmon ME, Frank CW (2002) Macromolecules 35:6377–6383
26. Crassous JJ, Witteman A, Siebenbürger M, Schrinner M, Drechsler M, Ballauff M (2008) Colloid and Polymer Science 286:805–812
27. Harmon ME, Kuckling D, Pareek P, Frank CW (2003) Langmuir 19:10947–10956
28. Kuckling D, Hoffmann J, Plötner M, Ferse D, Kretschmer K, Adler HJ, Arndt KF, Reichelt R (2003) Polymer 44:4455–5562
29. Richter A, Kuckling D, Howitz S, Gehring T, Arndt KF (2003) J Microelectromech Syst 12:748–753
30. Kuckling D, Pareek P (2008) Polymer 49:1435–1439
31. Heijl JMD, Du Prez FE (2004) Polymer 45:6771–6778
32. Toomey R, Freidank D, Rühe J (2004) Macromolecules 37:882–887
33. Beines PW, Klosterkamp I, Menges B, Jonas U, Knoll W (2007) Langmuir 23:2231–2238
34. Vidyasagar A, Majewski J, Toomey R (2008) Macromolecules 41:919–924
35. Matsukuma D, Yamamoto K, Aoyagi T (2006) Langmuir 22:5911–5915
36. Singh N, Bridges AW, Garcia AJ, Lyon LA (2007) Biomacromolecules 8:3271–3275
37. Szilagy A, Sumaru K, Sugiura S, Takagi T, Shinbo T, Zrinyi M, Kanamori T (2007) Chem Mater 19:2730–2732
38. Hirata I, Okazaki M, Iwata H (2004) Polymer 45:5569–5578
39. Jin X, Hsieh YL (2005) Polymer 46:5149–5160
40. Reuber J, Reinhardt H, Jonhannsmann D (2006) Langmuir 22:3362–3367
41. Schmaljohann D, Nitschke M, Schulze R, Eing A, Werner C, Eichhorn KJ (2005) Langmuir 21:2317–2322
42. Tamirisa PA, Hess DW (2006) Macromolecules 39:7092–7097
43. Hegewald J, Schmidt T, Gohs U, Günther M, Reichelt R, Stiller B, Arndt KF (2005) Langmuir 21:6073–6080
44. Burkert S, Schmidt T, Gohs U, Mönch I, Arndt KF (2007) J Appl Polym Sci 106:534–539
45. Bryant SJ, Hauch KD, Ratner BD (2006) Macromolecules 39:4395–4399
46. Lei M, Gu Y, Baldi A, Siegel RA, Ziaie B (2004) Langmuir 20:8947–8951
47. Lal Das A, Mukherjee R, Katiyer V, Kulkarni M, Ghatak A, Sharma A (2007) Adv Mater 19:1943–1946
48. Wang B, Hong Y, Feng J, Gong Y, Gao C (2007) Macromol Rapid Commun 28:567–571
49. Gonuguntla M, Sharma A, Subramanian SA (2006) Macromolecules 39:3365–3368
50. Cao Z, Du B, Chen T, Li H, Xu J, Fan Z (2008) Langmuir 24:5543–5551
51. Wang W, Troll K, Kaune G, Metwalli E, Ruderer M, Skrabania K, Laschewsky A, Roth SV, Papdakis CM, Müller-Buschbaum P (2008) Macromolecules 41:3209–3218
52. Kaneko T, Tanaka S, Ogura A, Akashi M (2005) Macromolecules 38:4861–4867
53. Roth EA, Xu T, Das M, Gregory C, Hickman JJ, Boland T (2004) Biomaterials 25:3707–3715

54. Baird IS, Yau AY, Mann BK (2008) Biotechniques 44:249–256
55. Zhang R, Liberski A, Khan F, Diaz-Mochon JJ, Bradley M (2008) Chem Comm 2008:1317–1319
56. Knoll W (1998) Annu Rev Phys Chem 49:569–638
57. Andersson O, Larsson A, Ekblad T, Liedberg B (2009) Biomacromolecules 10:142–148
58. Harmon ME, Kuckling D, Frank CW (2003) Langmuir 19:10660–10665
