Feedback Control Systems Using Environmentally and Enzymatically Sensitive Hydrogels

Irma Y. Sanchez and Nicholas A. Peppas

Abstract A large number of hydrogels can be classified as smart materials that offer a natural integration of sensing, actuating, and regulating functions applicable to feedback control systems. This multifunctionality added to biocompatibility and enzyme-based selectivity characteristics enables self-regulation or implicit control in hydrogels-based devices to maintain physiological variables at a desired level or range by appropriate drug release. Therefore, hydrogels can enhance the performance of individual actuator and sensing units. Applications of hydrogels in explicit and implicit controller systems are presented based on recent experimental and theoretical research studies. Integration of cascade and feedforward control types of functionalities in hydrogels systems is suggested from their capability to respond to more than one stimulus. Enzymatic glucose sensing and insulin delivery are often used as references for the discussion of hydrogels in the development of sensor, actuator, and control technology due to the relevance of the diabetes disease.

Hydrogels as Basic Functional Elements of a Control System

Hydrogels material properties enable the necessary functions for an automatic system: sensing a key environmental variable whose value must be maintained at a desired level or range, providing a means for a corrective action to eliminate a deviation in such variable, and correlating appropriately the sensed environmental condition with the active interference in the environment. These functions may be implemented individually in separate devices or integrated in a single device. Hydrogels can be applied in both cases. Their responsive nature makes them suitable to design effective sensors and actuators as well as to perform as self-regulated systems.

When the hydrogels volume change is stimulated by a signal external to the process or the close environment, the hydrogels system constitutes an actuator. The volume change of the hydrogels may cause an event by itself or by activating and allowing the intervention of additional elements frequently of different material and structure. The aforementioned event will lead to a change in an environmental condition that may be detected by another device or component of the external source that manipulates or triggers the hydrogels swelling behavior. In this case, the hydrogels system is an actuator that can be part of a regulation system.

I.Y. Sanchez • Department of Mechatronics and Automation, Tecnologico de Monterrey, Monterrey, NL 64849, Mexico
e-mail: isanchez@itesm.mx
N.A. Peppas • Pratt Chair of Engineering, Department of Biomedical Engineering, The University of Texas Austin, TX, 78712, USA

R.M. Ottenbrite et al. (eds.), *Biomedical Applications of Hydrogels Handbook*,
DOI 10.1007/978-1-4419-5919-5_3, © Springer Science+Business Media, LLC 2010

Hydrogels may be used as components of sensor devices. A sensor is composed of a sensing element and a transducing element or transducer. The sensing element is exposed to the process and changes with a particular variable. The transducer converts the response of the sensing element into an output signal, which can be used in a monitoring system to report the measurement or in a control system as a feedback signal. Electrochemical action is a typical transduction principle for analytical measurements. Electrodes covered with an enzyme containing hydrogels layer are manufactured for substrate concentration measurements. In such sensors, nonswelling hydrogels are used. Hydrogels with swelling behavior have been widely characterized showing an effective primary sensing function. However, transducing systems for their swelling response have not been investigated to the same extent.

Feedback is essential for an automatic system, since it allows a reactive response to a change in the environment or process to be controlled regardless of the cause of such variation. Environmentally responsive hydrogels may function as feedback systems for the delivery of therapeutic or other beneficial agents either contained in the hydrogels material or in a reservoir with a hydrogels cap. The interaction of hydrogels with the environment is based on a reciprocal effect: (a) a particular condition of the environment can produce a volume change of the hydrogels; (b) its inter- and intramolecular spaces change in size, thus modulating the resistance for the outward diffusion of the contained drug; and (c) the released drug changes the environmental condition in question, which is detected again by the same hydrogels, closing a loop. The *controller* element of the system is implicit in this interaction. Since all the basic control functions are assumed by the hydrogels, the resulting systems are called self-regulated (Fig. 1).

Specific body analytes reflect different physiological conditions which need to be controlled for the effective treatment of a disease. Hydrogels can be pH and the ionic strength. Concentrations of acids and bases are reflected by the pH, while those of salts by the ionic strength of the medium. Hydrogels responsiveness to other species can be achieved by the incorporation of enzymes that allow their transformation into any of the previously mentioned compounds. A typical example is the oxidation of glucose upon interaction with glucose oxidase that produces gluconolactone and hydrogen peroxide; the first product hydrolyses immediately giving gluconic acid. Hydrogels can also exhibit temperature sensitivity. Moreover, hydrogels are viable for the preservation of biological components and for in vivo implantations. Therefore, they can act as feedback systems for a wide variety of medical purposes.

It should be noted that all the basic functional elements for process control could be implemented by either on/off or continuous devices. Both categories include hydrogels-based sensors and actuators as well as self-regulated hydrogels systems. When the hydrogels response shows a sharp transition with respect to time and stimulation or input-environmental variable, an on/off behavior can be obtained. A balance between the width of the transition range and the time response is necessary for continuous operation of the hydrogels systems.

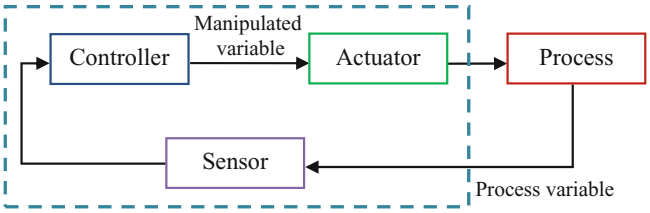

Fig. 1. Configuration of a feedback control system. Elements of control systems (*continuous rectangles*) and integration of sensor, controller and actuator in a self-regulated or implicit controller system (*dashed rectangle*).

Hydrogels in Sensors

The sensor implements the essential feedback for automatic regulation. Feedback control systems have been applied to different medical systems. Some of them are based on the sensing of physical variables (like in the case of an automatic defibrillator that responds to an abnormal heart beat with an electrical discharge to the heart) while others on the sensing of chemical variables (like the adjustment of the frequency of a pace maker according to the oxygen consumption rate) [1]. Further applications of feedback systems depend on their ability to sense different chemical and biochemical variables continuously in the body. Miniaturization and proper communication are necessary for their integration with the controller and actuator components for implantable and high compliance applications. Hydrogels are suitable materials for implicit control of diverse variables since enzymes, antibodies or mimics can be incorporated to provide selectivity for different species. However, the application of hydrogels for monitoring purposes and implementing feedback signals to external controllers requires a transduction system. Transduction methods for hydrogels-based sensors, besides methods to improve their sensitivity and stability, are the subject of current investigations. Frequently, enzymatic glucose sensing is a context for proof-of-concept and development of sensor technology due to the relevance of the diabetes disease.

Optical Transduction

Fluorescence and refraction are common transduction principles adapted to hydrogels systems [2]. Hydrogels color variations resulting from their volume changes allow the use of optical transduction principles for sensor applications such as contact lenses or intraocular lenses for glucose sensing from tears. Polystyrene nanospheres with attached glucose oxidase are imbedded in a hydrogels membrane by carrying out the polymerization process from a reaction solution containing the nanoparticles. The glucose-dependant swelling of the hydrogels causes the wavelength of the diffracted light to shift as the distance between the nanoparticles change, producing an observable color variation (Fig. 2a) [3]. Similarly, glucose binding to boronic acid derivatives in a polyacrylamide gels [4] and binding of avidin or antibiotin to a biotinylated poly(*N*-isopropyl acrylamide-co-acrylic acid) hydrogels [5] produce crosslinking and volume reduction leading to a change in the refractive index and the observed color. Fluorescence detection of calcium levels in T-cells has been used to monitor the activity triggered by an antigen in a poly(ethylene glycol) hydrogels platform for clinical diagnostics or biodefense [6].

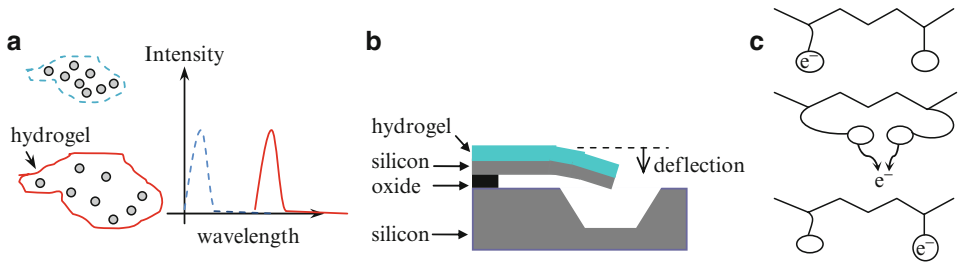

Fig. 2. Transduction mechanisms for hydrogels-based sensors. (**a**) wavelength shift of diffracted light from hydrogels with polystyrene particles (**b**) microcantilever deflection and (**c**) enzyme wiring through tethers of redox centers for electron, e^-, transfer. Adapted from [2], [7], and [1], respectively.

