

Advanced Micromolding Approach toward Scaling-Up Smart Hydrogel Microvalves

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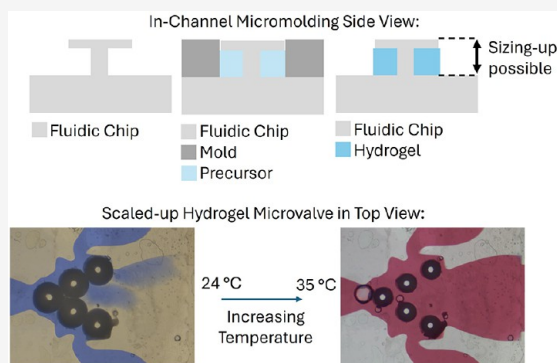


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ABSTRACT: Smart hydrogel valves are a promising technology for autonomous process control. At the macroscale, hydrogel valves offer high flow rates with slow response times, whereas hydrogel microvalves offer low flow rates with fast response times. This contradiction limits the practical applicability of these valves, particularly in industry. Scaling-up refers to the process of transferring the benefits and results of microfluidics from the laboratory scale to the production scale. In this paper, we present advanced fabrication methods and corresponding promising concepts toward scaling-up responsive hydrogel microvalves to achieve higher throughput while maintaining fast response times. Using selective laser-induced etching (SLE), precise three-dimensional (3D) microfluidic structures and corresponding molds can be produced from fused silica, allowing hydrogel to be molded and anchored directly within the microchannel. This method enables the sizing-up of hydrogel microstructures in both horizontal and vertical directions. The influence of this scaling, in the form of various hydrogel dimensions up to 1500 μm , was investigated with regard to their suitability for an autonomous hydrogel valve. As a proof-of-principle, three hydrogel valves with different depths were fabricated using this method, whereby the response time decreases with increasing depth while the flow rate is increased simultaneously.



INTRODUCTION

Stimuli-responsive hydrogels can undergo significant volume changes in response to variations in environmental conditions, such as temperature or pH. Consequently, they are capable of responding autonomously to specific stimuli without the need for external control.^{1,2} This has enabled a wide range of applications in recent years, such as in medical technology for drug release,^{3,4} but also in reactor technology for autonomous process control.^{5,6}

Process intensification and the associated adaptive components in reactor technology are an important part of the ongoing transformation from the use of fossil to renewable raw materials in the chemical value chain.⁷ As energy-autonomous actuators without the need for external control, hydrogels can influence the process flow in a self-regulating manner, allowing the manufacturing of smart actuators that can respond to fluctuating parameters.⁶ One well-studied thermoresponsive hydrogel is poly-*N*-isopropylacrylamide (pNIPAM). This smart hydrogel undergoes a volume phase transition (VPT) in response to changes in temperature. Below the lower critical solution temperature (LCST), it can absorb water into the polymer matrix inducing swelling, while exceeding the

temperature beyond the LCST induces the collapsing of the structure with water expulsion.⁸

Due to the diffusion-limited mass transport within the gel matrix, stimuli-responsive hydrogels have been used primarily in microsystems actuators for fast response due to short diffusive pathways, for example in the form of microvalves. Responsiveness is a fundamental parameter for valves and, due to transport limitations, is highly dependent on the dimensions of the valve. Response times in the range of seconds have been demonstrated for microfabricated hydrogel valves: Beebe et al. demonstrated the production of various pH-responsive microvalves, which were manufactured using in situ photopolymerization in channels of 50 μm to 200 μm in depth and are characterized by response times of less than 10 s. In this manufacturing process, the precursor solution is applied into a closed microchannel, a specific structure is polymerized

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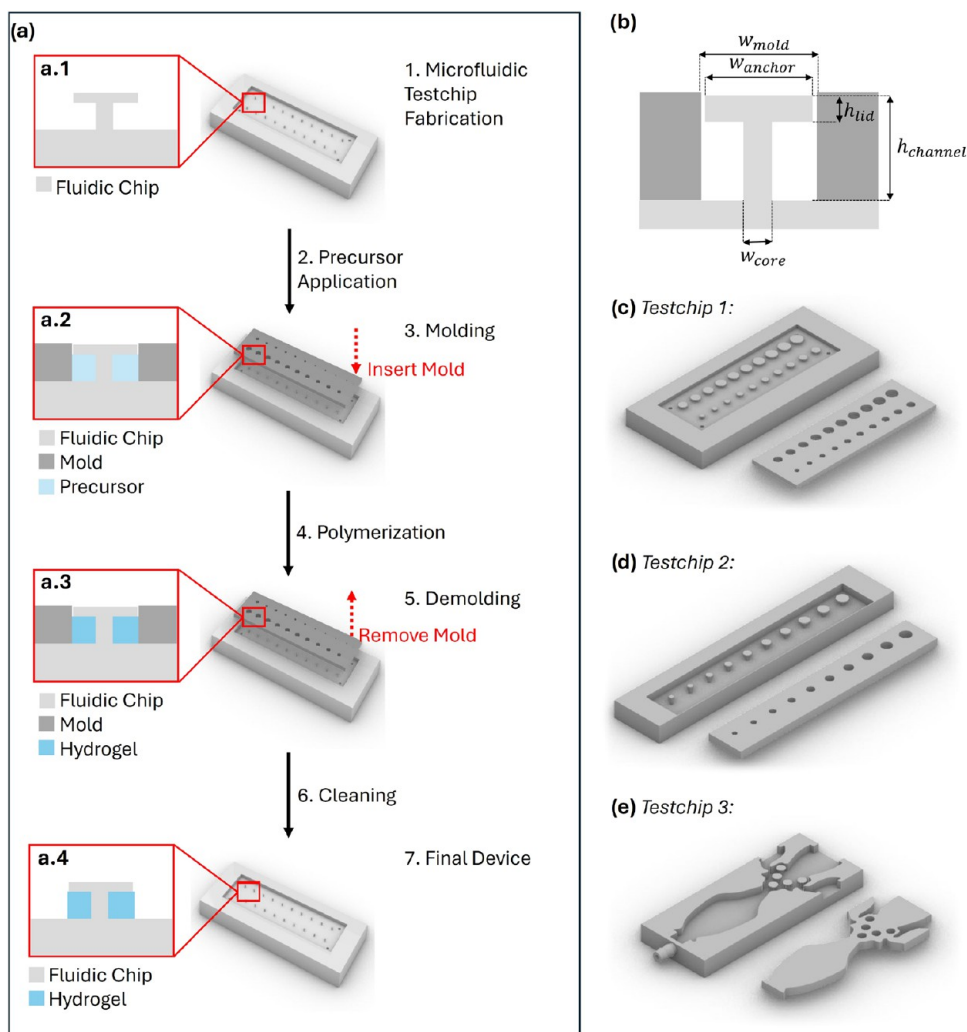


Figure 1. Process flow of the in-channel molding (a) with details in a 2D side view (a.1–a.4): SLE-fabricated microfluidic chip with anchor structures (a.1), applied precursor and shaped using a precise mold (a.2), polymerization of the precursor (a.3) and removal of the mold (a.4). Cross-sectional view of the anchor structure and mold (b). Designs of the three testchips: *testchip 1* and corresponding mold for top view experiments (c), *testchip 2* and corresponding mold for side view experiments (d) and *testchip 3* and corresponding mold for valve application (e).

using a mask and UV light. Subsequently, the unpolymerized remaining solution is flushed from the channel. Pillar structures were used as anchors to improve the stability of the hydrogel structures within the channel. In Serksen et al. the same manufacturing principle was used for a light-responsive hydrogel with the same channel depths, achieving response times of 4 s.¹⁰ Sugiura et al. also successfully demonstrated the same manufacturing process in a channel depth of 100 μm for light-responsive hydrogels with response times of 18–30 s and for thermoresponsive hydrogels with response times of 5 s, respectively.¹¹

Despite their different designs, the microvalves mentioned above, as well as other examples,^{12–14} are based on in situ photolithography as a manufacturing method. Other hydrogel microvalves have been demonstrated that use alternatives to masks for in situ polymerization.^{15,16} Nevertheless, the depth of the microfabricated hydrogels is limited to 100–200 μm . Especially when using mask-based photolithography, the maximum depth is typically limited by the divergence of light resulting in a tapered profile.⁹ This also highlights the biggest restriction in lithography-based manufacturing in terms of achievable volume flow: the short response time of the

valves conflicts with the maximum achievable volume flow. In macroscopic hydrogel valves, the achievable throughput is significantly higher, but so are the response times.⁶ However, for the application of hydrogel valves as adaptive components in reactor technology, both a short response time and a high achievable throughput are crucial factors.