59. Wang Z, Kuckling D, Jonannsmann D (2003) Soft Matter 1:353–364
60. Irwin EF, Ho JE, Kane SR, Healy KE (2005) Langmuir 21:5529–5536
61. Yu Q, Bauer JM, Moore JS, Beebe DJ (2001) Appl Phys Lett 78:2589–2591
62. Richter A, Arndt KF, Howitz S, Kuckling D (2004) Sens Actuators B Chem 99:451–458
63. Kuckling D, Richter A (2006) Responsive polymers in microfuidic devices. In: Minko S (ed) Responsive polymer materials: design and application. Blackwell, Ames, pp 147–167
64. Eddington DT, Beebe DJ (2005) Biomed Microdev 7:223–230
65. He H, Cao X, Lee LJ (2004) J Control Release 95:391–402
66. Hoare TR, Kohane DS (2008) Polymer 49:1993–2007
67. Agarwal AK, Sridharamurthy SS, Beebe DJ (2005) J Microelectromech Syst 14:1409–1421
68. Richter A, Klatt S, Paschew G, Klenke C (2009) Lab Chip 9:613–618
69. Richter A, Paschew G (2009) Adv Mater 21:979–983
70. Tokarev I, Minko S (2009) Adv Mater 21:241–247
71. Kim J, Serpe MJ, Lyon LA (2005) Angew Chem Int Ed 44:1333–1336
72. Dorrer C, Prucker O, Rühe J (2007) Adv Mater 19:456–460
73. Sidorenko A, Krupenkin T, Ashley A, Fratzl P, Aizenberg J (2007) Science 315:487–490
74. Sidorenko A, Krupenkin T, Aizenberg J (2008) J Mater Chem 18:3841–3846
75. Günther M, Kuckling D, Corten C, Gerlach G, Sorber J, Suchaneck G, Arndt KF (2007) Sens Actuators B Chem 126:97–106
76. Günther M, Gerlach G, Corten C, Kuckling D, Sorber J, Suchaneck G, Arndt KF (2008) Sens Actuators B Chem 132:471–476
77. Bashir R, Hilt JZ, Elibol O, Gupta A, Peppas NA (2002) Appl Phys Lett 81:3091–3093
78. Richter A, Paschew G, Klatt S, Lienig J, Arndt KF, Adler HJ (2008) Sensors 8:561–581
79. Zourob M, Gough JE, Ulijn RV (2006) Adv Mater 18:655–659
80. Yamada N, Okano T, Sakai H, Karikusa F, Sawasaki Y, Sakurai Y (1990) Makromol Chem Rapid Commun 11:571–576
81. Canavan HE, Cheng X, Graham DJ, Ratner BD, Castner DG (2005) Langmuir 21:1949–1955
82. Ebara M, Yamato M, Hirose M, Aoyagi T, Kikuchi A, Sakai K, Okano T (2003) Biomacromolecules 4:344–349
83. Edahiro J, Sumaru K, Tada Y, Ohi K, Takagi T, Kameda M, Shinbo T, Kanamori T, Yoshimi Y (2005) Biomacromolecules 6:970–974
84. Schmaljohann D, Oswald J, Jorgensen B, Nitschke M, Beyerlein D, Werner C (2003) Biomacromolecules 4:1733–1739
85. Hudalla GA, Eng TS, Murphy WL (2008) Biomacromolecules 9:842–849
86. Okajima S, Sakai Y, Yamaguchi T (2005) Langmuir 21:4043–4049
87. Peppas NA, Hilt JZ, Khademhosseini A, Langer R (2006) Adv Mater 18:1345–1360
88. Burdick JA, Khademhosseini A, Langer R (2004) Langmuir 22:5153–5156
89. Cheng X, Wang Y, Hanein Y, Böhringer KF, Ratner BD (2004) J Biomed Mater Res 70A:159–168
90. Reska A, Gasteier P, Schulte P, Moeller M, Offerhäusser A, Groll J (2008) Adv Mater 20:2751–2755
91. Hahn MS, Miller JS, West JL (2006) Adv Mater 18:2679–2684