I-SECTION

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Stimulus-sensitive hydrogels and their applications in chemical (micro)analysis

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In this tutorial review the use of stimulus-sensitive hydrogels as sensors and actuators for (micro)analytical applications is discussed. The first part of the article is aimed at making the reader familiar with stimulus-sensitive hydrogels, their chemical composition and their chemo-physical behavior. The prior art in the field, that comprises a number of sensors ranging from metal ion-sensitive sensors to antigen-sensitive sensors and a few actuators, is also treated in this part. The second part of the article focusses on the use of stimulus-sensitive hydrogels for microsensors and microactuators as well as their application in micro total analysis systems. The benefits of stimulus-sensitive hydrogels, their miniaturisation and the use of 365 nm UV-photolithography as a fast economical manufacturing technique are discussed.

Introduction

Stimulus-sensitive hydrogels are water-filled polymers which undergo large volume changes in response to small changes in so-called stimuli. Stimuli include pH,[1] temperature,[1] ion concentration,[2] electrical field,[3] solvent composition[1] and light.[4]

The unique behavior of these hydrogels has been researched intensively and used for a large number of applications. Stimulus-sensitive hydrogels have been tested for: bioseparation,[5,6] drug delivery,[6,7,8,9,10] biomedical applications,[11] sensors and actuators.

The scope of this review is limited to the use of stimulus-sensitive hydrogels for sensor and actuator purposes. Furthermore the use of these hydrogels in the microanalysis field is emphasized. For information on the other subjects the reader is referred to the articles mentioned above.

Gel-based sensors include ion-sensitive sensors for dissolved ions like Ba^{2+} and Na^{+},[12] antigen sensitive sensors,[13] enzyme sensors,[12] pH sensors[14] and gas sensors.[15] Gel-based actuators have been used for: artificial muscles,[16] microvalves,[17,18] pH controllers[19] and blood microsamplers.[20]

It is the aim of this tutorial review to give a reader, who is new to this field, a basic understanding of stimulus-sensitive hydrogels and explain why these gels can be used as sensors and actuators. Special attention is given to the use of these hydrogels in the novel field of micro total analysis systems (μTAS).

The chemistry and physics behind stimulus-sensitive hydrogels

A hydrogel consists of a polymer matrix containing water. The amount of water in the polymer matrix can be very large and can reach values of 99% by weight.[21]

The polymer matrix is made up of a very large number of long molecular chains, also called backbones, which are held together by interconnections between these chains, called crosslinks. The crosslinks keep the chains in the polymer matrix together, thus circumventing the dissolution of the long molecular chains and increase the mechanical stability of the hydrogel. The physics behind the effect of the gel network composition on the mechanical properties of the network have been investigated by Flory and Rehner,[22,23] which led to the Flory-Rehner equation.

The long molecular chains in turn are composed of small molecular units called monomers and comonomers which have

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been attached to each other during the chemical synthesis of the polymer network. For a visual representation of a hydrogel matrix see Fig. 1.

The family of stimulus-sensitive hydrogels can largely be subdivided into two types of gels: pH-sensitive hydrogels and temperature-sensitive hydrogels. Other types of gels exist and some examples will be given below.

Temperature- and pH-sensitive hydrogels are very different in their physical behavior and swelling mechanism. These properties of these kinds of gels will be discussed independently in the next section.

Temperature-sensitive hydrogels

A common group of monomers, used in the synthesis of temperature-sensitive hydrogels, are the *N*-alkyl acrylamides. A well-known monomer from this group is *N*-isopropyl acrylamide (NIPAAm). This monomer has sidechains which have favorable interactions with water in the form of hydrogen bonds. This causes a hydrogel made from this monomer, called a poly-NIPAAm hydrogel, to attract water molecules and swell around room temperature.

The efficiency of the hydrogen bonding process has a negative temperature dependency and above a certain temperature, called the lower critical solution temperature (LCST), the hydrogen bonds between the monomer sidegroups and water molecules will increasingly be disrupted with increasing temperature.

The backbones of the polymer, the long chains of C–C bonds to which the sidechains are attached, are hydrophobic and wish to reduce their surface area exposed to the highly polar water molecules. They can do so by forming aggregates, as shown in Fig. 2.

Normally when the hydrogen bonds between the sidegroups and the water are present, the aggregation of the backbones is prevented because the hydrogen bond interactions with the water molecules are stronger than the backbone interactions. When the hydrogen bonds are broken, due to increasing thermal agitation, the aggregation process takes place. This results in the shrinkage of the thermosensitive hydrogel with increasing temperature.