Further possibilities for microfabricating hydrogels have been well summarized by Beck et al. and Yanagawa et al. and, in addition to lithography, divided into the following methods: (i) microgel synthesis, (ii) 3D printing, and (iii) micro-molding.¹⁸ However, for applications as hydrogel valves, not only the microfabrication capabilities but also the integration of the valves into microfluidic systems is relevant. In microgel synthesis, this integration must be carried out manually in a subsequent process step,^{19,20} which complicates microvalves manufacturing. With 3D printing, in particular two-photon-polymerization (2PP) as a method with a resolution in the low micrometer range,²¹ complex 3D geometries can be realized for hydrogels. However, compared to lithography, the 2PP process poses special requirements for the hydrogel precursor, such as the need for a photoinitiator and consideration of the adhesion of the layer-by-layer fabrication method. In micro-

molding, on the other hand, the precursor can be polymerized in various ways, which means that the hydrogel synthesis is more diverse and can also be optimized for the application rather than the polymerization process. However, to our knowledge no responsive hydrogel microvalves based on 2PP or micromolding have been found in the literature.¹⁷ This can be explained by the special requirements for the hydrogel precursor in 2PP and the difficulty of integration into microfluidics for micromolding. Since the mold must be removed after polymerization and it is useful to anchor the hydrogel structures,⁹ integration is more difficult when using traditional microsystem technology methods, which are limited to 2.5D.²²

Trieu et al. have demonstrated new approaches for complex microfabrication with their 3D toolbox for microelectromechanical systems (MEMS). This toolbox combines the advantages of 3D printing and methods from traditional semiconductor technology to realize more complex manufacturing processes and systems. In particular, they refer to the process of selective laser-induced etching (SLE), which has already been demonstrated for the fabrication of complex 3D microstructures in fused silica.²³ Furthermore, the SLE process can be used to fabricate structures within substrates several millimeters thick,²³ which represents a significant advantage over conventional semiconductor and microsystem fabrication technologies. Both microfluidic systems^{23,24} and micromolds²⁵ have already been realized using this process. Trieu et al. claim with their toolbox that these advantages can be exploited and integrated into the iterative process flow of traditional semiconductor technology and microsystem technology for the realization of a new class of complex 3D MEMS. In particular, new approaches for scaling-up can be pursued for applications in microfluidics and for the design of hydrogel microvalves. When introducing microfluidics to industrial applications, scaling-up is the process of transferring the benefits and results from the laboratory scale to the production scale. Strategies for this process include numbering-up by increasing the channel number and sizing-up by increasing the channel length or diameter.²⁶

The aim of this work is to use SLE as an innovative 3D microfabrication technology to develop an advanced manufacturing process for the in-channel molding and integration of responsive hydrogels and to investigate the scalability of structures manufactured using this process. The approach of scaling-up is pursued by sizing-up the aspect ratio while maintaining the dimensions of the structures in the lateral direction. To this end, we will analyze the dimensional accuracy of the fabrication process and how varying the dimensions of responsive hydrogel cylinders affects the response times. As a proof of concept demonstrating the feasibility of this manufacturing process for temperature-responsive structures, the prior results are transferred to a hydrogel valve to investigate how the throughput can be increased while maintaining a short response time.

EXPERIMENTAL SECTION

To realize the hydrogel microstructures, this work presents an in-channel micromolding approach that combines the advantages of traditional micromolding and novel 3D microfabrication processes. Figure 1 (a) provides an overview of the fundamental process flow for manufacturing the responsive hydrogel structures in-channel. The necessary materials and manufacturing methods are described in more detail in the following subsections.

In a first step, a fluidic lidless microstructure with anchor structures is manufactured, as shown in Figure 1 (a.1). The precursor is then filled into the channel and distributed by a precisely designed micromold structure so that it is only located in the intended area around the anchor structure and is displaced in the later cavities, as shown in Figure 1 (a.2). In a next step, the structured precursor is then polymerized (Figure 1 a.3) and finally the mold is removed and the structure is cleaned of any hydrogel residues, with a resulting structure depicted in Figure 1 (a.4).

Design

In this study, the stimulus-responsive hydrogel components are each manufactured as hollow cylinders around the T-shaped, rotation-symmetrical anchor structure surrounded by a cylindrical mold, as shown in the cross-section in Figure 1 (b). The thickness of the anchor cover is $h_{\text{lid}} = 150 \mu\text{m}$ and the diameter of the anchor cylinder is $w_{\text{core}} = 360 \mu\text{m}$, both dimensions are the same for all samples manufactured. The diameter and height of the molded hollow cylinders vary depending on the experiment. The diameters of the cylindrical molds are increased by $50 \mu\text{m}$ compared to the corresponding anchor diameters.

To investigate the responsive behavior dependent on the cylinder diameter and the aspect ratio, respectively, two different testchips are designed. Figure 1 (c) illustrates *testchip 1*, that can be used in top view to analyze the influence of cylinder diameters from $w_{\text{anchor}} = 600 \mu\text{m}$ to $1550 \mu\text{m}$ at a channel depth of $h_{\text{channel}} = 500 \mu\text{m}$. *Testchip 2*, depicted in Figure 1 (d), can be used in side view to examine the impact of different channel depths varied from $h_{\text{channel}} = 500 \mu\text{m}$ to $1000 \mu\text{m}$ with cylinder diameters from $w_{\text{anchor}} = 600 \mu\text{m}$ to $1500 \mu\text{m}$. Furthermore, to demonstrate the feasibility of the in-channel micromolding process and the scaling-up strategy for a hydrogel valve, *testchip 3* is designed. Figure 1 (e) shows the valve in form of a bypass configuration. The design is developed and optimized using a finite element analysis simulation (COMSOL Multiphysics 6.3) toward efficient fluid exchange and efficient flushing of the hydrogel structures. The five hydrogel cylinders in the valve design each have a diameter of $w_{\text{anchor}} = 1100 \mu\text{m}$ and the channel depth is varied from $h_{\text{channel}} = 500 \mu\text{m}$ to $1500 \mu\text{m}$. A major advantage of this valve design, fabricated using SLE, is the ability to size-up in the vertical direction, and thus also to size-up the in-channel molded hydrogel structures. The channel cross-section of the valve can thus be increased without altering the design in the horizontal direction and, consequently, without affecting the characteristic distance of the transport processes within the hydrogel in the horizontal direction. The dimensions of all designed structures are summarized in Table 1.

Table 1. Dimensions of the Microfluidic Channel and the Anchor Structure of the Three Testchips

chip	dimension	value
Testchip 1 (top view)	h_{lid}	$150 \mu\text{m}$
	w_{core}	$360 \mu\text{m}$
	h_{channel}	$500 \mu\text{m}$
	w_{anchor}	$600 \mu\text{m} - 1550 \mu\text{m}$
	w_{mold}	$650 \mu\text{m} - 1600 \mu\text{m}$
Testchip 2 (side view)	h_{lid}	$150 \mu\text{m}$
	w_{core}	$360 \mu\text{m}$
	h_{channel}	$500 \mu\text{m}, 1000 \mu\text{m}$
	w_{anchor}	$600 \mu\text{m} - 1500 \mu\text{m}$
	w_{mold}	$650 \mu\text{m} - 1550 \mu\text{m}$
Testchip 3 (valve)	h_{lid}	$150 \mu\text{m}$
	w_{core}	$360 \mu\text{m}$
	h_{channel}	$500 \mu\text{m}, 1000 \mu\text{m}, 1500 \mu\text{m}$
	w_{anchor}	$1100 \mu\text{m}$
	w_{mold}	$1150 \mu\text{m}$