Mechanical Transduction

Cantilevers have been proposed as transduction systems for hydrogels volume transitions. A hydrogels deposited on the surface of a cantilever may cause a displacement of the free end of this structure or a decrement in the natural frequency of vibration upon swelling (Fig. 2b). A pH microsensor has been developed, achieving high sensitivity and repeatability [7]. A poly(methacrylic acid-g-ethylene glycol) was covalently attached to a silicon surface. Synthesis and patterning of the hydrogels was carried out by UV lithography, a common procedure in planar technologies in the integrated circuit industry. The deflection of the hydrogels covered microcantilever showed a pH sensitivity two orders of magnitude greater than those of pH microsensors based on electrochemical principles (ion selective field-effect transistors (ISFET), metal oxide electrodes). The incorporation of an enzyme in the hydrogels can enhance the sensitivity of cantilever sensors for the quantification of a substrate or analyte in comparison with other enzyme immobilization techniques. The mass increment due to the enzyme–substrate coupling is accompanied by the absorption of water onto the hydrogels patterned surface. In the case of glucose oxidase, the conversion of glucose into gluconic acid causes a pH drop and the cationic hydrogels to swell, and produces a deflection which can be correlated with the environmental glucose concentration. The combination of hydrogels and silicon microstructures can also be used for the development of ultrasensitive immunosensors.

Electric Transduction

Electron transport from a selective electrochemical reaction suggests the use of electrode transducers. The glucose oxidase enzyme, GOx, catalyzes the redox reaction of glucose with oxygen producing an electron exchange. The active site of the enzyme is surrounded by electrically insulating protein, which hinders the charge transfer on the surface of an electrode-based transducer. To overcome this difficulty, the enzyme is "wired" or connected through an electron conductive hydrogels to the electrode [1]. The wiring of the enzyme GOx consists in its immobilization in a hydrogels with fast redox centers at the ends of tethers of the polymer structure (Fig. 2c). Electrons are transferred when the pendant redox centers approximate to each other. In this way, the flavin adenine dinucleotide (FAD) centers of the active site of the enzyme are reduced (to $FADH_2$) by the glucose substrate, and reoxidized on the surface of the electrode. The hydrogels layer on the electrode allows for a high density of wired enzymes per unit area favoring electrode kinetics and limiting glucose diffusion. The high current density achieved makes this electrode configuration suitable for miniaturization [1] and its integration in a closed loop system.

Limitation of Enzyme Secondary Substrate

The specificity and the reversibility of enzymatic reactions impart desirable characteristics for hydrogels-based sensors. Therefore, proper conditions for these reactions must be controlled, such as the presence of a secondary substrate. The glucose sensitivity of a hydrogels-based system through the incorporation of GOx depends on oxygen availability. The catalase enzyme is often added to the system to regenerate oxygen from the hydrogen peroxide produced by the enzymatic glucose oxidation. The catalase reaction serves the double purpose of replenishing a reactant (oxygen) and eliminating a toxic inhibiting substance (hydrogen peroxide). In spite of the use of catalase, oxygen may still limit the response of the glucose-sensitive hydrogels system due to the low solubility of oxygen in aqueous solutions and blood. In order to enhance oxygen transport to the system, the use of macroporous

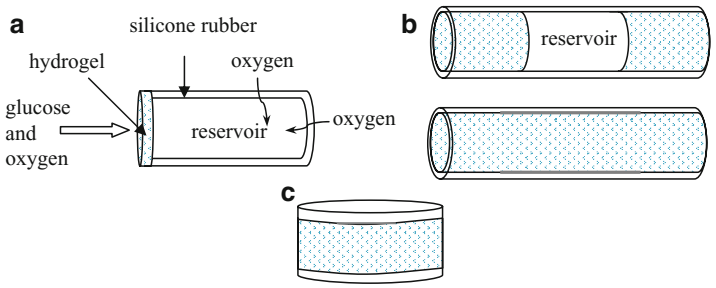

Fig. 3. Membrane (**a**), tube (**b**), and sandwich (**c**) configuration of enzymatic hydrogels devices with silicone rubber-covered surfaces for oxygen transport. Glucose oxidase is contained in the hydrogels. Reservoirs may contain an insulin solution or a gas (air or tissue gases). Adapted from [8].

hydrogels and silicone rubber components has been proposed. The latter are intended to create exclusive pathways for oxygen penetration into a hydrogels material that may contain insulin or cap an insulin reservoir [8].

Different configurations favor oxygen diffusion over glucose diffusion to solve oxygen limitation for the GOx reaction inside the hydrogels (Fig. 3), as discussed in [8]. Silicone rubber-covered surfaces impede glucose diffusion but are permeable to oxygen. Those devices based on a hydrogels membrane cap and a reservoir encased by silicone rubber allow glucose and oxygen to transport through the membrane and only oxygen to diffuse through the reservoir walls. In this work, a silicone rubber "tube" with hydrogels-filled sections and a hydrogels material sandwiched by silicone rubber disks offer adjustable two-dimensional diffusion systems. In the tube design, glucose and oxygen diffuse in the axial direction and only oxygen diffuses also in the radial direction. In the "sandwich" configuration, glucose and oxygen diffuse radially and only oxygen permeates through the silicone rubber disks. The oxygen concentration within the hydrogels can be increased by changing the length of the tube or the radius of the sandwich.

Studies on oxygen limitations in the GOx reaction within the hydrogels membrane, tube and sandwich delivery systems have been reported disregarding the swelling of the hydrogels, which would be less restricted in the sandwich design [8]. The authors developed mathematical models that produced the same qualitative results as the experimental systems. Their analysis was based on the square of the Thiele modulus, φ^2, the Biot number, Bi, and the relative consumption rates of oxygen and glucose, O/G. The square of the Thiele modulus is the ratio of the internal diffusion time ($L_i^2/\alpha_i D_i$, where L_i is the diffusional distance inside the gels, α_i is the equilibrium partition coefficient or ratio of the concentration inside the gels over the concentration in the solution, and D_i is the diffusivity in the membrane for the species i) to the reaction time (c_i/v, where c_i is the concentration in solution and v is the velocity of the enzymatic reaction). The Biot number expresses the ratio of the internal diffusion time over the external diffusion time or characteristic time for the diffusion through the hydrogels-medium interface (L_i/k_i, where k_i is the mass transfer coefficient). The analysis of the consumption ratio O/G revealed an optimal value for glucose response indicated by the pH of the hydrogels.

The following trends were observed in a hydrogels membrane system [8]. A considerable increase in oxygen availability, without a corresponding noticeable decrease in glucose concentration or in the hydrogels pH, indicated either an excess of glucose or a process limited by glucose oxidation kinetics. When the same area was available for both oxygen and glucose transport through the membrane, a pH plateau was reached near 50 mg/dL. Excess of oxygen, attained with a gas reservoir, produced lower pH values in the gels, high O/G values and a wider range of response, from 0 to 500 mg/dL.

The two-dimensional designs outperformed the membrane system. Changes in pH were greater than those with the membrane. The sandwich system reached a plateau at 200 mg/dL. The tube design filled with hydrogels was sensitive to glucose concentrations up to 350 mg/dL. The pH for the case of the tube design with a gas reservoir could still be reduced at glucose concentrations beyond 500 mg/dL. The tube designs, compared to the sandwich design, were more effective to enhance oxygen delivery to the hydrogels because of the higher oxygen transfer area. The tube with central gas reservoir achieved O/G ratios 33% greater than those for the tube completely filled with hydrogels due to the high diffusivity of oxygen through a gas. Under similar conditions of glucose limited diffusion, Biot number and gels volume but different geometric proportions, membrane systems only achieved two-thirds of the maximum response (total conversion of glucose in the hydrogels), while the tube and sandwich designs approximated much closer to the maximum response.

Regarding the dynamic behavior, the tube and sandwich systems showed greater response times than the membrane system. Settling times for the response before glucose concentration step changes were greater at higher concentration values. The larger sizes and geometric factors resulted also in increased response times.

Both the Biot and Thiele numbers determine the system dynamics. When the Biot number of the system is high, as in the tube and sandwich designs, internal diffusion is expected to dominate over external transport conditions such as the convective transport of glucose from the body. Enzyme loading directly affects the Thiele modulus. A high enzyme loading will not significantly reduce the response time since the system would be diffusion limited. However, when the Thiele modulus is low, the time response of the system will depend on enzyme loading.

Preservation of Enzyme Activity

The duration of the activity of the enzymes is an important determining factor for the useful life of enzymatic sensors. The hydrophilicity of hydrogels produces a proper environment for the preservation of enzyme activity and the diffusion of the analyte or substrate. Therefore, enzyme immobilization in hydrogels improves the performance of diverse composite sensors. Silicon sensor platforms can be used taking advantage of the compatibility of photopolymerization procedures with microfabrication techniques. For example, ISFET have been used as transduction systems for urea measurements based on the basic nature of products from urease interactions and the pH sensitivity of silicon semiconductors [9].