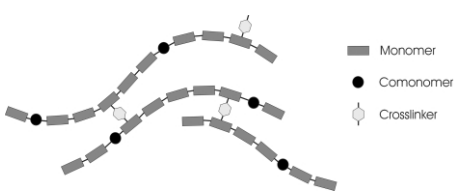

Fig. 1 The chemical structure of a hydrogel matrix. Water has been omitted for clarity.

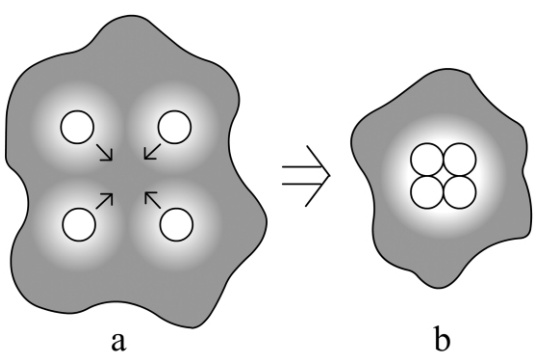

Fig. 2 (a) Backbones of the temperature-sensitive hydrogel in the swollen condition. (b) The backbones in the aggregated condition. Note the reduction of the surface area exposed to water.

The temperature behavior of a poly-NIPAAm hydrogel is shown in Fig. 3. This kind of graph is used commonly to depict the swelling behavior of stimulus-sensitive gels as a function of a stimulus and is called a swell curve.

pH-sensitive hydrogels

Hydrogels that respond to pH (and ion concentration, as explained below) contain (co)monomers with weak acidic or weak basic sidegroups. These sidegroups are ionizable and their charge will be a function of the pH.

Structure examples of pH-dependent monomers and their ionisation behavior are shown in Fig. 4. On the left the ionisation *versus* pH is shown for the weak acidic monomer acrylic acid (AAc) and on the right this is shown for the weak basic monomer dimethylamino ethylmethacrylate (DMAEMA).

The swelling of a pH-sensitive hydrogel is the result of the interplay of the pH and the ionic strength of the solution which the hydrogel is exposed to. The ionizable monomers inside the hydrogel will dissociate as a function of the pH and the resulting free counterions in the hydrogel exchange with salt ions from

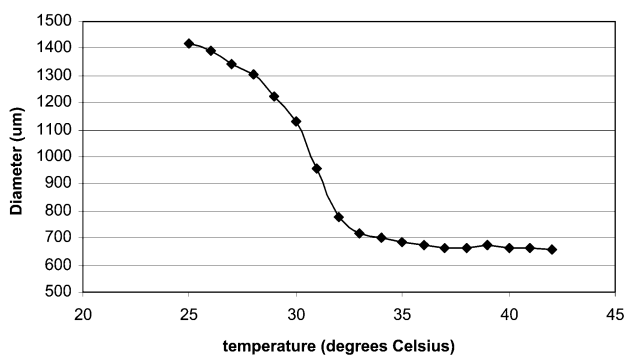

Fig. 3 Swell curve of a disc-shaped poly-NIPAAm hydrogel. Note the large diametral change with temperature.

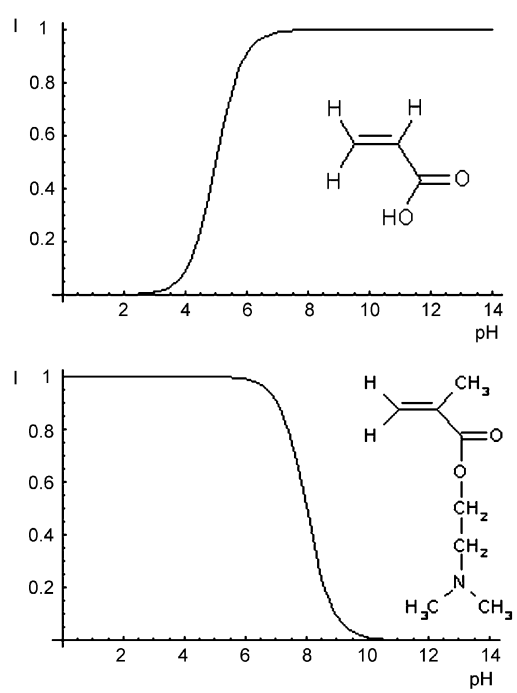

Fig. 4 Ionisation behavior of acrylic acid and dimethyl aminomethacrylate. The degree of ionisation (*I*) is plotted *versus* the pH. Acrylic acid is ionized at high pH and dimethyl aminomethacrylate at low pH.

the solution. Inside the hydrogel a certain counterion concentration will develop, that causes an osmotic pressure difference to develop between the gel and the solution. Consequently the hydrogel will swell until the elastic forces inside the hydrogel are in equilibrium with the osmotic force.