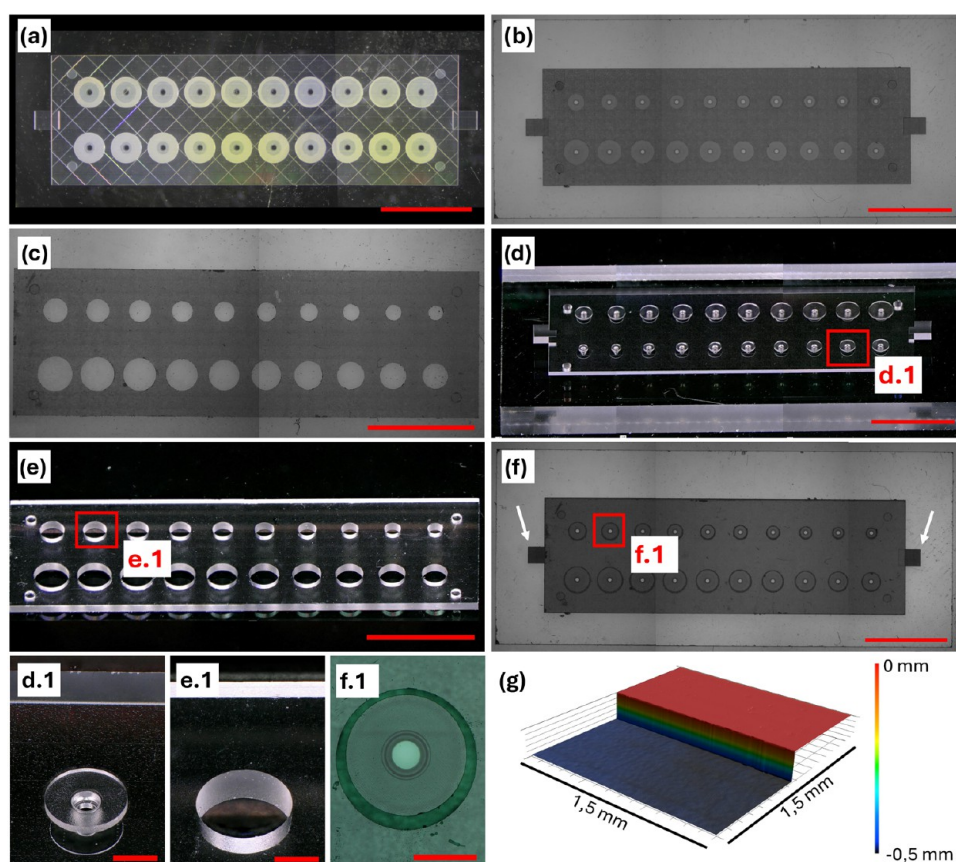


Figure 2. Intermediate steps of the fabricated samples: Femtosecond laser modified fused silica *testchip 1* with illuminated areas appear opaque (a), etched fused silica structure *testchip 1* in top view (b) and 45° tilted side view (c), etched fused silica molding structure corresponding to *testchip 1* in top view (d) and 45° tilted side view (e). Mold inserted into the *testchip 1* with visible constant gap by design and due to overetching (f) with white arrows indicating recesses for easier removal of the mold. The indicated details in (d–f) are depicted in enlarged form in (d.1–f.1): Designed 1 mm anchor structure in 45° tilted view (d.1), corresponding cylindrical mold in 45° tilted view (e.1) and mold inserted in *testchip 1* in top view (f.1). Profilometer measurement of the fluidic channel height of *testchip 1* (g). Scalebars correspond to 5 mm in (a–f) and 500 μm in (d.1–f.1).

Selective Laser-Induced Etching

The process flow shown in Figure 1 (a) requires a precise fit of the micromold within the fluidic structure. Additive manufacturing is known to be less accurate than subtractive manufacturing, even though it can achieve a greater complexity.^{27,28} The higher accuracy in subtractive manufacturing can be explained by the fact that material integrity is maintained during production, while material is selectively removed from a homogeneous bulk substrate. In typical additive layer-by-layer manufacturing, on the other hand, the material can shrink and exhibit mechanical weaknesses or stresses.^{27,28} Consequently, despite the ongoing successes of additive manufacturing, subtractive manufacturing is commonly used for micromold fabrication, as shown by von Pöblitzki et al., for example. For the process presented here, subtractive selective laser-induced etching is an ideal method for the fabrication of fluidics and molds.

The SLE process itself can be considered a two-step process that can be used to subtractively microfabricate transparent materials. Fused silica (*virgin polished grade*, Toppan Photomask Inc.) is used as the starting material for the structures manufactured here. With the help of a Lightfab 3D printer (Lightfab GmbH, Germany), the fused silica is selectively modified in the laser voxel using a femtosecond laser and strong focusing of the laser beam (20x lens, 0.4 NA). In the modified area, multiphoton absorption creates nanogratings, which lead to high chemical etchability compared to unexposed areas.²⁹ The process parameters used in this work are a laser wavelength of 1030 nm at a frequency of 750 kHz, a pulse duration of 0.5 ps, a pulse energy of 300 nJ, and a writing speed of 200 mm/s. The modified areas are slightly opaque, as visualized in Figure 2 (a). In a second step, the fused silica structures are then etched at 82 °C in 8 mol/L

potassium hydroxide in an ultrasonic bath, where selectivities of up to 1400 can be achieved.²³ In order to etch the modified structures, they must be in contact with the surface. After an etching process of approximately 36 h, the final structures are created, as shown for *testchip 1* in Figure 2 (b–e). A top view of *testchip 1* and the corresponding mold are shown in Figure 2 (b,c), respectively. To illustrate the 3D geometry, *testchip 1* and the mold are shown in a tilted view in Figure 2 (d,e), respectively, with enlarged views of the indicated details in Figure 2 (d.1, e.1). The close-ups illustrate the anchor geometry with a designed diameter of 1 mm (d.1) and the corresponding cylindrical mold with a designed diameter of 1.05 mm (e.1). Since the unmodified fused silica substrate is also etched at approximately 300 nm/h,²³ constant overetching can be found on all contact surfaces of the fluidic structure and mold. This is advantageous in order to allow the mold to be inserted and removed more easily. The uniform overetching, combined with the designed offset between the anchor and mold diameters, results in a constant gap between the *testchip 1* and the mold. Figure 2 (f.1) shows a close-up of the indicated detail in Figure 2 (f), providing a clearer view of the gap of approximately 75 μm . A slight misalignment of the mold relative to the anchor is visible, but this does not affect the analysis or functionality, as this misalignment is identical for all cylinders. The confinement of the hydrogel precursor during the polymerization and thus the determination of the hydrogel cylinder dimensions and position is defined by the mold, ensuring that all cylinders on the chip are aligned relative to one another without misalignment. To verify the dimensions in the vertical direction, the height profile was measured using a profilometer (Keyence VK-X3000, Keyence Corporation, Japan) as shown in Figure 2 (g). The step height

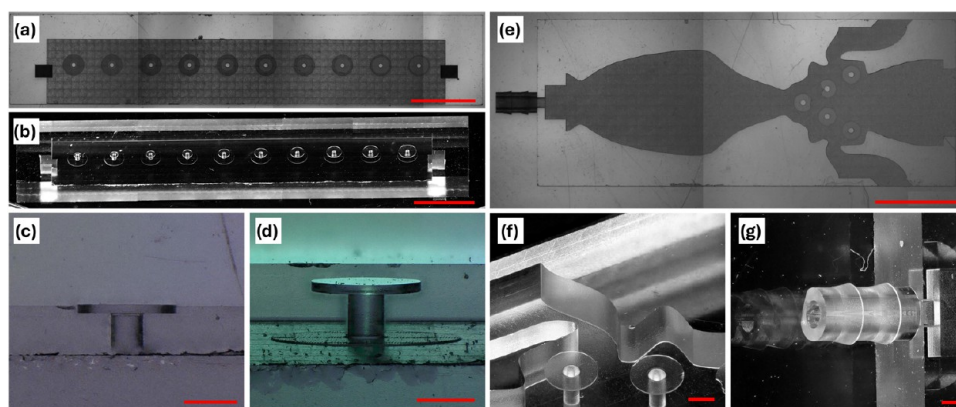


Figure 3. Fabricated fused silica *testchip 2* and *testchip 3*: Etched fused silica structure *testchip 2* in top view (a) and 45° tilted side view (b) with magnified tilted view of designed 1 mm diameter anchor structure in cross section (c) and tilted view (d) in a channel depth of 500 μm . Etched fused silica structure *testchip 3* in top view (e) with enlarged tilted view of anchor structures inside the fluidic channel (f) and the 3D tubing connection (g). Scalebars correspond to 5 mm in (a, b, e) and 500 μm in (c, d, f, g).

corresponds to the design specification of 500 μm , and additionally a surface roughness of $R_a = 0.8 \mu\text{m}$ was observed on the etched surface.