Immobilization procedures often include the difunctional component of glutaraldehyde, which acts as a crosslinking agent between enzymes. Glutaraldehyde can provide better retention of enzymes within a system as well as longer preservation of their activity [9]. Incorporation of poly(ethylene glycol) in the enzyme containing material helps to preserve enzyme activity and prevent immunoreactions to implanted systems [10, 11]. However, pegylation and glutaraldehyde crosslinking increase the density of the system and the diffusion limitations for the detection of substrate concentrations.

The limited activity of natural enzymes can be overcome by the use of mimics. Hydrogels have been used as a support polymer for imprinting cavities with catalytic activity. A chymotrypsin mimetic has been produced with a hydrogels (the volume changes switch the enzymatic activity on and off by altering the diffusivity of the substrate) with enhanced activity and stability [12].

Hydrogels as Actuators

Actuators respond to an external signal intended to cause a change in the process. The external signal comes from a device or controller that may be operated either in an open loop or in a closed loop. The controller of an automatic drug delivery system, for instance, uses

the information of the state of the patient (fed back through a sensor device) and an algorithm to determine the control signal to be sent to the actuator to deliver the proper amount of drug. In the manual mode, the application time and magnitude of the dose is decided by the patient who directly determines the control signal or manipulation of the actuator (on-demand function of the actuator). Hydrogels-based actuators can be manipulated through a continuous or an on/off control signal. This signal or manipulation can be of different nature [13, 14]: magnetic, ultrasonic, electric, optic, thermal, chemical, or biochemical.

Magnetically Controlled Systems

The responsiveness to a magnetic field can be achieved through the incorporation of magnetic beads into the hydrogels material. Copolymer matrices of ethylene with vinyl acetate and crosslinked alginate matrices with imbedded magnets have achieved enhanced drug release rates with increasing frequency of the oscillating magnetic field [15]. Repeated magnetic pulsatile or on/off stimulations required a higher frequency to compensate gradual drug depletion.

Ultrasonically Controlled Systems

Ultrasound increases diffusion and erosion controlled drug delivery rates [14]. The response to ultrasound does not require any modification in the synthesis of the polymeric material. Poly(ethylene-co-vinyl acetate) matrices have also been studied under ultrasound excitation. Solid drug particles in the dry material absorb ultrasound energy impeding stimulation for drug release. In the swollen state, the drug particles dissolve and ultrasound energy produces a higher increment in release rates than in the nonswollen state. Reversible increments in drug release were observed at low ultrasound frequencies from swollen systems [16]. Self-assembled monolayers responsive to ultrasound energy were used as coatings for drug-containing polymeric systems. The ultrasound energy disassembles the coating, which is rebuilt when ultrasound applications ceases [17]. This system has been used to deliver an anti-biofilm formation agent [18].

Electronically Controlled Systems

Electric fields can be applied on a membrane or in the solution to control the solute transport. A switching electrical field has been used to direct the binding of charged surfactant molecules to one or other side of an ionic hydrogels strip producing a controlled "worm-like motion" [19], illustrating an actuation mechanism with possible application for an artificial muscle or a drug delivery system. Hydrogels volume changes controlled by pulse width modulation have been experimented for the electric manipulation of hydrogels-based valves or pumps [20, 21]. The electric stimulated swelling dynamics was improved due to the added electrostatic effects by using the hydrogels as an electrolyte material in an electrolysis cell where protons are produced at one electrode and attracted to the other.

Photo-Controlled Systems

Photo-sensitive gels experience volume transition or chemical degradation when exposed to light [14]. These changes can be produced by the isomerization of chromophores in the excited photoreceptors in some materials [22, 23]. Azobenzene transition from the *trans* to the *cis* form by exposure to UV radiation causes dipole interactions that strip water from hydrogels materials [12]. Ophthalmic drug delivery systems have been designed using azobenzene copolymers whose molecular openings are regulated by changing the polarization of

laser irradiation [24]. Visible light has also been investigated as a safe and available stimulus source for rapid hydrogels phase transition based on light heating [25]. Other compounds such as cinnamic acid derivatives and fumaric amide have also been used in the fabrication of photo-sensitive hydrogels [26, 27].

Fumaric amide can give photosensitivity to biomaterials shown through gels–sol phase transitions [27]. The motion of F_1-ATPase (enzyme-based molecular motor) tethered with beads has been manipulated by the *trans–cis* isomerization of fumaric amide inside a self-assembled supramolecular hydrogels. Supramolecular hydrogels, in contrast to polymeric hydrogels, are built from supramolecular units or gelating agents which bond noncovalently (through hydrogen bonds, π–π stacking and van der Waals interactions) to produce fibers and crosslinking among fibers [27, 43]. The gelating agents consist of a hydrophilic sugar head, a hydrophobic lipid tail, and a hydrogen bonding spacer (Fig. 4). Fumaric amide was inserted in the spacer. Upon UV radiation, the entangled fibers in the gels state turned into spherical aggregates in the sol state. The recovery of the gels state was possible under visible light and in the presence of bromine. The phase transition was effective for the release of preloaded vitamin B12, concanavalin A and 100-nm beads. Moreover, Brownian motion of beads could be stopped at a specific bead size and gelating agents concentration. These materials were designed for on/off control of the Brownian motion of bacteria and enzymes whose activity depend on their mobility. The same motion control was achieved with hydrogels without fumaric amide or any covalent insertion of a "switching" unit by changing the environment temperature around the gels–sol transition temperature [28]. Localized stimulation allowed the gels–sol transition in specific parts in contrast with a bulk response of the material.

Gold nanoshells covered with a temperature-sensitive poly(*N*-isopropyl acrylamide-co-acrylic acid) hydrogels have been studied for potential drug delivery application [29]. Silicon dioxide particles with a seed-grown gold layer can be fabricated with the proper dimensions to absorb light in the near-infrared range from 800 to 1,200 nm. Radiation within this range can penetrate through skin, tissue, and water. Light absorption in these systems causes an increase in temperature and subsequent shrinking of the hydrogels (Fig. 5). Changes in the composition of acrylic acid adjust the lower critical solution temperature

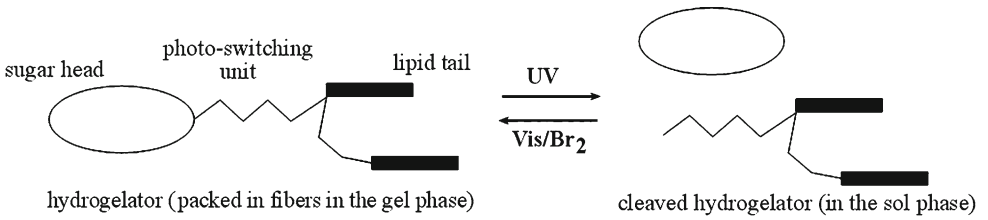

Fig. 4. Supramolecular hydrogels with fumaric amide photo isomerizable unit for a photo-actuated system. The material experiences a reversible phase transition in response to light stimuli. Adapted from [27].

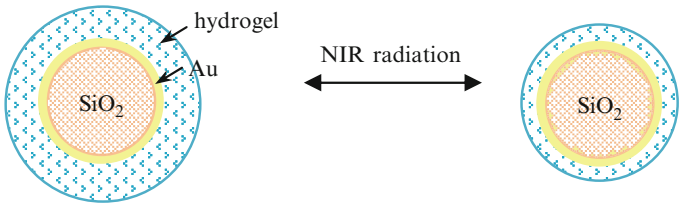

Fig. 5. Gold nanoshells with silica cores covered by a poly(*N*-isopropyl acrylamide-co-acrylic acid) hydrogels (photothermically controlled actuator system). Heating by NIR excitation of gold plasmon resonance results in hydrogels shrinking. Adapted from [29].

and enhance the reversibility of volume changes. Drug loaded hydrogels can also release the drug by collapsing the gels upon external photo-excitation.

Thermally Controlled Systems

Thermal energy can produce hydrogels swelling or contraction. Polymer networks of acrylic acid (AA) and acrylamide (AAm) show a direct swelling response with respect to an increment in temperature. The formation of hydrogen bonds between carboxylic and amide groups at low temperature causes the collapse of the polymeric structure. On the other hand, the disruption of hydrogen bonds at a high environmental temperature allows the expansion of the material. Interpenetrating networks with an equimolar composition of AA and AAm and low crosslinking agent content (0.1 mol%) to produce more abrupt volume transition and higher temperature sensitivity than the corresponding homopolymers and random copolymers [30], both traits are convenient for drug delivery applications. Temperature responsiveness of interpenetrating networks has been employed as the actuation mechanism of gold composite systems for drug delivery [31].