An important condition in the swelling of a pH-sensitive hydrogel is the fact that the hydrogel has to maintain global charge neutrality inside itself: a hydrogel cannot give off an ion to the surrounding solution without receiving a suitable counterion in return.

When a hydrogel with an acidic comonomer, *e.g.* polyhydroxy ethylmethacrylate-co-acrylic acid (poly-HEMA-co-AAc), is exposed to pure water (at pH 7) no osmotic swelling will take place in the gel, although the pH of the solution is higher than the pK_a of the acrylic acid comonomers (the pK_a of acrylic acid comonomers is around 5).

The hydrogel can give off protons to the solution, but to maintain electroneutrality the hydrogel also has to take up counterions from the solution. At neutral pH and low ionic strength, the only counterions available are protons resulting from the autoprotolysis of water. As a result, the pH inside the hydrogel will be low and all the acrylic acid groups in the hydrogel will be in the protonated, and uncharged, state. Consequently there will be no free counterion concentration inside the hydrogel which would cause osmotic swelling.

When the ionic strength of the solution is increased, the hydrogel can exchange ions with the solution. By doing so, the hydrogel maintains charge neutrality and the concentration of free counterions inside the hydrogel increases. An osmotic pressure difference between the hydrogel and the solution arises which causes the gel to swell.

When the ionic strength is increased to high levels (1 M–10 M), the hydrogels will shrink. This is due to the loss of the osmotic pressure difference between the gel and the solution (the solution now has osmotic pressures in the range of the osmotic pressure inside the gel, Fig. 5).

Hydrogel sensors

Roughly, all hydrogel sensors consist of two main parts: a hydrogel element and a transducer. The transducer converts the swelling signal of the hydrogel to the electrical or optical domain.

A number of different hydrogels has been used to function as the sensing element: (1) pH-sensitive hydrogels; (2) ion-sensitive hydrogels; (3) antigen-sensitive hydrogels; and (4) glucose-sensitive hydrogels. These gels will be discussed in more detail below.

pH-sensitive hydrogels

pH-sensitive hydrogels with one kind of monobasic or monoacidic sidegroups will respond to the pH in a restricted operating window around the pK_a of the sidegroups. With these gels a pH sensor for a specific pH range can be created.[14,24–27] To enlarge the operating window, a hydrogel containing two or more different ionisable monomers, with different pK_a values, or a monomer with two pK_a values could be used.

The applicability of a pH-sensitive hydrogel for sensors can be extended greatly by adding an intermediate step where an analyte is converted to pH, as for example in the hydrogel-based Pco_2 sensor that is being developed in our group.[15,28] Here, CO_2 gas forms carbonic acid in water, resulting in a change in the pH and thus indirectly in the volume of the pH-sensitive hydrogel.

Ion-sensitive hydrogels

To make a hydrogel sensitive to a specific dissolved ion it is necessary to attach groups to the hydrogel which selectively bind to the ion. One such approach is to incorporate crown ethers into the gel. The crown ethers selectively form charged complexes with the ion. This brings free charges into the gel network which consequently cause hydration and thus gel swelling. Sensors of this kind have been reported for the detection of Na^+,[29] Pb^{2+},[2,12] Ba^{2+}[12] and K^+.[12,29]

Antigen-sensitive hydrogels

Antigen-sensitive hydrogels change volume in response to a specific antigen. Miyata *et al.* have reported an antigen sensor, that uses a neutral hydrogel with an antigen and its corresponding antibody immobilized in the gel.[13] Binding between the antigen and the antibody introduces reversible crosslinks in the gel network. A change in volume is evoked by exposing the hydrogel to a solution containing the free antigen. Competitive binding of the free antigen with the antibody results in a decrease in the amount of reversible crosslinks. The resulting