In addition, Figure 3 shows the fluidic structures of *testchip 2* and *testchip 3*. Figure 3 (a, b) show *testchip 2* in its entirety from a top view and tilted view, respectively. Enlarged views of the anchor structure with a designed diameter of 1 mm are shown in Figure 3 (c) (side view) and in Figure 3 (d) (10° tilt from side view), illustrating the precision and dimensional accuracy of the subtractive SLE process. In addition to the controllable overetching, there is no subsequent shrinkage or distortion caused by fabrication-related internal stresses. Details regarding dimensional precision are listed in Table 4 in a later section. Figure 3 (e) shows a top view of *testchip 3*, including the five anchor structures and a tubing connection on the left side for connecting a syringe pump. The enlarged view in Figure 3 (f) shows two of the anchor structures in a tilted view in relation to the channel sidewall. Figure 3 (g) depicts an enlarged view of the tubing connection, illustrating the possibilities for complex 3D patterning in the SLE process.

Precursor

A *N*-isopropylacrylamide (NIPAM)-based solution is prepared for the synthesis of the hydrogel precursor solution. The detailed formulation is shown in Table 2. After preparation, the solution is homogenized

Table 2. Final Formulation of the Hydrogel

material	amount	purity
<i>N</i> -isopropylacrylamid (NIPAM)	400 mg	≥98%
<i>N,N'</i> -methylenebisacrylamid (MBA)	10 mg	99%
diphenyl(2,4,6-trimethylbenzoyl)phosphinoxid (TPO-L)	2 mg	≥99%
triethylenglykol (TEG)	450 μL	99%
H ₂ O	450 μL	–

using a stirrer-heater plate (IKA C-MaG HS4, IKA-Werke GmbH & Co. KG, Germany) for 30 min at 30 °C and 1500 rpm. In addition, the solution is bubbled for 15 min with nitrogen to degas oxygen. This work does not focus on the investigation and optimization of the hydrogel formulation, but rather on the design and molding process. Research on hydrogel optimization is being conducted at the coauthors' institute, as described for example by Eckert et al.³⁰

Polymerization and Postprocessing

After dispensing the precursor solution into the fluidic structure and inserting the mold, the structure is placed in a UV radiation chamber (Hoenle LED Cube 100 IC, Hoenle AG, Germany) for polymerization and exposed to a wavelength of 365 nm for 40 s at 50% power (=300 mW/cm²). Due to the very low adhesion between fused silica and the pNIPAM, the mold can be easily lifted off using tweezers. For

easier handling, recesses for the tweezers were designed into the structures, as can be seen in Figure 2 (f).

After molding and polymerization, remaining precursor and hydrogel residues are removed by rinsing with distilled water. Final fluidic structures with in-channel molded hydrogel cylinders are depicted in Figure 4 with *testchip 1* in (a–c), magnified view of *testchip 2* with 500 μm and 1000 μm height in (d–g) and *testchip 3* in (h). In some of the molded cylinders, hydrogel fragments from the molding process are visible (for example the light-colored, irregular edge segments on the left cylinder in Figure 4 f). Due to capillary forces, the precursor can flow underneath the mold and polymerize there. During the demolding and cleaning, some residuals remain, but these do not impact the performance and are therefore not considered further. In Figure 4 (g), the side view shows that these fragments are only a few micrometers in thickness.

In case of the *testchip 3*, a 1 mm thick fused silica cover plate is additionally glued to close the open-top fluidic structure. A more sustainable option for attaching a cover in the case of fused silica is precise laser welding using a femtosecond laser.³¹ Prior to all experiments, the prepared samples undergo an initial preswelling process. The samples are first left to swell in H₂O at 23 °C, then heated once above the critical temperature and swelled again for 24 h at 23 °C to remove unstable polymer chains and solvent residues.

Measurement Setup and Data Processing

The samples were examined optically in all experiments using a stereomicroscope (Zeiss Stemi 305, Carl Zeiss Microscopy Deutschland GmbH, Germany). As shown in the measurement setup in Figure 4 (i), *testchip 1* and *testchip 2* are placed in a beaker with H₂O at fixed filling height. This beaker is placed in a water bath, which is heated by a hot plate and the temperature is measured by a thermometer. To examine the valve designs in *testchip 3*, the setup is slightly modified by removing the beaker and pumping the tempered H₂O through the valve using a syringe pump. The syringe and supply lines are insulated to minimize temperature fluctuations.

The images and videos recorded are then processed using MATLAB (Mathworks Inc., USA). The basic workflow is shown in Figure 4 (j). First, the raw data are imported into MATLAB, then the regions of interest are cropped and the image data are converted to black-and-white images. The threshold for the binarization of the image data is determined for each image to reduce the influence of fluctuating brightness. The diameters of the hydrogel cylinders are extracted from the binary images, and the resulting area $A(T, t)$ is then calculated as a function of temperature or time for different hydrogel dimensions. The degree of swelling is determined using eq 1, where A_0 represents the area in the swollen state. An absolute change in area ΔA_{abs} is determined using eq 2. Furthermore, the change in surface area of a stimuli-responsive hydrogel can be described using a sigmoid function model.³² Equation 3 is used here to fit the

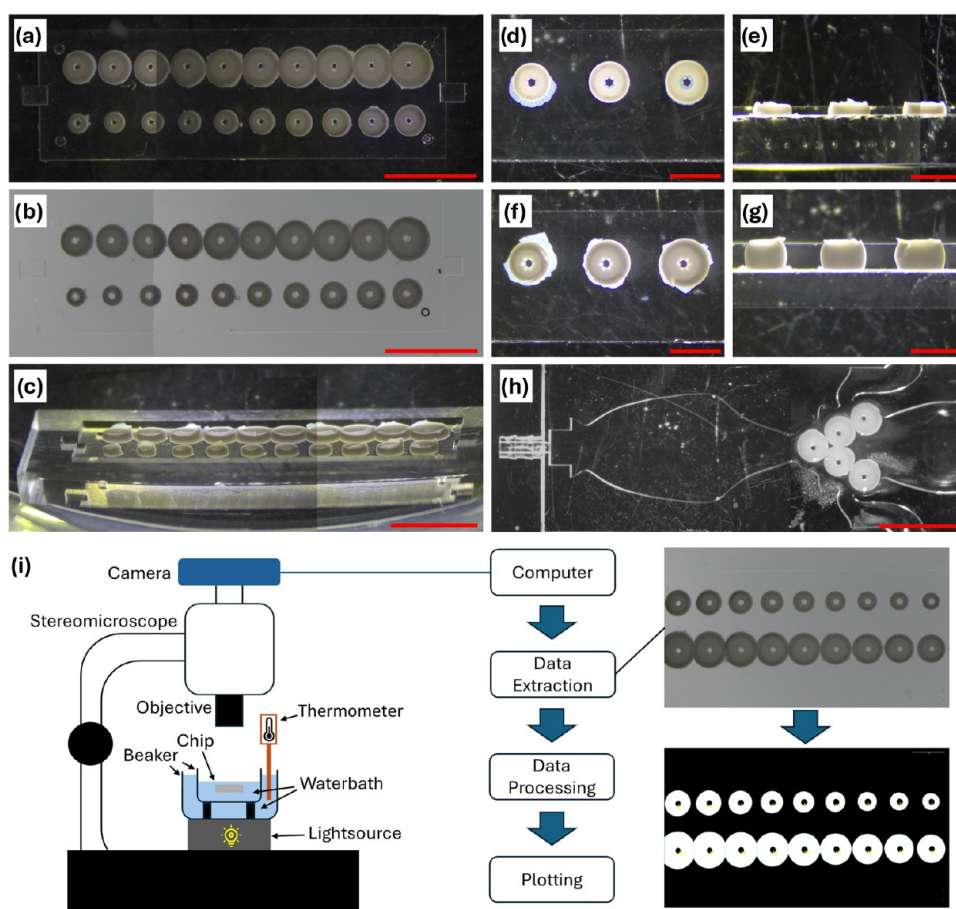


Figure 4. Final fluidic structures with in-channel molded hydrogel cylinders and measurement setup. *Testchip 1* in top view with hydrogel cylinders in swollen state in oblique illumination (a) and brightfield (b) and in tilted view (c). Top view (d) and side view (e) of the hydrogel cylinders in swollen state with designed anchor diameters of 1 mm, 1.1 mm, and 1.2 mm (left to right) on *testchip 2* with a depth of 500 μm . Top view (f) and side view (g) of the hydrogel cylinders in swollen state with designed anchor diameters of 1 mm, 1.1 mm, and 1.2 mm (left to right) on *testchip 2* with a depth of 1000 μm . Top view of *testchip 3* with hydrogel cylinders in swollen state resulting in a closed valve (h). Measurement setup for the experiments (i) with the testchips aligned in a tempered water bath. A camera connected to a stereomicroscope captures pictures and videos of the experiments and the data are then analyzed on a computer. Scalebars correspond to 5 mm in (a–c) and (h) and 2 mm in (d–g).