A temperature change can provoke not only a volume variation but an optical response of a hydrogels system. The volume of poly(acrylic acid-co-acrylamide) hydrogels determines the level of optical transparency. Dal et al. found that changes in hydrogels optical properties were more reversible when the temperature range for the transmittance transition narrows and the temperature in the inflection point is lower for smaller monomer concentrations [32]. A monomer ratio (AA/AAm) of 0.5 maximizes the number of bonds, widens the optical transition range and shifts this range to higher temperature values. High crosslinking agent concentration and high initiator concentrations lead to denser materials and wide transition ranges at higher temperature values. Release kinetics studies showed consistent higher decay rates of exponential profiles at higher temperature and less diffusion resistance. If the temperature forcing input is produced within the hydrogels system, for example, by the heat from an enzymatic reaction, an optical transducer could be used to produce an analyte measurement and, simultaneously, the volume transitions would allow self-regulated drug delivery.

Thermally actuated enzymatic hydrogels systems have been used in bioreactors. The swollen state of the hydrogels promotes absorption of the substrate while the collapse of the hydrogels may help to expulse enzymatic products, both effects can be achieved by cycling the hydrogels stimulation in order to favor the conversion of the substrate. The conversion in a packed-bed reactor and in a continuous stirred-tank reactor was investigated using poly(*N*-isopropyl acrylamide-co-acrylamide) hydrogels beads with immobilized β-galactosidase enzyme [33]. Temperature oscillation just below the hydrogels transition temperature (lowest critical solution temperature, LCST) outperformed isothermal conversion of the enzymatic reaction. Fast heating and cooling rates could lead to higher conversions as long as reversible volume changes were produced. However, several factors provoked the restricted reversibility of the swelling of the beads and affected the conversion in the reactors. Heating and cooling rates were limited by the viscoelastic dynamics of the hydrogels systems. In addition, the expansion at a temperature above the LCST was slower than below the LCST, and thermal heating from the exterior of the hydrogels beads approaching the LCST may have caused the formation of a "skin" that reduced the squeezing effect of the hydrogels syneresis. Optimization of temperature cycles was recommended for packed columns to reduce or avoid reactant tunneling among collapsing beads.

Chemically Controlled Systems

Chemical species can also stimulate actuator systems. The response of enzymatic materials can be triggered by the availability of an activating agent. For example, calcium addition can be used as a control signal to produce the conformational changes of calmodulin

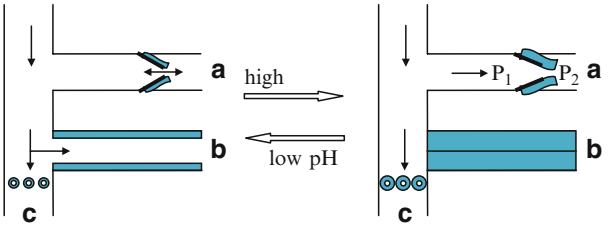

Fig. 6. Chemically controlled actuators based on an anionic hydrogels. The check valve (**a**) is activated at high pH and flow is allowed when pressure P_1 is greater than pressure P_2; channel covered with hydrogels strips (**b**) and hydrogels jackets on rigid posts (**c**) restrict flow area as pH increases. Adapted from [39], [38] and [37], respectively.

protein molecules contained in a hydrogels drug delivery system [34]. Fibrous hydrogels materials used for the regeneration of dental tissues are crosslinked at high calcium concentrations and can be deformed by the action of a collagenase enzyme [35]. A chemically controlled system has been made of a micellar dithiol crosslinked N-isopropyl acrylamide gels [36]. The presence of glutathione degrades the material by breaking the disulfide bonds. A preloaded drug release could therefore be controlled by the induced degradation.

Microfluidic devices can be controlled chemically. Hydrogels have been used to manipulate microflows in response to pH changes (Fig. 6) [20]. A poly(2-hydroxyethyl methacrylate-co-acrylic acid) hydrogels on the walls of a microchannel was observed to regulate the flow resistance by varying the cross section area for the flow according to the pH with diffusion limitations along the channel [37]. Faster regulation was achieved by the application of a hydrogels coating on posts at the entrance of a channel [38]. Nonresponsive materials have been used for different supporting structures, such as two close nonparallel flexible walls for a check valve. Strips made out of a pH-sensitive hydrogels attached to these walls reduced the space allowing opening or complete closure with a positive or negative pressure differential, respectively. The check valve was pH activated, since it required a swollen hydrogels to close [39].

Protein Responsive and Controlled Systems

Specific ligands can be incorporated in the hydrogels to affect the cell behavior [2]. Arg-Gly-Asp (RGD) peptides in a hydrogels system for tissue regeneration allow cell adhesion by the interaction with integrin proteins on the cell surface [40, 41]. Hydrogels with Ile-Lys-Val-Ala-Val (IKVAV) peptides have been applied to direct stem cell differentiation into neuronal cells [42].

Drug delivery systems activated by the presence of enzymes in the environment have been proposed [43]. This activation mechanism allows targeted drug delivery as in the case of tumors where specific proteases are found. For example, polyacrylamide hydrogels have been synthesized with enzyme cleavable peptides [44]; the enzymes in the medium degrade the material and can produce gradual release of the drug content.

An esterase sensitive system consisting of a self-assembled supramolecular hydrogels has been studied. The gelating agent can incorporate a prodrug (inactive drug precursor) with an ester bond susceptible of cleavage by the hydrolysis reaction catalyzed by esterases. A second drug can be encapsulated in the material for simultaneous release of two possibly complementary drugs upon degradation of the material (Fig. 7). Gelating agents of an acetaminophen (analgesic)-based prodrug were used to fabricate these materials to encapsulate curcumin (antioxidant). The amphiphilic properties of gelating agents effectively incorporated the hydrophobic curcumin and provided the necessary hydration for lipase-induced degradation. The release rates increased with enzyme concentration and temperature. The acetaminophen-based gelating agents were not cytotoxic. Gel–sol reversible transition was not intended to

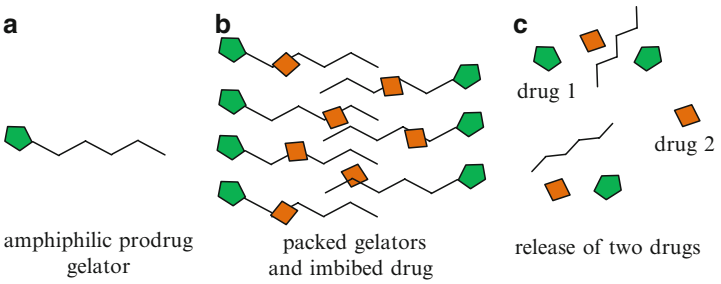

Fig. 7. Supramolecular hydrogels from prodrug gelators as a protein-controlled actuator system. Amphiphilic prodrug gelator from a well known therapeutic (**a**), packing of prodrug gelator and encapsulation of a second therapeutic (**b**), release of therapeutics upon esterase degradation (**c**). Adapted from [43].

control drug delivery in the described lipase responsive system. Nevertheless, the effect of temperature on phase transition and the effect of enzymes on degradation can be combined. A temperature range may ease enzyme diffusion toward cleavable links in a two step mechanism [45–47] for drug release.

Self-Regulated Hydrogels-Based Systems

In self-regulated systems, the controller function is implicit in the hydrogels material structure as well as on the device design. The static and dynamic characteristics of a self-regulated system correlate the input feedback variable with an output variable [48]. The input variable drives the hydrogels response or the output variable change. These variables represent the main interactions with the surroundings. The autonomous systems presented here are based on feedback variables that allow hydrogels actuation by the environment for controlling a particular condition.

Miniaturized systems offer the possibility of painless, economic, continuous, and optimal drug infusion since they allow the management of small quantities of samples, reactants, and drugs. Low costs and easier operation are also possible for diagnostics systems when scaled down. The reduction of response times of small systems facilitates taking advantage of the integration of multiple functions in a hydrogels material. Some characteristics may be lost by miniaturization, such as the drug storage capacity within a hydrogels, but can be compensated by combining elements of different structures and materials. However, the complexity of such hybrid systems is reduced by the elimination of processing circuits (transducers, control algorithms), energy sources, wires and separate sensors and actuators due to hydrogels multifunctionality. *In situ* photopolymerization of hydrogels is easily incorporated in the manufacturing procedure of microfluidic platforms [20]. This technique is also convenient as part of an implantation procedure of monolithic drug delivery devices or tissue engineering applications.

pH Feedback Systems

The pH sensitivity of anionic hydrogels provides temporal release control in systems proposed for oral drug administration [49]. The hydrogels-based system prevents drug delivery in the stomach where the acidic pH causes the polymeric matrix to contract. When the hydrogels reaches the upper small intestine, where the pH is higher, the polymeric structure swells and eases drug diffusion. This on/off self-regulated system is active during its digestion process.