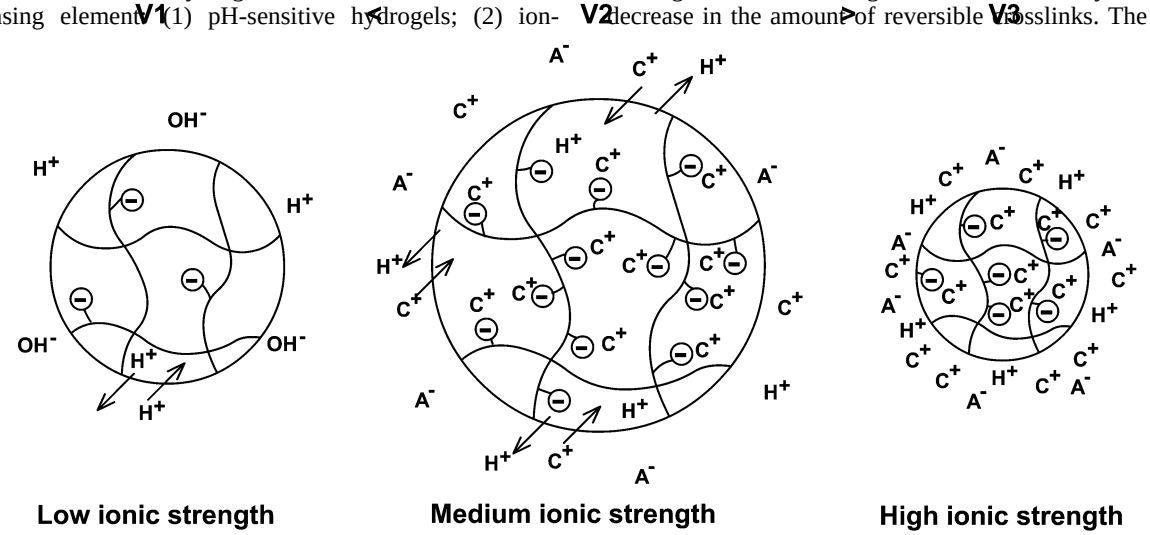

Fig. 5 The swelling of a pH-sensitive hydrogel as a function of the ionic strength. (A^-, C^+ mean anion and cation respectively).

gel network allows more expansion which results in the swelling of the gel.

Glucose-sensitive hydrogels

Phenylboronic acid has been used to make glucose-sensitive hydrogels. The phenylboronic acid forms a complex with glucose and releases a proton during this process. Arnold *et al.*[39] have immobilised phenyl boronic acid inside a hydrogel and used conductimetry to measure the conductance increase due to the release of protons after glucose reacted with the phenylboronic acid groups inside the hydrogel.

Transduction methods

Different types of transduction methods have been explored to measure the volume change of a hydrogel. These include optical, conductometric, amperometric and mechanical methods.

Optical methods

The optical methods have been widely explored with different techniques. The change of fluorescence intensity in relation to the swelling of a fluorophore-labelled hydrogel has been shown.[30] Also an interferometric method has been presented for measuring hydrogel swelling.[31,32] Here, the sensor material is part of an optical thin-film system which transforms the variation in volume into spectral information.

Another optical method makes use of the diffraction of light from a hydrogel containing a crystalline colloidal array (CCA). The group of Asher polymerised a CCA of spherical polystyrene colloid particles in a thin hydrogel film.[2,12] The particles in the CCA are regularly spaced and cause the gel to display Bragg diffraction. Because of this the CCA gels are brightly colored. When the hydrogel changes volume, the spacing of the particles in the CCA is changed, causing a change in the diffraction process and the color of the gel.

Hydrogel swelling has also been detected by refractometry; the refractive index of a gel changes during swelling.[33–36] Lowe *et al.* used a reflection hologram to characterize polymer swelling.[29] Holographic diffraction gratings which act as a reflector of light were realised in a hydrogel. The reflection spectrum of the hologram changes with changing hydrogel volume. Another technique is based on the reflectance of hydrogels; the intensity of light reflected from a hydrogel depends on the volume of the polymer.[37,38]

Conductimetric and amperometric methods

A conductometric method for detection was developed by Sheppard *et al.*[14,25] and further explored by Arnold *et al.*[39] A thin hydrogel layer was deposited on a planar interdigitated conductivity electrode array. The hydrogel changes volume in response to pH leading to a corresponding increase or decrease in ion mobility inside the hydrogel layer and a change in conductivity.

Another method of detection is amperometric.[40] A glucose sensor has been constructed where the swelling of the gel leads to increased diffusion of ion species and thus to measurable current increases.