experimental data and evaluate the swelling behavior. A_{low} and A_{high} describe the surface areas below and above VPT, respectively, T_c is the critical transition temperature representing the inflection point of the sigmoid function and k is a slope parameter.

$$SR_A(T, t) = \frac{A(T, t)}{A_0} \quad (1)$$

$$\Delta A_{\text{abs}} = A_0 - A(T, t) \quad (2)$$

$$A(T) = A_{\text{low}} + \frac{A_{\text{high}} - A_{\text{low}}}{1 + \exp(-k(T - T_c))} \quad (3)$$

RESULTS AND DISCUSSION

The experiments using the materials and methods listed above are divided into three parts: temperature response of the hydrogel cylinders to evaluate the swelling behavior, time response of the hydrogel cylinders and the functionality as a hydrogel valve. To determine temperature response, *testchip 1* is used with all molded hydrogel cylinders. To examine the time response, a selection of cylinders listed in Table 3 is used in *testchip 1* and *testchip 2* to provide a clearer overview.

Prior to these experiments, the selected cylinders were examined with regard to dimensional accuracy in the SLE

Table 3. Selected Hydrogel Cylinder Dimensions Used for Dimensional Accuracy Characterization and Time Response Experiments

Testchip1 (top view)			
#cylinder	w anchor design	w mold design	
1	800 μm	850 μm	
2	900 μm	950 μm	
3	1000 μm	1050 μm	
4	1250 μm	1300 μm	
5	1350 μm	1400 μm	
6	1450 μm	1500 μm	
Testchip2 (side view)			
#cylinder	w anchor design	w mold design	h_{channel}
7	1100 μm	1150 μm	500 μm
8	1100 μm	1150 μm	1000 μm

process and the molding process. For the SLE process, the diameters of the anchor structures and the diameters of the molds were optically characterized for each of the listed cylinder dimensions with a sample size of $n = 3$ using an optical profilometer (Keyence VK-X3000, Keyence Corporation, Japan). The mean values, including standard deviations, are listed in

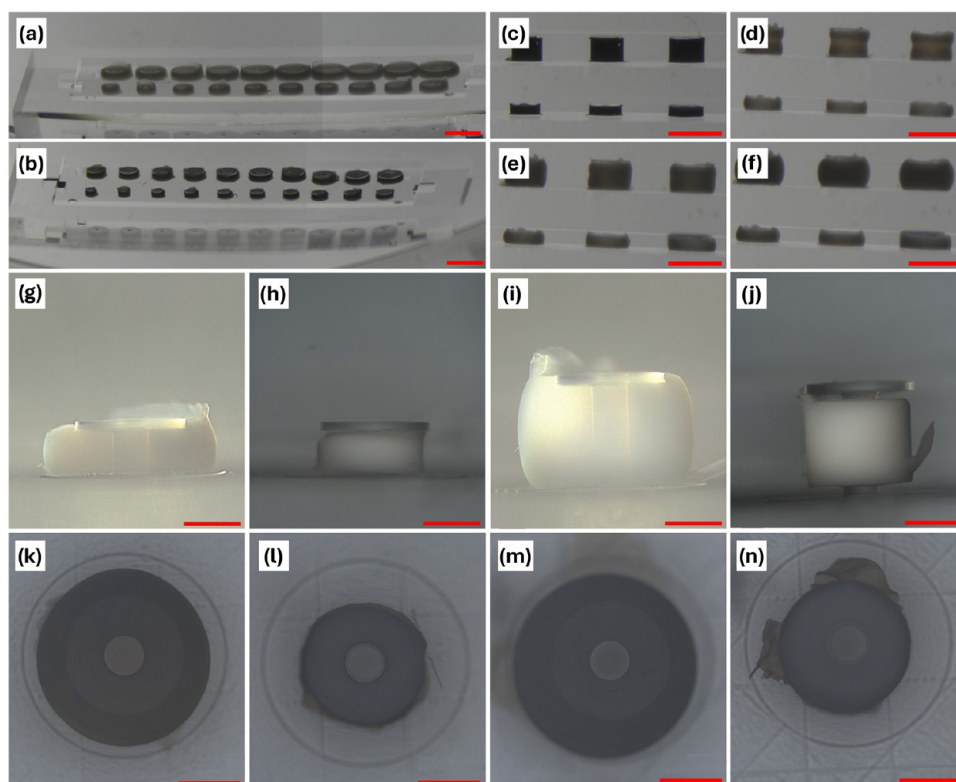


Figure 5. Temperature behavior of the hydrogel cylinders. *Testchip 1* in swollen (a) and shrunken (b) state at tilted view. *Testchip 2* in side view (designed anchor diameters of 1 mm, 1.1 mm, and 1.2 mm (left to right) at channel heights of 500 μm and 1000 μm) during the swelling process due to an abrupt temperature decrease from 40 $^{\circ}\text{C}$ to 23 $^{\circ}\text{C}$ (c–f). Side view of hydrogel cylinder with designed anchor diameter of 1 mm at a channel height of 500 μm in swollen state at 24 $^{\circ}\text{C}$ (g) and shrunken state at 40 $^{\circ}\text{C}$ (h) and at a channel height of 1000 μm in swollen state at 24 $^{\circ}\text{C}$ (i) and shrunken state at 40 $^{\circ}\text{C}$ (j). Top view of hydrogel cylinder with designed anchor diameter of 1 mm at a channel height of 500 μm in swollen state at 24 $^{\circ}\text{C}$ (k) and shrunken state at 40 $^{\circ}\text{C}$ (l) and at a channel height of 1000 μm in swollen state at 24 $^{\circ}\text{C}$ (m) and shrunken state at 40 $^{\circ}\text{C}$ (n). For comparison purposes, the focus is always set to the top of the anchor structure in (k–n). Scalebars correspond to 2 mm in (a–f) and 500 μm in (g–n).

Table 4. Overetching is evident as a constant offset between designed and fabricated dimensions, and the standard deviations are in the range of a few micrometers, which overall indicates high precision and repeatability. To determine the accuracy of the molding process, the diameters of the hydrogel cylinders in the swollen state at 23 $^{\circ}\text{C}$ and in the shrunken state at 35 $^{\circ}\text{C}$ were analyzed with a sample size of $n = 3$, and the results are also listed in Table 4. After the polymerization prior to demolding, the diameters of the hydrogel cylinders correspond to the diameters of the molds. After the initial swelling, the diameters increase by a factor of 1.48 ± 0.01 at a channel depth of 500 μm , regardless of the absolute diameter. In the shrunken state, the cylinder diameters approach the diameters of the molds. This demonstrates that the cylinders can be fabricated quite precisely and reproducibly using the presented in-channel molding. The standard deviations are slightly higher than that of the SLE process, which can be attributed to minor deviations in the hydrogel dimensions due to measurement inaccuracies in temperature, friction of the hydrogel against the surface roughness of the etched glass, and the lower optical resolution of the microscope in the experimental setup compared to the profilometer used for SLE process characterization.

Figure 5 illustrates the temperature behavior of the hydrogel cylinders. *Testchip 1* is shown in a tilted view in its swollen state (Figure 5 a) and in its shrunken state (Figure 5 b). The

side views of *testchip 2* in Figure 5 (c–f) show the hydrogel cylinders with designed anchor diameters of 1 mm, 1.1 mm and 1.2 mm at channel heights of 500 μm and 1000 μm during the swelling process in response to an abrupt temperature decrease from 40 $^{\circ}\text{C}$ to 23 $^{\circ}\text{C}$. The vertical side walls in the shrunken state and the bulging side walls in the swollen state are visible. A comparison between the two channel heights shows that the taller hydrogel cylinder swells slowest in the center, because there is less contact area with the surrounding medium. Figure 5 (g–n) show the hydrogel cylinder with a designed anchor diameter of 1 mm in side view and top view at heights of 500 μm and 1000 μm at 24 $^{\circ}\text{C}$ in the swollen state and at 40 $^{\circ}\text{C}$ in the shrunken state. The anchor structure is particularly visible relative to the swollen and shrunken volumes, as the hydrogel is slightly transparent in the swollen state. At a channel height of 1000 μm , the bulge of the cylinder in the swollen state is even more prominent compared to the cylinder in the 500 μm channel, causing the diameter in the top view to increase slightly for taller cylinders. In the top view pictures, the top lid of the anchor structure is in focus so that it can be used as a reference area. In the swollen state, the initial swelling after molding, as determined in Table 4, can be seen in relation to the anchor structure. In the shrunken state at 40 $^{\circ}\text{C}$, the cylinder diameter approximately matches the diameter of the anchor structure.