The incorporation of enzymes in ionic hydrogels can transform the pH sensitivity into responsiveness to the concentration of the enzyme substrate in the environment. The enzymatic reactions that produce acid or basic compounds modify the pH of the system leading to a volume change and inherent diffusivity variations. Since the pH changes are a function of the substrate concentration, continuous (as opposed to on/off) drug release regulation can be achieved for periods of time that are limited by enzyme activity, drug depletion, polymer degradation or body elimination [10, 50]. Urease-containing anionic hydrogels deliver drug in response to high concentrations of urea because of the swelling driven by the increment in the pH from the production of ammonium hydroxide (NH_4OH). While a cationic hydrogel with glucose oxidase can open its mesh structure for insulin delivery as glucose concentration increases due to its transformation into gluconic acid and the consequent pH decrement.

Autonomous pH regulation in a microfluidic system has been designed based on the sensing and actuating functions of a hydrogels component [51]. The objective was to achieve a neutral pH in the output flow from a T-junction where an acid input was mixed with a compensating basic input. A poly(acrylic acid-co-2-hydroxyethyl methacrylate) hydrogels postpressing on a poly(dimethyl siloxane) membrane (PDMS) on top of the orifice influenced the input of the basic solution. The orifice sealing increased at high pH of the output by tensing the PDMS membrane upon radial swelling of the post. The occluded area of the orifice decreased when the output pH was very acidic due to the radial shrinking of the anionic hydrogels post and the raising of the PDMS membrane (Fig. 8). The geometry of the orifice determined the type of regulation for the basic input: a circular orifice caused an on/off action and an oscillatory pH of the output flow, while a star geometry provided a stable output pH by gradual adjustments of the compensating basic flow. The pH regulation was limited by saturation effects due to pressure conditions in the channels. The proposed valve mechanism responsive to the environmental pH could be applied to drug delivery systems.

Anionic and cationic hydrogels (with opposite responses to pH) have been combined in a microfluidic sorter system by placing valves on each side of the T-junction of two microchannels. At the T-connection, the course of an input flow could be directed to one or another side depending on which valve was opened at the pH of the flow [38]. This type of combination allows the manipulation of flows according to their chemical characteristics.

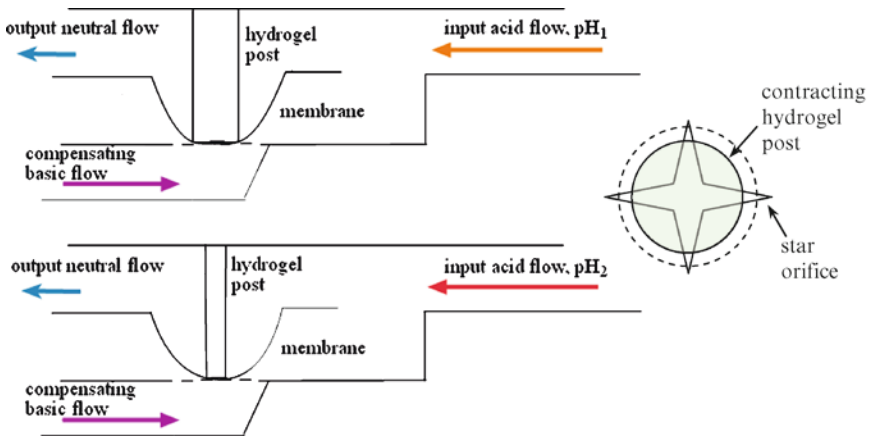

Fig. 8. Self-regulated system for pH control of the output flow. If the input flow has lower pH ($pH_2 < pH_1$), the hydrogels contracts radially allowing more free area for the pass of the compensating basic flow. A star orifice is obstructed by the hydrogels post. Adapted from [51].

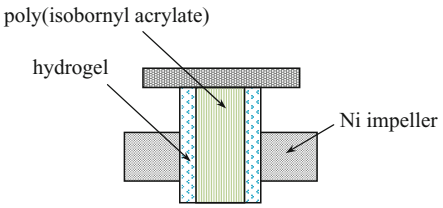

Fig. 9. Self-regulated system for temperature control. A hydrogels with negative swelling sensitivity with respect to temperature on the surface of the shaft of a magnetically impulsed propeller allows cooling flow above the LCST. Adapted from [52].

Temperature Feedback Systems

A temperature-sensitive hydrogels has been used for an autonomous cooling system in a lab-on-a-chip device (Fig. 9) [52]. The hydrogels formed around the axis of a nickel propeller for cooling water recirculation exerted on/off control of the rotation. The propeller was driven by an external magnetic stirrer, whose rotation speed determined the cooling flow rate. The hydrogels was a crosslinked copolymer of N-isopropyl acrylamide (NIPAAm) and 3-methacrylamidopropyltrimethylammonium chloride (MAPTAC), the latter was included to raise the LCST or onset operation temperature for the propeller. The hydrogels ring around the propeller was fabricated by the liquid-phase photopolymerization technique. When the temperature reached the LCST, the hydrogels collapsed allowing free movement of the propeller. At lower temperatures, the swollen hydrogels clutched the propeller. Temperature responsive systems may be also applied for closed loop drug delivery for the management of fever or infections.

Protein Concentration Feedback Systems

Proteins attached to hydrogels materials increase the possibilities for self-regulated systems. Hydrogels have been grafted with antigen and antibodies to create crosslinks that can be undone by the competitive binding with free antigen in the environment. The number of undone noncovalent crosslinks depends on the exogeneous antigen concentration which determines the degree of hydrogels swelling that enables controlled drug delivery [53, 54]. Hydrogels may also be designed as enzyme-sensitive systems, for example, biodegradable hydrogels for delivery of anti-inflammatory drugs. The gels degradation is promoted by enzymes as well as hydroxyl radicals that are produced at inflamed sites. This system could provide osteoarthritis treatment in a closed loop mode [14].

Enzyme Cofactor Feedback System

Enzymatic reactions offer different possibilities for drug delivery control by an immobilized oxidase enzyme that depends on the availability of an oxidizing cofactor or secondary substrate [2]. The concentration of the latter mediates the regulation of drug release. The constant presence of glucose in blood and the oxygen limitations do not favor reversible changes in ionic hydrogels for insulin delivery in diabetes treatment. However, the glucose composition of the blood as well as the possibility of other oxidizing agents make the glucose oxidase enzyme useful for the delivery of other drugs in the context of different pathologies. Oxidizing agents concentrate in inflammation sites and tumors and can induce drug release from the swelling of hydrogels through gluconic acid enzymatic production [2]. As a secondary substrate for glucose oxidase, polysulfide nanoparticle systems with glucose oxidase oxidize sulfides in the presence of glucose to produce swelling and drug release [55].

Glucose Concentration Feedback Systems

Research on closed loop control of glucose levels in a diabetic patient highlights important aspects for the application of autonomous systems. The feasibility of an insulin self-regulated delivery system based on injectable hydrogels microparticles with glucose sensitivity has been evaluated for the purpose of blood glucose regulation [56]. Synthesis parameters determine the capacity of hydrogels microparticles to: (a) respond to glucose concentration, (b) store enough insulin to reduce frequency of injections (3 days sparse at least), (c) circulate in blood capillaries, and (d) degrade at a rate that allows diffusion-controlled insulin depletion. Particles of 30 μm in size exhibit instantaneous response to pH changes [10]. This observation was used to simplify the analysis by neglecting the viscoelastic behavior of the hydrogels. The analysis considered the kinetics of the glucose oxidation and constant diffusivities for glucose, gluconic acid and insulin. Results showed the direct effect of the crosslinking ratio (number of moles of crosslinking agent per mol of monomer) on the maximum swelling and the degradation rate. The number of injected particles as well as the insulin loading determined the release rate but did not affect the release duration. The size of the collapsed hydrogels particles was directly correlated to the duration of the release. However, the swelling of hydrogels particles before high glucose concentrations produced an incremental change in the mesh size that increased the diffusion path for insulin delivery. A low crosslinking ratio produced higher delivery rates and shorter release durations. For higher transition pH values, the cationic particles tended to have higher volume and lower internal pH values making hydrogels contraction improbable. Higher content of basic functional groups led to an increase in the initial pH value of the microparticles and lower rates of gluconic acid production or decreased sensitivity of the system. The large size of the hydrogels particles to achieve acceptable release duration would inhibit them to circulate through capillaries. The simulation with a physiological model at a basal state produced wide oscillations in glucose levels.