Mechanical methods

Mechanical detection of polymer swelling can be done in different ways. Strong *et al.* used a capacitive transducer.[24] By swelling, a hydrogel deflects one of the two capacitor plates resulting in a change in capacity. Another method is attaching a hydrogel to a magnetoelastic element.[26,27] The magnetoelastic element mechanically vibrates at a resonant frequency which depends upon the hydrogel mass. The resonant frequency changes when the mass of the hydrogel changes. Another mechanical detection method is used by Seitz *et al.*[41] They have used a strain gauge to measure the swelling of a very small spherical hydrogel bead.

As already mentioned, a Pco_2 sensor is being developed in our group. We use a pressure sensor to observe hydrogel swelling. pH-sensitive hydrogel microspheres are placed in the cavity of the pressure sensor and the cavity is enclosed by a porous metal screen, shown schematically in Fig. 6. On top of the metal screen is a chamber filled with sodium bicarbonate solution and sealed with a CO_2 permeable membrane.

CO_2 will diffuse through the CO_2 permeable membrane and change the pH. The pH change is doubled by the presence of the bicarbonate (Severinghaus principle).[42] Because the sensor cavity volume is fixed, a pressure will be generated when the hydrogel microspheres swell in response to the pH change. Fig. 7 shows the pressure and pH response to a change in Pco_2. As can be seen, the pressure decreases because the hydrogel shrinks as a result of the increase in the Pco_2. Simultaneously, the pH was measured to observe the reaction of CO_2 with bicarbonate.

Although stimulus-sensitive hydrogel-based sensors seem to be promising for the future, they suffer a common problem. Stimulus-sensitive hydrogels such as for instance pH-sensitive hydrogels have a low selectivity, resulting in cross-sensitivity. These gels do not only respond to pH but also to ion concentration (as explained above). In the literature different tactics are used to eliminate the cross-sensitivity. Qing and Grimes [26] used a reference hydrogel. They constructed a salt-independent pH sensor which makes use of two types of hydrogel. One is a pH and ion concentration sensitive polymer and the other a hydrogel responsive only to the ion concentration. Differential measuring between the two hydrogels eliminates the effect of salt on pH measurements.

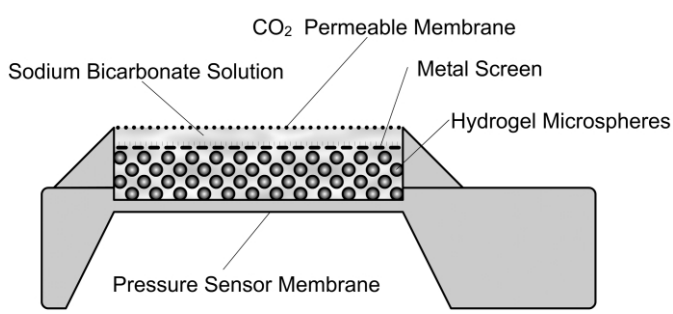

Fig. 6 Schematic representation of the hydrogel-based pCO_2 sensor.

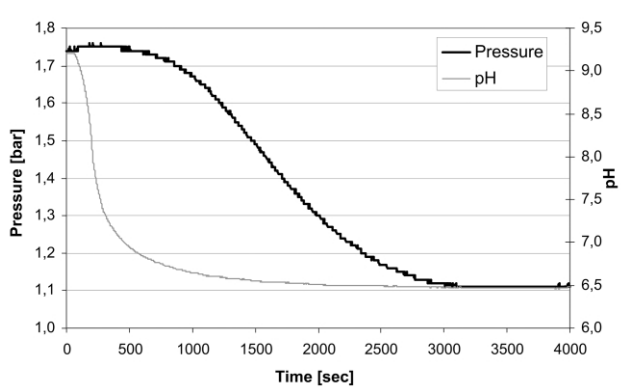

Fig. 7 Plot of pH and pressure change of the hydrogel-based CO_2 sensor as a result of a pCO_2 change.

Arnold *et al.* used a different technique for their glucose sensor.[39] Their hydrogel is encapsulated within a bipolar ion exchange membrane impermeable for ions, but freely permeable for glucose. This way the hydrogel response to glucose can be measured without the interference of ions. Other methods, discussed above, are based on making the hydrogel selective for the analyte by incorporating antibodies or crown ethers into the polymer.

An overview of the discussed stimulus-sensitive hydrogel sensors is given in Fig. 8.