Table 4. Results of the Characterization of Dimensional Accuracy of the SLE Process and the Molding Process for Selected Hydrogel Cylinder Dimensions

Testchip1 (top view) - precision SLE process		
#cylinder	w anchor fabricated ($n = 3$)	w mold fabricated ($n = 3$)
1	749.1 $\pm$ 4.4 μm	909.3 $\pm$ 2.1 μm
2	848.6 $\pm$ 4.1 μm	1008.6 $\pm$ 0.8 μm
3	948.3 $\pm$ 3.9 μm	1109.0 $\pm$ 1.4 μm
4	1199.1 $\pm$ 3.5 μm	1359.8 $\pm$ 0.8 μm
5	1299.6 $\pm$ 4.9 μm	1457.5 $\pm$ 3.2 μm
6	1398.6 $\pm$ 4.2 μm	1563.0 $\pm$ 4.2 μm
Testchip1 (top view) - precision molding process		
#cylinder	w hydrogel cylinder after initial swelling at 23 $^{\circ}\text{C}$ ($n = 3$)	w hydrogel cylinder at 35 $^{\circ}\text{C}$ ($n = 3$)
1	1343.6 $\pm$ 23.8 μm	962.9 $\pm$ 9.4 μm
2	1488.4 $\pm$ 14.4 μm	1038.4 $\pm$ 16.4 μm
3	1642.6 $\pm$ 9.4 μm	1159.1 $\pm$ 11.9 μm
4	2026.5 $\pm$ 14.4 μm	1425.4 $\pm$ 16.4 μm
5	2142.9 $\pm$ 16.4 μm	1504.1 $\pm$ 19.7 μm
6	2297.1 $\pm$ 19.7 μm	1601.7 $\pm$ 14.4 μm

Temperature Response (Swelling and Shrinkage)

To investigate the temperature response of the hydrogel cylinders, *testchip 1* (top view) is initially used and the temperature in the water bath is gradually increased in 1 $^{\circ}\text{C}$ increments from 24 $^{\circ}\text{C}$ to 37 $^{\circ}\text{C}$. After the temperature has stabilized at each set point, an additional 3 min waiting period is observed before a photo is taken. This measurement was performed 3 times and the results of all cylinder dimensions were used for the evaluation. Figure 6 (a) shows the results of the temperature-dependent swelling ratio and the sigmoid fit function with the corresponding values of the fit in Table 5. The fit determines a critical transition temperature of $T_C = 30.06$ $^{\circ}\text{C}$ and represents the experimental analysis well ($R^2 = 0.9958$) with larger deviations occurring only in the region of the critical temperature. This can be explained by a greater influence of measurement inaccuracies in this range, as the strongest swelling behavior occurs in a region of only a few degrees Celsius. Regardless of the diameter of the hydrogel cylinder, comparable results are achieved in the degree of swelling of approximately 45% relative to the swollen state (24

Table 5. Fitted Parameters of the Sigmoid Function Model

A_{low}	A_{high}	T_C [$^{\circ}\text{C}$]	R^2/RMSE
0.9689	0.4418	30.06	0.9958/0.0170

$^{\circ}\text{C}$), although the absolute change in area differs significantly. Consequently, the diameter of the hydrogel cylinders have no noticeable influence on the temperature behavior of the hydrogels within these dimensions using this manufacturing method. This result is expected as the hydrogel diameter does not influence its responsiveness, which is primarily governed by the hydrogel composition.

Furthermore, to provide an initial estimation of the repeatability of the swelling ratio under temperature changes, *testchip 1* was heated to 40 $^{\circ}\text{C}$ and then cooled back to 23 $^{\circ}\text{C}$ in three alternating cycles. The averaged swelling ratios in the swollen and shrunken states and the corresponding standard deviations across the selected hydrogel cylinders from Table 3 are shown in Figure 3 (b). Good repeatability can be observed during the first cycles.

Time Response

To investigate the response kinetic of the hydrogel structures, *testchip 1* and *testchip 2* were abruptly placed in a water bath at 40 $^{\circ}\text{C}$ in their swollen state and a video was recorded. In reverse, the hydrogel was also abruptly placed in a water bath of 23 $^{\circ}\text{C}$ in its shrunken state. For a clearer overview of the results, only the selected fabricated geometries summarized in Table 3 are shown. It is important to note that the precise starting time is difficult to determine in this experimental setup, as movements of the water bath when the samples are placed inside cause the image to blur. Furthermore, the absolute change in area is not necessarily identical to the real change in area, as the extracted values depend on a specified threshold during the binarization of the image. Consequently, repeated measurements are difficult to compare, even if they show a similar trend. However, it is reasonable to compare the results on a single testchip.

Figure 7 (a) shows the step response of the hydrogel cylinders of different diameters in top view (*testchip 1*) to an abrupt temperature increase. Since the relative swelling ratio in this dimension range is approximately identical for all diameters, the maximum achievable absolute change in surface

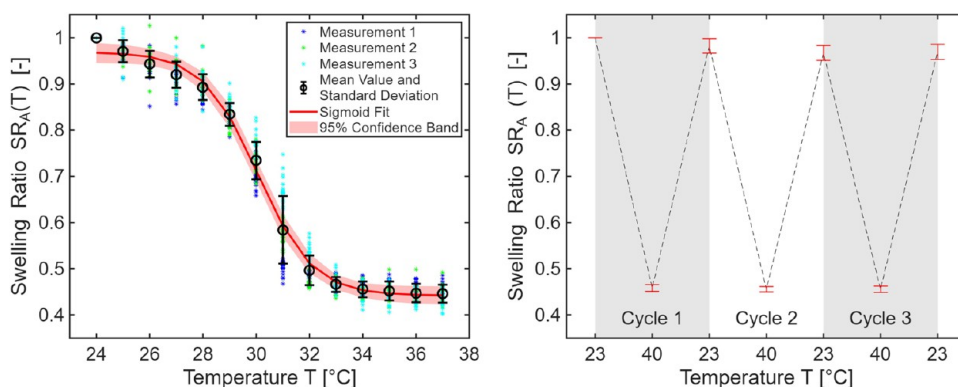


Figure 6. Swelling ratio SR_A of hydrogel cylinders on *testchip 1* with various diameters from 600 μm to 1550 μm at a height of 500 μm dependent on the temperature in multiple measurements. Blue, green and turquoise indicate results from different measurement rows. Black circles and bars represent mean values and standard deviation. Continuous red line shows the fitted sigmoid function with shadowed 95% confidence band of the fitted function. (a) Swelling Ratio SR_A of hydrogel cylinders with selected diameters from Table 3 at a height of 500 μm dependent on the temperature in alternating cycles. Mean values and standard deviations are pictured in red. (b).