Some disadvantages of hydrogels microparticles for injectable systems could be avoided by using implantable membranes. Limitations of size for release duration and for stable glucose control are clearly solved in macrosystems because of their longer response times. However, the effects of the buffer physiological medium, the continuous presence of glucose and the Donnan equilibrium suggest restricted volume changes for the hydrogels system regardless of its size. A simulation study of glucose responsive hydrogels membranes for insulin delivery in a diabetic patient with a diet of three meals per day showed they could be useful for days, but insulin release profiles decreased monotonically in spite of the elevated glucose levels during the meals (Fig. 10) [50]. Specific viscoelastic effects of the hydrogels membrane and GOx–catalase reaction kinetics in the hydrogels medium were based on experiments with poly(methacrylic acid-g-ethylene glycol). The Sorensen model was used for the simulation of the glucose–insulin physiologic process for an adult male of 70 kg. The initial interaction of the implanted hydrogels membrane with the glucose containing physiological fluids dominated the volume response of the membrane over the pH changes caused by the meals. The small variations in the pH of the membrane during the meals were due to a combination of the glucose composition and the buffer effect of the blood. Even at fasting glucose levels, glucose would tend to diffuse into the gels causing a sustained production of gluconic acid that would oppose the recovery of the higher physiological pH. Furthermore, the Donnan equilibrium inside the gels would determine the conservation of a local pH different from the pH of the physiological environment.

Apart from the particular diabetes application characteristics, those of the hydrogels in a self-regulated system can be improved in order to produce flexible delivery profiles similar to those that can be obtained with an explicit controller [57–59]. A hydrogels-based insulin delivery system should achieve mesh size variations around the size of insulin at a physiological pH. Mesh size and transition pH can be adjusted by modifying the number, the type and the

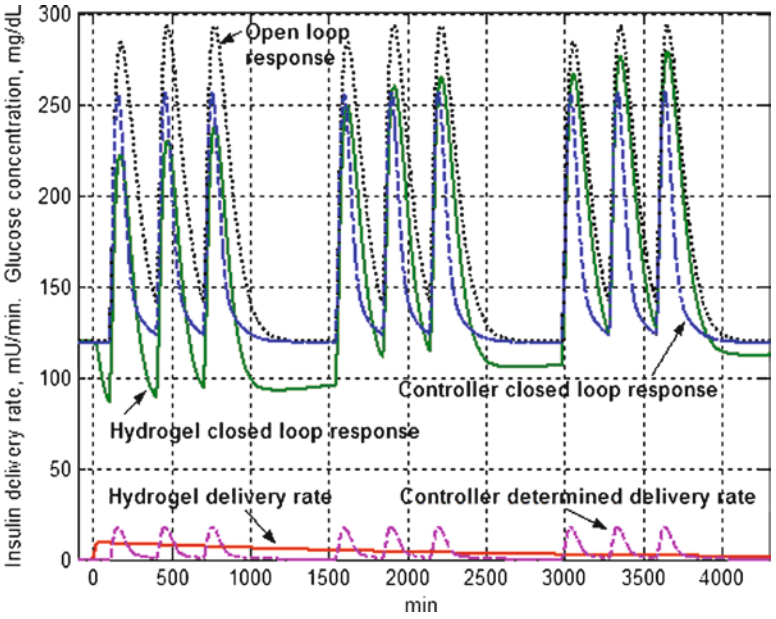

Fig. 10. Hydrogels membrane as a self-regulated control system of blood glucose levels in a diabetic patient. Simulation results are shown using a hydrogels membrane insulin delivery system and an explicit controller during 3 days with three meals per day. Reprinted with authorization from [50], © AIChE Journal.

concentration of monomers. Even if the critical pH of an ionic hydrogels was adjusted closer to a neutral value, the buffer characteristic of physiological fluids would offer a resistance to the volume changes of the membrane. Hydrogels materials with temperature and glucose sensitivity can be suggested from the possibility to couple the energy produced by the enzymatic reaction of glucose to the modulation of molecular openings and drug delivery. Hydrogels without pH sensitivity would eliminate the limitations due to the buffer environment and the Donnan equilibrium effect. However, they would also be subjected to the saturation of the glucose oxidase enzyme due to the constant presence of glucose in the physiological environment. Limitations of hydrogels monolithic systems for continuous blood glucose regulation may be overcome by hydrogels-based devices. Hydrogels may be used in hybrid systems for a more effective insulin delivery.

Alternative insulin delivery systems have been suggested by combining membrane and particle structures and using non-covalent enzyme immobilization. Covalent attachment requires exposure to fabrication steps involving high temperatures and violent mixing that may diminish the activity of the enzyme. Physical attachment may be less aggressive to the enzyme although the possibility for enzyme leakage is higher. Researchers have proposed a self-regulatory system consisting of poly(*N*-isopropyl acrylamide-co-methacrylic acid) hydrogels nanoparticles supported in a hydrophobic enzymatic membrane (Fig. 11) [60]. Glucose oxidase and catalase were mixed with dissolved ethyl cellulose and hydrogels nanoparticles. The membrane was formed after evaporation of the solvent. The analysis of washing water showed no loss of enzymes in spite of their physical immobilization. The activity of the physically immobilized enzymes was 80% of the enzymes in solution. Optimal values for the ratio of glucose oxidase units to catalase units (1:11) and the amounts of each enzyme in the system were determined by comparing the pH behavior at different glucose concentrations. The permeability values, obtained through diffusion cell experiments, were not higher for the maximum enzyme content but only the determined optimal quantities. Insulin transport was dependent on glucose concentration as shown by varying the glucose concentration in the

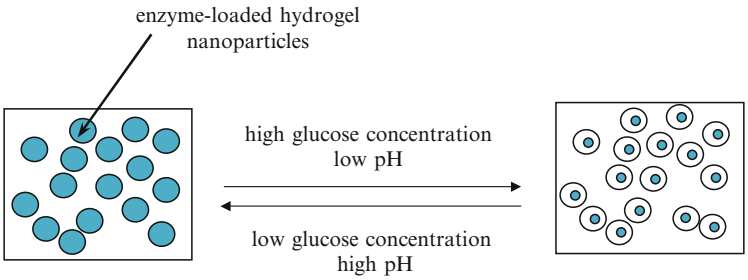

Fig. 11. Hydrophobic membrane with hydrogels nanoparticles for a self-regulated system. Nanoparticles contain glucose oxidase and catalase. The composite membrane increases insulin permeability before high glucose concentrations. Adapted from [60].

receptor cell. The small thickness of the membrane and diameter of the hydrogels particles favored fast and reversible responses compared to hydrogels membranes [50]. The membrane structure would ease implantation in specific parts of the body (avoiding problems of an injectable system) and the microparticles would contribute to the fast response necessary for appropriate action before glucose levels.

Drug availability can limit the use of self-regulated systems. The drug is usually imbedded in the responsive material or contained in an attached reservoir. In order to overcome the disadvantage of drug depletion from these systems, the production of the drug may be added. Insulin-secreting cells, for instance, can be sustained in a proper reservoir or compartment that allows flux of cell metabolites through the reservoir walls and controlled insulin release through the responsive material cap. Fibroblasts, myoblasts, and hepatocytes from the same patient have been genetically engineered to express insulin and used as an insulin source for a self-regulated delivery system [61]. These non-β cells have better immunological acceptance than transplanted human corpse β cells, but show a slow reaction to physiological conditions. Insulin accumulated in a compartment can be dosed through the dynamic diffusion barrier provided by the responsive material. A possible insulin feedback inhibition effect on the cells might be useful to prevent excessive insulin accumulation.

A cell-material hybrid device for controlled insulin release that incorporates the insulin-secreting autologous non-β cells mentioned and a concanavalin A-glycogen hydrogels has been proposed [61]. This material changes from a gels to a sol state when exposed to high glucose concentrations. The concanavalin A acts as a crosslinking agent in a material with glycogen pendant groups. At high concentrations, glucose from the environment competitively binds to concanavalin A destroying the crosslinks of the material. If the exterior glucose concentration is low, internal crosslinks are reestablished. The device was constructed as a 6 cm in diameter disk, 1 cm thick. Silicon sheets and polycarbonate plates were used as structural materials to support the cell layer and the hydrogels layer separated by a 0.02 μm Anodisc™ membrane. In vitro tests showed induced insulin release at glucose concentrations above physiological levels. Oxygen limitation diminished cell viability. Accumulated death cells also caused less cell viability. Toxicity and leakage of concavalin A toward the cell layer affected cell viability and glucose sensitivity. The responsive material can be redesigned to show sol–gel transitions in the physiological range.