Stimulus-sensitive hydrogel actuators

Stimulus-sensitive hydrogels have been tested for a number of actuator applications. In most cases a chemical signal in the form of a pH change was directly converted to mechanical work.

The main reasons for the development of hydrogel actuators are: (1) their considerable power density which is close to that of a human muscle; (2) the large displacements that are obtained with these actuators; and (3) the high resilience of the actuators because of the high water content of the polymer matrices which makes them suitable to handle fragile substrates.

Examples of actuator research include: artificial muscles,[43] a gel looper[44] (a worm-like device that moves by repeatedly curling and straightening itself), and a gel eel which could propell itself under the influence of an electrical field.[45] Recently a number of actuators based on miniaturised stimulus-sensitive hydrogels has been shown.[17,19]

Important parameters of any actuator are the type of input needed to control the actuator, for instance electrical or magnetical input, and the operation speed of the actuator. These parameters will set the limits for the applicability of the actuator. We will discuss these two parameters here for stimulus-sensitive hydrogel actuators.

Hydrogel actuator control

The control parameters for a hydrogel actuator depend on the type of hydrogel used in the actuator *i.e.* temperature-sensitive or pH-sensitive type.

When a temperature-sensitive hydrogel is used, the actuator can be controlled by changing the temperature of the actuator. The temperature change can be generated by heaters, hot fluids, IR light and endo- or exothermic chemical reactions.

When the hydrogel is composed of a pH-sensitive hydrogel different control strategies are needed. These include the use of solutions with different pH values, electrolysis of water which generates pH changes at the electrodes, the use of a compound that releases protons under irradiation with light, such as pyridine[4] and the use of electrical fields.[3] The diversity of the control parameters opens up a lot of possibilities to make hydrogel actuator systems.

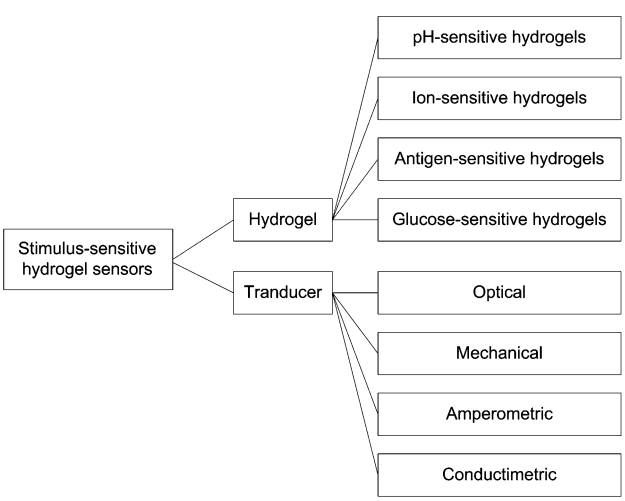

Fig. 8 Overview of the types of hydrogels and tranducers used in stimulus-sensitive hydrogel sensors.

Operation speed of hydrogel actuators

Because the volume changes in a hydrogel actuator are caused by a diffusion process, hydrogel actuators are intrinsically slow. The gel swelling kinetics have been studied by Tanaka and Fillmore[46] which resulted in the discovery of a simple relation between the swelling kinetics and the dimensions of a hydrogel. For instance the kinetics of a hydrogel sphere are a function of the diameter of the sphere and the apparent diffusion coefficient of the polymer network into the water phase, as expressed in the following equation:

$$\text{Time} = \frac{r^2}{D_{\text{gel}}} \quad (1)$$

The radius of the hydrogel sphere is given by r and the apparent diffusion coefficient of the hydrogel network into the water phase is given by D_{gel}.

Calculations using this equation reveal that the swelling of large hydrogels is prohibitively slow and the best way to increase the operation speed of hydrogel actuators is to make their dimensions very small. To give an idea of the influence of the dimensions on the swelling time of a hydrogel actuator see Table 1.

As can be seen from this table the hydrogels need to have dimensions in the micrometer range or a higher value of the apparent diffusion coefficient to have reasonable operation frequencies. This can be done by making the polymers themselves smaller or by changing the polymer morphology to make the gels more porous. Both these methods are done by changing the chemistry used to synthesize the polymers.

By using a special synthesis technique called emulsion inversion polymerisation it is possible to synthesize micrometer scale polymer spheres called hydrogel microspheres.[47] During the synthesis the formed polymer precipitates from the solvent and induces the formation of the microspheres. These spheres have a very rapid response to pH changes which lies in the millisecond range.