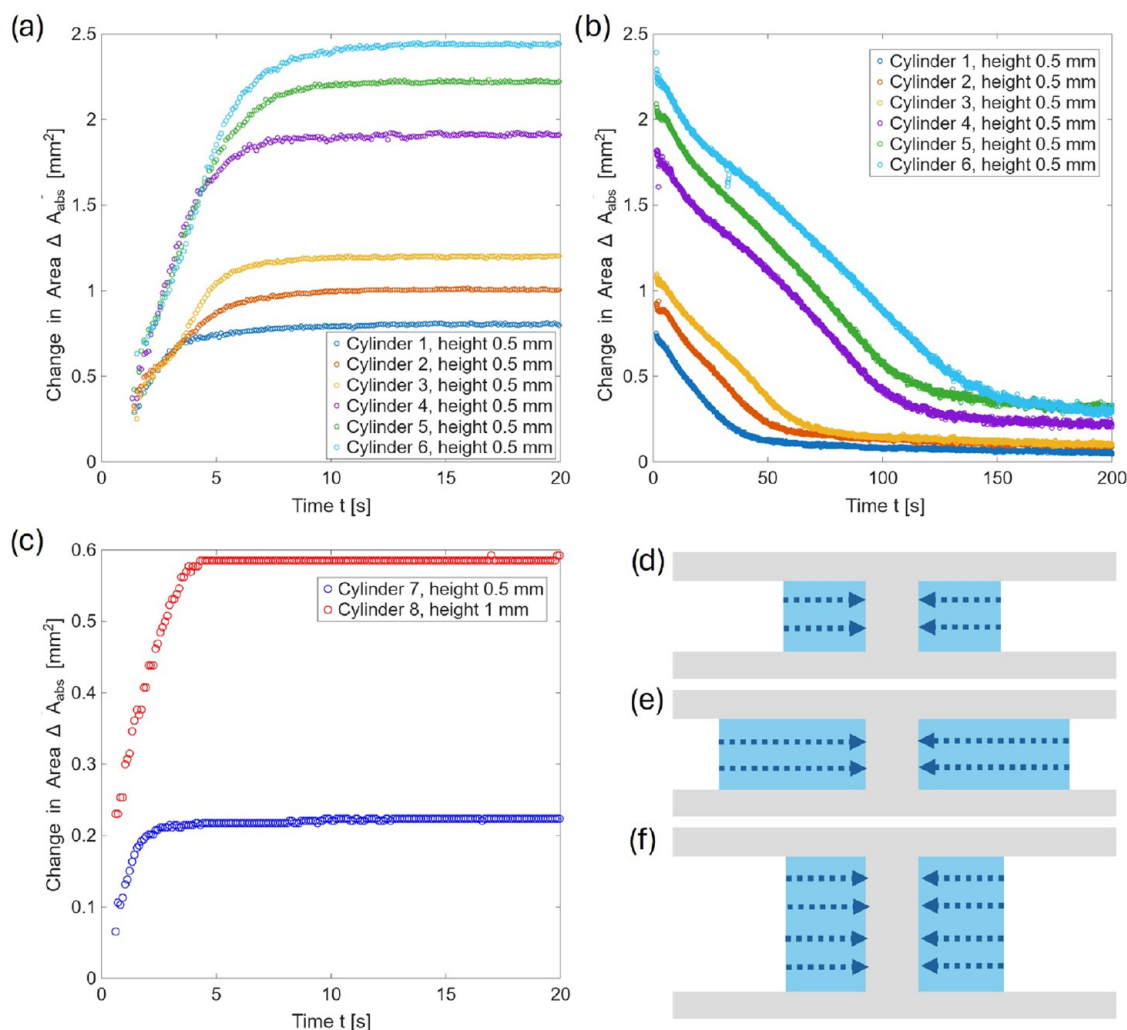


Figure 7. Absolute area change over time of the hydrogel cylinders with different diameters in top view (*testchip 1*) for an abrupt temperature increase (a) and decrease (b). Absolute area change over time for hydrogel cylinders with different heights (*testchip 2*) (c). Illustrated side view of a hydrogel cylinder inside a channel with anchor structure initially (d), sized-up in horizontal direction (e) and sized-up in vertical direction (f). The gray color indicates the chip, the light blue indicates the hydrogel and dashed dark blue arrows indicate the shortest diffusion path with the length representing the characteristic transport distance.

area increases approximately quadratically with the diameter of the molded cylinders. The time required to reach the maximum change increases by only a few seconds as the diameter increases, however, all cylinders have nearly reached their final swollen state after a maximum of 10 s. The change in surface area per unit time is slightly higher for larger diameters, which is also evident from the slope of the curves. In this investigated size range, the diffusion limitation and heat transport thus appear to have no significant influence on the shrinkage of the hydrogels.

A more significant influence of the cylinder diameter on the temporal behavior can be seen in Figure 7 (b) in the step response to an abrupt temperature decrease of the samples. A larger diameter results in a longer time constant until the maximum swollen state is reached. In this case, the time increases approximately quadratically with the diameter of the molded cylinders. The relative change is therefore nearly identical, as can also be seen from the similar slopes of the curves and indicates a good mass transport, which is not limiting for the swelling or shrinkage. Since the change in cross-sectional area is more relevant than the top view for

scaling-up the flow rate in a hydrogel valve, it is important to notice that the effective absolute change in area scales linearly with the cylinder diameter in the considered size range. Overall, the choice of a suitable cylinder diameter for a hydrogel valve with a large area change is thus a trade-off between a slightly longer response time during shrinkage and a significantly longer swelling time. When sizing-up the valve horizontally, an increased absolute area change is therefore possible, whereby the significantly longer swelling time can be explained by the longer characteristic transport distance illustrated by the difference in the graphs in Figure 7 (d, e).

As mentioned earlier, the fabrication method shown here allows for further sizing-up in the vertical direction, which does not significantly affect the critical transport distance, as illustrated by the difference in Figure 7 (d, f). Figure 7 (c) examines the effect of scaling the hydrogel cylinders in height. Shown is the step response of a hydrogel cylinder fabricated in a channel with a height of 500 μm and a channel with a height of 1000 μm (*testchip 2*). The diameters of the cylinders after polymerization are identical, however, after the initial swelling, the taller cylinder exhibits a slightly larger diameter, as also

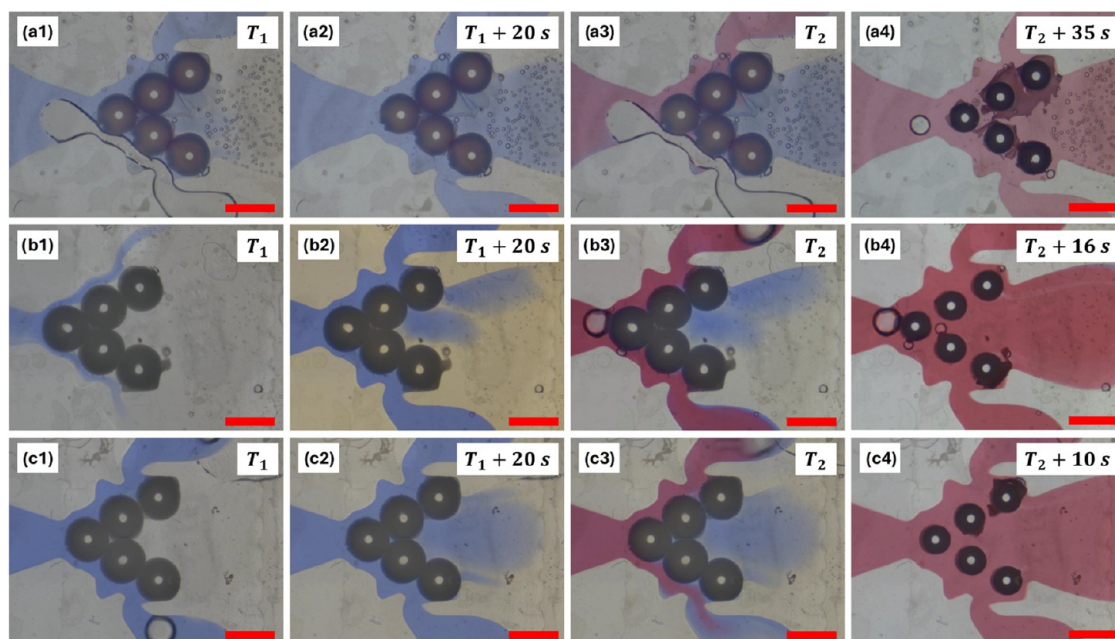


Figure 8. Snapshots of the hydrogel valve under test for a channel depth of 500 μm (a), 1000 μm (b) and 1500 μm (c). First column (a1, b1, c1): Water at 24 $^{\circ}\text{C}$ (dyed blue) is inserted in the channel with the hydrogel valve at a swollen (closed) state at time T_1 . Second column (a2, b2, c2): After water at 24 $^{\circ}\text{C}$ (dyed blue) was flowing through the channel for 20 s. Third column (a3, b3, c3): Water at 35 $^{\circ}\text{C}$ (dyed red) is inserted in the channel at time T_2 . Fourth column (a4, b4, c4): Valves open completely (hydrogel fully shrunken). Scalebars correspond to 2 mm.

visible in the different bulges in the side walls of the hydrogel cylinders in the Figure 5 (g,i). As a result, the maximum achievable area change scales more than linearly with the diameter of the cylinder. The time to reach the maximum area change remains in the range of a few seconds. As a result of the advanced manufacturing methods and the molding process shown here, sizing-up is possible not only horizontally but also vertically, which offers new advantages, such as the constant characteristic transport distance during sizing-up.