Hydrogels-Based Feedforward and Cascade Systems

In many processes, feedback control is not enough to keep the process variable within the control limits, especially in presence of disturbances. When an external variable to the control system changes, the time and difficulty to correct the deviation caused in the process

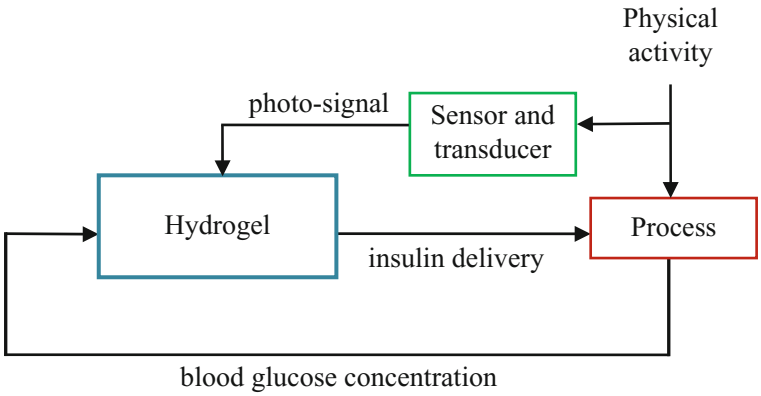

Fig. 12. Feedforward scheme applied by double responsiveness to the environment. The system is based on a single hydrogels component. If physical activity increases, the increment of the heart rate can be detected and used to produce a photo-signal to cause the hydrogels to decrease insulin delivery before blood glucose level drops. Heart rate external detection would help to prevent a hypoglycemic event due to the increment in physical activity by anticipating its effect. The basic glucose sensitivity of the hydrogels-based insulin delivery systems allows a reactive response before other disturbances like meals.

variable increases. To improve the performance of the feedback systems, the control system is modified to attenuate or compensate for effects. The variety of environmental stimuli on hydrogels systems as well as possible combinations of materials and physical structures could be used to take advantage of control schemes, such as feedforward and cascade.

In a feedforward system, the detection of a disturbance before it affects the process variable or controlled variable is used to apply an additional manipulation in order to compensate the disturbance effect. This strategy could be applied, for example, in an enzymatic hydrogels-based insulin delivery system to adjust release based on the heart frequency. The heart frequency reflects the level of physical activity of the patient. If the heart rate increases, as detected by an extensiometric gauge or pulsoxymeter, a transduction system could generate a radiation signal that would decrease hydrogels swelling [29] and insulin release before glucose levels decreased to avoid a hypoglycemic episode (Fig. 12). The glucose–oxidase reaction that determines the pH of the microenvironment of the hydrogels would implement the glucose concentration feedback, the pH responsiveness of the hydrogels would implement a basic control function, and the responsiveness to near-infrared radiation determined from the external variable would produce the feedforward control function. The resultant hydrogels action would come from the net effect of the driving inputs: pH and irradiated energy.

The cascade control strategy consists in the attenuation of the effect of a disturbance by controlling an auxiliary variable that manifests the presence of the disturbance before it causes a variation of the main variable. If the secondary variable is returned to its normal value quickly enough, then the effect on the main variable will be reduced or even eliminated. This scheme tries to interfere in the cascade or domino sequence of effects from a disturbance source to the main controlled variable through nested control loops. In the sense of a cascade propagation of effects and corrective actions, a cascade arrangement could correspond to concentric hydrogels systems imbedded with different drugs. When the physiological condition that activates the response of the external hydrogels allows extreme swelling such that the interior hydrogels gets exposed to another physiological condition, the response of the inner system may deliver drug before a complex symptom. For example, an external glucose oxidase containing hydrogels may be kept swollen at persistent high glucose levels. This situation leads to malfunction of kidneys, which can be manifested by high urea concentrations

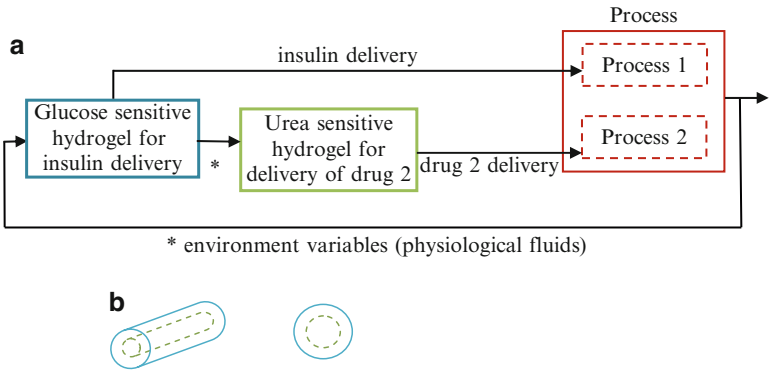

Fig. 13. Cascade scheme applied by concentric hydrogels materials. Conceptual diagram (**a**) and possible physical structures (**b**) are shown for sequential activation from the external hydrogels component in direct contact with physiological environment.

detected by an internal urease-containing hydrogels that may allow the release of a drug to decrease urea levels (Fig. 13). In this case, the nested systems produce independent actions on the environment instead of reinforcing actions for the control of a single variable.

Summary

Monolithic hydrogels systems have several limitations regarding drug-loading capacity, velocity, and reversibility of response and mechanical strength. Hybrid systems compensate for these limitations and take advantage of the responsiveness of hydrogels to varied environmental conditions. The hydrogels materials used for sensors and actuators in a multicomponent control system require special transduction means for continuous feedback systems.

Physical and biochemical hydrogels stimuli may not exclusively correspond to one type of feedback system, but can be related mainly to explicit controller and implicit controller biomedical feedback systems, respectively. Ultrasound, magnetic, light, electrical and thermal signals with high energy content are not appropriate for biological environments; typically, they require an external source or controller. The flexibility of explicit controllers encourages the use of hydrogels in the development of separate sensor and actuator units. External physical stimulation by ultrasound, magnetism, electric fields, or temperature can enhance drug diffusion delivery by increasing the mobility of the drug molecules. Therefore, physical external stimulation may also augment drug delivery rates from hydrogels, even if there is no interference with the swelling behavior. Ultrasound provides a mechanical actuation mechanism for drug delivery systems that do not require special hydrogels synthesis procedures and are expected to have less impact on the integrity of the drug. Continuous external stimulation and hydrogels reversible response may mediate the regulation of variable drug release profiles in a continuous closed loop treatment with an explicit controller. A system chemically stimulated may act irreversibly and, therefore, not be suitable for continuous control. The same applies for any kind of stimulated degradation based drug delivery system. However, a scheme of on/off activation of multiple drug hydrogels compartments may allow modifications in the release profile for temporal closed loop control in these cases. Even when research on hydrogels systems aim to achieve implantable applications, the concepts related to their operation may be a reference for the development of diverse advanced products for health care.