Another method, called photopatterning, uses UV light and a photoinitiator to locally control the polymerisation reaction. When UV light strikes a photoinitiator molecule in the solution from which the hydrogel is to be synthesized it forms a free radical that initiates the polymerisation reaction. By using masking techniques commonly found in photolithographic techniques to control the topography of the UV light, it is possible to control the formation of the hydrogel network on the micrometer scale and make hydrogels with small time constants.

Finally by using a method similar to the synthesis of the microspheres it is possible to make hydrogels that contain large pores in the polymer matrix. During the synthesis reaction the formed polymer also precipitates but instead of forming microspheres it forms larger aggregates resulting in a very porous hydrogel. Because of the porous nature of the network the diffusion time of the network is greatly reduced and fast actuators are possible.

Table 1 The effect of the radius of a spherical actuator on the swell time of the hydrogel. (For D a value of 3.2×10^{-7} cm^2 s^{-1} has been used[8])

Gel radius	10 cm	1 cm	100 μm	10 μm	1 μm
Time constant	10 years	36 days	9 h	5 min	3 s

As described in the above paragraph it is necessary to make hydrogel actuators as small as possible. This together with the advantages of hydrogels such as the high power density and high resilience have led to a large interest from the micro total analysis field (μTAS field) as will be discussed below.

Micro total analysis systems

The μTAS field is focussed on the development of very small total analysis systems for performing for instance blood analyses. The keywords in the μTAS field are miniaturisation and mass-fabrication. By miniaturising standard analysis equipment a number of advantages is achieved. For instance the volume needed for a blood analysis is greatly reduced from the mL range to the nL range. With nanoliter volumes needed for blood analyses it is possible to perform a large number of point-of-care measurements without endangering the patient. Another advantage is the drastic increase in speed when operations are performed on a small scale.

The μTAS field relies heavily on the miniaturisation techniques that have been developed in the microelectronics industry. By using the same techniques and the substrates as in the micro electronics industry, like silicon, it has been possible to fabricate miniature sensors and actuators with very fast response times and very small volumes. As in the micro electronics industry the application of mass-production techniques is expected to greatly lower the unit cost of micro total analysis devices which could lead to very wide-spread application of these devices.

Because it is not the aim of this paper to review the μTAS field and the benefits of miniaturisation interested readers are referred to van den Berg[48] and Feynman.[49]

Hydrogels and their applications in μTAS

Hydrogels have become a focus of attention in the μTAS field because of a number of reasons: they are powerful actuators but at the same time they are soft because of their high water content. This makes them suitable for μTAS systems where living substrates like cells or embryos are handled.

The use of (365 nm) UV-photolithography is ubiquitous in the cleanroom laboratories where ICs and μTAS systems are made. The photopatterning technique described above can be used in conjunction with the UV-photolithography equipment to make a large number, *i.e.* 100–1000, of stimulus sensitive hydrogels, with micrometer dimensional precision, at the same time. This process is fast, with exposure times from 10 to 100 s, and very suited for the mass-production of stimulus hydrogel sensors and actuators or μTAS systems containing these.

Finally the simplicity of the systems needed to control the hydrogel actuators make them superior over a large number of other actuators used in μTAS systems.

Hydrogel microsensors

In spite of the advantages not many hydrogel microsensors have been developed up to now, though miniaturization is crucial to make sensors based on polymer swelling with fast response times. Some of the sensors discussed in the stimulus-sensitive hydrogel sensors section are actually microsensors. An example is the salt-independent pH sensor by Qing and Grimes[26,27] They coated a 8 μm thick hydrogel layer on small magnetoelastic elements. Sheppard *et al.* made a microfabricated conductimetric pH sensor.[14,25] Their hydrogel layer was photolithographically patterned on the electrodes and also had a thickness of 8 μm. They varied the pH with steps of 0.2 pH units and found a response time of 350 s.

Hydrogel microactuators

Although this field is very young, already a number of research groups across the world have shown examples of stimulus-sensitive hydrogel actuators.

Kobayashi and Suzuki have shown a blood sampling system called the μmosquito, that uses a temperature sensitive hydrogel to obtain a blood sample from a patient.[20]

Beebe *et al.*[17] showed the use of pH-sensitive hydrogel as valves for the control of liquid flow through microchannels. By changing the pH of the solution that was run through the microchannels the hydrogel valves were closed or opened. The hydrogel microvalves were fabricated with UV-photolithography and showed promising results for μTAS applications.