Hydrogel Valve

In this section, building on the results obtained previously, sizing-up of the hydrogel structures in the vertical direction is used to achieve a bypass valve with both high throughput and an adequate response time. This is combined with an approach from the literature to enhance the channel cross-section by embedding multiple hydrogel structures within the channel.¹⁵ As shown in Table 4, the swelling ratio for a specific temperature is quite accurate and reproducible. As mentioned before, molded hydrogel cylinders in a channel depth of 500 μm increase their diameter by a factor of 1.48 ± 0.01 after the initial swelling. For larger channel depths, this factor tends to increase, as less friction relative to the hydrogel volume occurs at the contact surfaces. Consequently, it is possible to estimate with reasonable accuracy how the distance between the anchor structures must be selected so that the cylinders press against each other after the initial swelling, thereby closing the valve. Since the cylinder is limited at the top and bottom, it has a bulging shape with the largest diameter in the center. Consequently the diameter decreases toward the top and bottom and it is advisable to design the distance between the anchor structures to be clearly smaller than the center diameter of the hydrogel cylinders in their swollen state. Conversely, a gap between the cylinders that is too narrow results in a reduced opened cross section at high temperatures. This trade-off must be considered in the design and is related to the

relevance of achieving the tightest possible seal. Another trade-off is the selected diameter of the hydrogel cylinders. Larger cylinder diameters have a longer response time, especially during the swelling, while smaller cylinder diameters require more overlapping areas for the same channel cross-section to achieve a seal and thus result in a smaller opened cross section at high temperatures. Both the spacing as well as the number of cylinders and the diameter are therefore trade-offs and must be specifically adapted to the application. In this design, a spacing of 1.67 mm with at least 100 μm overlap of the cylinders was chosen for the initial proof-of-concept. The V-shaped arrangement also helps to seal the valve so that the flow is not directed straight to the contact areas between the cylinders as these are most sensitive for leakage. Furthermore, attention must be paid to ensuring that the bypasses are dimensionally designed so that the hydrogel cylinders do not block them in the swollen state.

The fabricated valve structure (*testchip 3*) is shown in Figure 8 with a channel depth of 500 μm (a), 1000 μm (b), and 1500 μm (c) in top view. To ensure meaningful comparability, the flow rate for all valves is set to 4800 $\mu\text{L}/\text{min}$ per millimeter of channel height.

To verify the functionality of the valve, water at 24 $^{\circ}\text{C}$ (dyed blue) is passed through the valve while being in its swollen state (Figure 8 a1, b1, c1). After 20 s (Figure 8 a2, b2, c2), a slight leakage can be observed in all valves, with the leakage appearing most severely in the case of the 500 μm channel depth. The leakage can be explained by the unavoidable diffusion of water through the hydrogel and by tiny gaps that may occur between the hydrogel cylinders due to their design. The valve is designed so that the distance between the cylinders is smaller than the diameter of the cylinders in their swollen state, ensuring that the cylinders are pressed against each other and thus closing the valve. Figure 5 (i) shows the vertical bulging of the hydrogel cylinders and indicates that the

diameter is bigger in the center of the cylinders than at the interfaces between the hydrogel and the fluidic structure. This causes the cylinders to be pressed less tightly against each other at these interfaces, allowing small gaps to form there. In shallower channel depths, this vertical bulging and the swelling ratio are less prominent due to a larger contact area between the etched rough glass and the cylinder relative to the hydrogel volume, causing the frictional forces to have a more significant influence. Based on the previous results, leakage can likely be reduced by decreasing the distance between the hydrogel cylinders in order to press them more tightly together in the swollen state. However, as mentioned previously, this would also increase the response time of the valve and reduces the maximum opened cross section of the valve. When optimizing the valve for a specific application, the relevance of leakage must therefore be assessed and taken into account. In this study, the focus is not on reducing leakage, but on increasing the throughput while maintaining a short response time. Specific application cases for this are discussed in the following chapter.

In a next step, red-dyed water at 35 °C is introduced into the channel (Figure 8 a3, b3, c3) and the time response behavior of the valves is observed. At a channel depth of 500 μm , the valve is fully opened after 35 s (Figure 8 a4), at a depth of 1000 μm after 16 s (Figure 8 b4) and at 1500 μm after 10 s (Figure 8 c4), with “fully opened” defined in this case as the point in time at which no further shrinkage can be visually detected using the measurement setup. Thus, the deeper the channel, the shorter the response time. This can be explained by the fact that friction has a greater influence on the threshold behavior at shallower channel depths, as was also shown by Kim and Beebe. Furthermore, a smaller contact area between water and the glass structure leads to reduced heat dissipation at bigger channel depths.

CONCLUSION AND OUTLOOK

This paper successfully presents and investigates a new molding method for the fabrication of responsive hydrogel structures inside a microchannel. It demonstrates that this method can be used to fabricate hydrogel cylinders with diameters ranging from 600 μm to 1550 μm and depths ranging from 500 μm to 1500 μm . This method therefore offers new possibilities for advanced designs, as typical fabrication techniques are generally limited to a few hundred micrometers. The study further investigates how sizing-up hydrogel structures in the horizontal and vertical directions influences the swelling characteristics. It is shown that sizing-up in the vertical direction, which is possible with this fabrication method, offers advantages for the application of a hydrogel valve.

In a proof-of-concept experiment, three hydrogel valves with channel depths ranging from 500 μm to 1500 μm are manufactured and their response to a thermal trigger is examined. The results demonstrate that sizing-up in the vertical direction significantly improves the response time and enables higher throughput. Practical limitations on sizing-up in the vertical direction arise primarily because the anchor structures become more fragile as they grow in size and are more prone to break during the manufacturing process, both in the SLE process and during molding. However, this did not pose a major problem for the dimensions used in this study. In such cases, a more stable anchor structure would be necessary. Furthermore, the SLE process using the Lightfab 3D Printer is

practically limited by a maximum processing thickness of 5–7 mm glass substrates.²³ However, adapted designs, such as the stacking of individual fluidic chips, could also counteract this limitation.

These initial successes of the demonstrated manufacturing approach and scaling-up may offer significant added value for the practical application of responsive hydrogel valves in the future. Enhancing the achievable flow rate without significantly increasing the response time could be a way to transition hydrogel valves from laboratory use to industrial applications, especially for autonomous process control. The temperature-sensitive hydrogel valve, which features high throughput and a short response time, is particularly useful for protecting enzymes in bioreactors by allowing the medium to drain rapidly when temperatures reach critical values. With these valves, this can be done autonomously and without external control, and can also be applied to other triggers than temperature. In this case, the leakage observed during the experiments is not particularly relevant either. More generally, by altering their volume and thus autonomously adjusting flow resistance and, consequently, residence time, the responsive hydrogel cylinders could autonomously regulate reactor operation without external control systems. Such feedback mechanisms offer the potential to maximize conversion, maintain optimal reaction conditions, and protect sensitive catalysts from deactivation. Furthermore, thermoresponsive valves or baffles could respond to local temperature hot-spots within the reactor and thereby alter local flow paths and residence times to prevent catalyst degradation. While the current approach focuses on thermoresponsive hydrogels, the concept can be broadened to include pH-, chemo-, and light-responsive materials. The manufacturing method offers the possibility to optimizing the precursor for the response characteristics rather than for a specific polymerization mechanism. This could enable and optimize direct coupling of material response to a (bio)catalytic reaction through stimuli such as substrate concentrations, product formation, or catalyst-inhibiting species. In this context, integrating such designs and fabrication processes into smart reactor systems supports sustainable industrial innovation and aligns with the objectives of SDG 9 (Industry, Innovation and Infrastructure) and SDG 12 (Responsible Consumption and Production) within the framework of the United Nations University (UNU) Hub at Hamburg University of Technology (TUHH).

In summary, this study demonstrates an advanced method for in-channel molding of responsive hydrogel structures, which is suitable for up-scaling and offers a variety of new designs and application possibilities. Together with additional results from the coauthors' research group regarding the optimization of hydrogel formulations, this method will be used in future studies to improve hydrogel valves and related responsive structures. Further characterization and optimization of the hydrogel valves, together with specifically tailored hydrogel formulations, are essential next steps.

ASSOCIATED CONTENT

Data Availability Statement

The data that support the findings of this study are openly available at the following URL/DOI: [10.15480/882.16910](https://doi.org/10.15480/882.16910).

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.iecr.6c01285>.

Snapshots of the fabricated hydrogel valves for an opening process (Figure S1); snapshots of the fabricated hydrogel valves for a closing process (Figure S2) (PDF)

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Notes

The authors declare no competing financial interest.

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