References

1. Heller A (2005) Integrated medical feedback systems for drug delivery. AIChE J 51(4):1054–1066
2. Ulijn RV, Bibi N, Jayawarna V, Thornton PD, Todd SJ, Mart RJ, Smith AM, Gough JE (2007) Bioresponsive hydrogels. Mater Today 10(4):40–48
3. Holtz JH, Asher SA (1997) Polymerized colloidal crystal hydrogel films as intelligent chemical sensing materials. Nature 389(6653):829–832
4. Ben-Moshe M, Alexeev VL, Asher SA (2006) Fast responsive crystalline colloidal array photonic crystal glucose sensors. Anal Chem 78(14):5149–5157
5. Kim J, Nayak S, Lyon LA (2005) Bioresponsive hydrogel microlenses. J Am Chem Soc 127(26):9588–9592
6. Kim H, Cohen RE, Hammond PT, Irvine DJ (2006) Live lymphocyte array for biosensing. Adv Funct Mater 16(10):1313–1323
7. Hilt JZ, Gupta AK, Bashir R, Peppas NA (2003) Ultrasensitive biomems sensors based on microcantilevers patterned with environmentally responsive hydrogels. Biomed Microdevices 5(3):177–184
8. Klumb LA, Horbett TA (1991) Design of insulin delivery devices based on glucose sensitive membranes. J Control Release 18:59–80
9. Jiménez C, Bartrol J, de Rooij NF, Koudelka-Hep M (1997) Use of photopolymerizable membranes based on polyacrylamide hydrogels for enzymatic microsensor construction. Anal Chim Acta 351(1):169–176
10. Podual K, Doyle FJ III, Peppas NA (2000) Dynamic behavior of glucose oxidase-containing microparticles of poly(ethylene glycol)-grafted cationic hydrogels in an environment of changing pH. Biomaterials 21:1439–1450
11. Owens DE, Peppas NA (2006) Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. Int J Pharm 307(1):93–102
12. Karmalkar RN, Premnath V, Kulkarni MG, Mashelkar RA (2000) Switching biomimetic hydrogels. Proc R Soc Lond, Ser A 456(1998):1305–1320
13. Kost J, Langer R (1992) Responsive polymer systems for controlled delivery of therapeutics. Trends Biotechnol 10(4):127–131
14. Traitel T, Goldbart R, Kost J (2008) Smart polymers for responsive drug-delivery systems. J Biomater Sci Polym Ed 19(6):755–767
15. Saslavski O, Couvrer P, Peppas NA (1998) In: Heller J, Harris F, Lohmann H, Merkle H, Robinson J (eds) Controlled release of bioactive materials, vol 1. Controlled Release Society, Basel, p 26
16. Aschkenasy C, Kost J (2005) On-demand release by ultrasound from osmotically swollen hydrophobic matrices. J Control Release 110(1):58–66
17. Kwok C, Mourad P, Crum L, Ratner B (2001) Self-assembled molecular structures as ultrasonically-responsive barrier membranes for pulsatile drug delivery. J Biomed Mater Res 57:151–164
18. Norris P, Noble M, Francolini I, Vinogradov AM, Stewart PS, Ratner BD, Costerton JW, Stoodley P (2005) Ultrasonically controlled release of ciprofloxacin from self-assembled coatings on poly(2-hydroxyethyl methacrylate) hydrogels for Pseudomonas aeruginosa biofilm prevention. Antimicrob Agents Chemother 49:4272–4279
19. Osada Y, Okuzaki H, Hori H (1992) A polymer gel with electrically driven motility. Nature 355:242–244
20. Eddington DT, Beebe DJ (2004) Flow control with hydrogels. Adv Drug Deliv Rev 56(2):199–210
21. Bassetti MJ, Chatterjee AN, De SK, Aluru NR, Beebe DJ (2005) Development and modeling of electrically triggered hydrogels for microfluidic applications. J Microelectromech Syst 14(5):1198–1207
22. West J (2003) Drug delivery – pulsed polymers. Nat Mater 2(11):709–710
23. Mamada A, Tanaka T, Kungwatchakun D, Irie M (1990) Photoinduced phase transition of gels. Macromolecules 23(5):1517–1519
24. Lee JK, Lee H, Jang E, Lee SD, Kim SJ (2005) Photo-triggering of the membrane gates in photo-responsive polymer for drug release. In: Engineering in medicine and biology society. 27th Annual International Conference of the IEEE-EMBS. Shanghai, China, pp 5069-5072
25. Suzuki A, Tanaka T (1990) Phase transition in polymer gels induced by visible light. Nature 346:345–347
26. Lendlein A, Jiang H, Junger O, Langer R (2005) Light-induced shape-memory polymers. Nature 434(7035):879–882
27. Matsumoto S, Yamaguchi S, Ueno S, Komatsu H, Ikeda M, Ishizuka K, Iko Y, Tabata KV, Aoki H, Ito S, Noji H, Hamachi I (2008) Photo gel-sol/sol-gel transition and its patterning of a supramolcecular hydrogel as stimuli-responsive biomaterials. Chem Eur J 14(13):3977–3986
28. Yamaguchi S, Matsumoto S, Ishizuka K, Iko Y, Tabata KV, Arata HF, Fujita H, Noji H, Hamachi I (2008) Thermally responsive supramolecular nanomeshes for on/off switching of the rotary motion of F_1-ATPase at the single-molecule level. Chem Eur J 14:1891–1896
29. Kim JH, Lee TR (2008) Thermo-responsive hydrogel-coated gold nanoshells for in vivo drug delivery. J Biomed Pharm Eng 2(1):29–35
30. Owens DE, Jian YC, Fang JE, Slaughter BV, Chen YH, Peppas NA (2007) Thermally responsive swelling properties of polyacrylamide/poly(acrylic acid) interpenetrating polymer network nanoparticles. Macromolecules 40:7306–7310

31. Owens DE, Eby JK, Jian Y, Peppas NA (2007) Temperature-responsive polymer-gold nanocomposites as intelligent therapeutic systems. J Biomed Mater Res 83A:692–695
32. Dai H, Chen Q, Qin H, Guan Y, Shen D, Hua Y, Tang Y, Xu J (2006) A temperature-responsive copolymer hydrogel in controlled drug delivery. Macromolecules 39(19):6584–6589
33. Park TG, Hoffman AS (1993) Thermal cycling effects on the bioreactor performances of immobilized beta-galactosidase in temperature-sensitive hydrogel beads. Enzyme Microb Technol 15(6):476–482
34. Ehrick J, Deo S, Browning T, Bachas L, Madou M, Daunert S (2005) Genetically engineered protein in hydrogels tailors stimuli-responsive characteristics. Nat Mater 4(4):298–302
35. Jun HW, Yuwono V, Paramonov SE, Hartgerink JD (2005) Enzyme-mediated degradation of peptide-amphiphile nanofiber networks. Adv Mater 17(21):2612–2617
36. Li CM, Madsen J, Armes SP, Lewis AL (2006) A new class of biochemically degradable, stimulus-responsive triblock copolymer gelators. Angew Chem Int Ed 45(21):3510–3513
37. Liu RH, Yu Q, Beebe DJ (2001) Fabrication and characterization of hydrogel based microvalves. J Microelectromech Syst 11:45–53
38. Beebe DJ, Moore J, Bauer J, Yu Q, Liu RH, Devadoss C, Jo BH (2000) Functional hydrogel structures for autonomous flow control inside microfluidic channels. Nature 404:588–590
39. Yu Q, Bauer JM, Moore JS, Beebe DJ (2001) Responsive biomimetic hydrogel valve for microfluidics. Appl Phys Lett 78:2589–2591
40. Zourob M, Gough JE, Ulijn RV (2006) A micropatterned hydrogel platform for chemical synthesis and biological analysis. Adv Mater 18(5):655–659
41. Hall H, Hubbell JA (2005) Modified fibrin hydrogels stimulate angiogenesis in vivo: potential application to increase perfusion of ischemic tissues. Materwiss Werksttech 36(12):768–774
42. Silva GA, Silva GA, Czeisler C, Niece KL, Beniash E, Harrington DA, Kessler JA, Stupp SI (2004) Selective differentiation of neural progenitor cells by high-epitope density nanofibers. Science 303:1352–1355
43. Vemula PK, Cruikshank GA, Karp JF, John G (2009) Self-assembled prodrugs: an enzymatically triggered-drug delivery platform. Biomaterials 30:383–393
44. Plunkett KN, Berkowski KL, Moore JS (2005) Chymotrypsin responsive hydrogel: application of a disulfide exchange protocol for the preparation of methacrylamide containing peptides. Biomacromolecules 6(2):632–637
45. Lee MR, Baek KH, Jin HJ, Jung YG, Shin I (2004) Targeted enzyme-responsive drug carriers: studies on the delivery of a combination of drugs. Angew Chem Int Ed 43(13):1675–1678
46. van Bommel KJC, Stuart MCA, Feringa BL, van Esch J (2005) Two-stage enzyme mediated drug release from LMWG hydrogels. Org Biomol Chem 3(16):2917–2920
47. Kumashiro T, Ooya T, Yui N (2004) Dextran hydrogels containing poly(*N*-isopropyl acrylamide) as grafts and cross-linkers exhibiting enzymatic regulation in a specific temperature range. Macromol Rapid Commun 25:867
48. Gupta P, Vermani K, Garg S (2002) Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov Today 7(10):569–579
49. Peppas NA, Wood KM, Blanchette JO (2004) Hydrogels for oral delivery of therapeutic proteins. Expert Opin Biol Ther 4(6):881–887
50. Sánchez-Chávez IY, Martínez-Chapa SO, Peppas NA (2008) Computer evaluation of hydrogel-based systems for diabetes closed Loop treatment. AIChE J 54(7):1901–1911
51. Lee SH, Eddington DT, Kim YM, Kim W, Beebe DJ (2003) Control mechanism of an organic self-regulating microfluidic system. J Electromech Syst 12(6):848–854
52. Agarwal AK, Dong L, Beebe DJ, Jiang H (2007) Autonomously-triggered microfluidic cooling using thermo-responsive hydrogels. Lab Chip 7(3):310–315
53. Miyata T, Asami N, Uragami T (1999) A reversibly antigen-responsive hydrogel. Nature 399:766–769
54. Nakayama G, Roskos K, Fritzinger B, Heller J (1995) A study of reversibly inactivated lipases for use in a morphine-triggered naltrexone delivery system. J Biomed Mater Res 29:1389–1396
55. Duncan R (2003) The dawning era of polymer therapeutics. Nat Rev Drug Discov 2(5):347–360
56. Farmer TG, Edgar TF, Peppas NA (2008) In vivo simulations of the intravenous dynamics of submicrometer particles of pH-responsive cationic hydrogels in diabetic patients. Ind Eng Chem Res 47(24):10053–10063
57. Sanchez-Chávez IY, Morales-Menéndez R, Martínez-Chapa SO (2009) Glucose optimal control system in diabetes treatment. Appl Math Comput 209(1):19–30
58. Parker RS, Doyle FJ III, Ward JH, Peppas NA (2000) Robust H_∞ glucose control in diabetes using a physiological model. AIChE J 46:2537–2549
59. Parker R, Doyle F III, Peppas NA (1999) Model-based algorithm for blood glucose control in type I diabetic patients. IEEE Trans Biomed Eng 46(2):148–157
60. Zhang K, Wu X (2002) Modulated insulin permeation across a glucose-sensitive polymeric composite membrane. J Control Release 80:169–178
61. Cheng SY, Constantinidis I, Sambanis A (2006) Use of glucose-responsive material to regulate insulin release from constitutively secreting cells. Biotechnol Bioeng 93(6):1079–1088