An important aspect of these valves is their high resilience due to their high water content. Dust contamination is a major source of malfunction in μTAS systems. Because dust is of the order of micrometers it can interfere with the function of the conventional hard mechanical microfluidic actuators in a μTAS system. Because the dust particles get caught in the moving parts of the actuators, which are almost always made out of rigid materials like silicon or glass, they cause such a high friction that the actuator function is compromised. Because hydrogels actuators are soft, dust particles will not get caught as the hydrogel actuator will shape itself around the dust particle. This resilience also makes it possible to use hydrogels to handle soft substrates like cells and embryos which would normally get damaged by the contact with actuators made out of hard materials.

Another example of hydrogel actuator work is the pH regulator for microflow applications shown by Eddington *et al.*[19] By using a pH-sensitive hydrogel throttle valve in a pH-regulated feedback system it was possible to adjust the pH of a solution coming into the regulator by mixing with a buffer of known pH. The pH of the solution coming out of the regulator was kept constant over a range of pH values for the input stream.

Madou *et al.* have fabricated very small pH responsive valves for drug dosing applications. These pH sphincter valves were used to regulate the amount of drug flowing out of a drug reservoir. A valve of this kind could be used to fabricate smart drug-dosing systems.

Of course hydrogel actuators are not restricted for uses as microvalves and more advanced microfluidic components can be made.

In our group a discrete peristaltic micropump is being developed that uses an array of pH-sensitive hydrogel actuators to direct the flow of water through an elastic microfiber. Instead of using the pH of a solution to control the actuators, local electrolysis of the water present in the device is used to create the necessary pH changes for actuator control. This approach is very interesting because only a low voltage of 2 V is needed to control the actuators. Compared to the piezo disc actuators commonly used in μTAS applications, which use 100–300 V, this is a major advantage. Also the 1–100 μA current needed to control the actuators is very small compared to the 1–100 mA currents needed to control electromagnetic actuators which are also used up to now in μTAS applications.

The German company Gesim Gmbh. has shown a microvalve that uses a temperature-sensitive hydrogel, controlled by a microheater.[18] The temperatures needed to control the valves are around physiological temperature which makes the valves interesting for biomedical and cell-handling applications. The voltage needed to control the microvalves was in the order of a few volts which again shows the advantage of hydrogel actuators.

Another method to control hydrogel micro actuators is the use of an electrical field over a pH-sensitive hydrogel in a 50:50 water–acetone mixture. The electrical field causes a stress to develop across the gel and leads to shrinking of the gel.[3]

Conclusions

Stimulus-sensitive hydrogels are very interesting materials for the fabrication of sensors and actuators. Because the kinetics of the swelling process is dictated by diffusion, miniaturisation is indispensable to make sensors and actuators with good characteristics.

It has been shown that through the chemical modification of hydrogels a large number of different sensors can be made. These include sensors for dissolved ions, gasses, enzyme substrates and antigens. To convert the swelling signal to an electrical signal a number of possibilities exist like conductimetry, light transmission measurement and the use of pressure sensors to measure the force generated by the gel swelling.

Stimulus-sensitive hydrogel actuators have a number of advantages over existing μTAS actuators. Their high resilience gives them superior dust tolerance over actuators made from hard materials and it makes them suitable for cell-handling applications. The fact that hydrogel actuators can be controlled with small voltages and currents gives them an extra benefit over conventional μTAS actuators. In contrast with these conventional actuators no elaborate interfacing electronics is needed to control hydrogel actuators and direct interfacing with microcontrollers is possible. By integrating the microelectronic circuits needed for the operation of the μTAS system on the same chip surface, a further degree of miniaturisation is achieved. This could lead to the development of extremely small total analysis systems that can operate for very long time periods and need only a small energy source.

Finally the fabrication of gel sensors and actuators with UV photolithography makes them compatible with the conventional fabrication techniques used in μTAS system fabrication and opens up the opportunity of mass production.

Future perspective

The use of stimulus-sensitive hydrogels for microsensor and microactuator applications looks very promising. In only a couple of years a number of interesting results have been obtained.

Additional research has to be conducted to overcome the kinetic limitations imposed by diffusion and to obtain more knowledge about the mechanical behavior of stimulus-sensitive hydrogels in micro total analysis systems.

The fabrication using UV-photolithography and the possibility of direct interfacing with control electronics makes stimulus-sensitive hydrogels interesting candidates for the fabrication of microsensors and actuators in commercially mass produced μTAS systems.

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