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Sensors and Actuators B: Chemical 233: 402-408 (2016)

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http://dx.doi.org/10.1016/j.snb.2016.04.116

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FLUIDIC FLOW DELAY BY IONOGEL PASSIVE PUMPS IN MICROFLUIDIC PAPER-BASED ANALYTICAL DEVICES

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Abstract

A new concept for fluid flow manipulation in microfluidic paper-based analytical devices ($\mu PADs$) is presented by introducing ionogel materials as passive pumps. $\mu PADs$ were fabricated using a new double side contact stamping process and ionogels were precisely photopolymerised at the inlet of the $\mu PADs$. The ionogels remain mainly on the surface of the paper and get absorbed in the superficial paper-fibers allowing for the liquid to flow from the ionogel into the paper easily. As a proof of concept the fluid flow and mixing behaviour of two different ionogels $\mu PADs$ were compared with the non-treated $\mu PADs$. It was demonstrated that both ionogels highly affect the fluid flow by delaying the flow due to their different physical and chemical properties and water holding capacities.

1. Introduction

Microfluidics enable the manipulation of small amounts of fluids at length scales from a few micrometers up to a milimeter, providing a set of fluidic unit operations, which are designed for easy combination within a well-defined fabrication technology, and generate a consistent way for miniaturisation, integration, automation and parallelisation of bio-chemical processes [1,2]. Microfluidic (continuous flow, microarray and droplet-based) systems which ensure a high degree of fluid control with minor consumption of expensive reagents, have increasingly been employed in miniaturisation of large-scale chemical assays and analytical techniques [3]. One of the greatest capabilities of microfluidic devices is the integration of multiple functional elements to produce absolute sample-in/answer-out systems [4]. The incorporation of functionalities such liquid handling, temperature control and detection components for sensing allows for fast analysis and screening protocols acquiring higher throughput and yields, and improved selectivity compared to conventional devices [3,4].

Due to the critical need of fluid control, and transport processes within these systems, microfluidic devices have adopted a large variety of passively or actively controlled, high performance components, such as mixers, actuators, reactors, separators, valves and pumps, which although sophisticated and able to fulfil their duties, are as well costly, increasing dramatically the price and so decreasing the final market possibilities of these type of devices.

In order to overtake these limitations "Lab on a paper" and "paper based microfluidics" have emerged to provide with easy answer to deliver simple protocols as well as cheap and autonomous devices which are easily manageable by the end-users [5,6]. These devices have the full potential of classical microfluidics but with a well focused commercialisation path [3].

Paper is now considered an attractive and promising substrate material for microfluidic devices not only due to its extremely low cost and ubiquity but also due to its mechanical properties comprising flexibility, lightness, and low thickness. In particular, μPADs are a relatively new group of analytical tools, capable of analysing complex biochemical samples, within one analytical run, where fluidic manipulations like transportation, sorting, mixing or separation are available [7]. According to the impressive properties of paper material, μPADs represent an innovative platform technology for fluid handling and analysis, with wide range of applications, featuring low cost, ease of fabrication/operation and equipment free [6].

Paper is basically made of cellulose material. Cellulose fibres in paper are the driving force for the wicking of fluids by capillary action. Thanks to capillary forces, there is no requirement for external pumps to provide fluid transport inside the paper unlike traditional microfluidic platforms. Nevertheless isotropic wicking behaviour of paper and its capability of transporting fluid by any exposed surface area becomes as a drawback in microfluidics, since the accurate control of the fluid transport kinetics in commercially available paper is highly challenging and complicated [8,9]. Lack of fluid control on paper is at this moment the main dragging force for researchers when looking for new capabilities of µPADs.

In order to provide fluid control in paper, several methods have been employed as such the different ways of obtaining patterned barriers by hydrophobic materials. Nevertheless, these patterning processes have never been sufficient to ensure proper fluidic control in the device. Consequently, switches, valves and fluidic timers have been recently introduced as the main mechanisms for fluid control in $\mu PADs$.

Li *et al.* for instance, developed the first microfluidic switch in a paper-based device, which allows or restricts capillary flow by applying pressure manually, by cutting a channel into two

parts and then separating the channels [10]. Later, Whitesides group built a similar but more complex valve mechanism in a three-dimensional paper-based microfluidic device, which delivers fluid flow by closing the gap between two vertically aligned fluidic channels and allowing wicking continuously by applying pressure [11]. Fu and co-workers, showed that in a multi-step processed 2D paper network, the timing for delivery of multiple fluids, *i.e.* arrival times and duration of flows, can be varied by changing the path length for fluid travel from each inlet and the volume of fluid applied to each inlet [12]. Recently, Houghtaling *et al.* demonstrated a novel dissolvable bridge structure as shut-off valve, in the important frame of autonomous delivery of multiple volumes of a fluid from a common source to different pathways in a paper network device [13]. Similarly, Lutz and his team developed dissolvable sugar fluidic restrictors for programming multistep assays in instrument-free paper diagnostics [14].

Stimulus responsive gel materials have been gaining increasingly high attention due to the autonomous behaviour in response to changes in their local environment [15]. They are referred as smart materials since they are able to perform functions by an external stimuli (magnetic or electric field, temperature, light, pH, solvent composition or chemicals), without the need of any human input [16]. Hydrogel materials, in particular, respond to this environmental stimulation by swelling or releasing a large amount of water, which leads to an abrupt change in volume. The volume change is often reversible, returning back to the original configuration when stimulus is removed. The advances in stimuli responsive materials based on hydrogels have leaded to new functionalities by the incorporation of smart micro/nano-structures in microfluidic channels for fluidic control and manipulation [17-19].

However, the practical applicability of hydrogels in microfluidic devices is limited due to their discrete shrinking with increasing temperature, low material robustness, rather slow expansion kinetics and degree of actuation. These drawbacks lead to look for alternatives to hydrogels. The use of ionogels, polymer gels that incorporate an ionic liquid (IL) within their polymer matrix, enables improvement in the physical robustness of the stimuli responsive gel. Moreover the brittle nature of conventional hydrogels under standard ambient conditions, which causes a problem during their storage, is avoided using ionogels. Moreover the low vapour pressure of ionic liquids and their ability to plasticise the gel polymer structure, improves the gel mechanical strength [20].

In this work we present a new concept for fluid flow manipulation in μ PADs by introducing ionogel materials as passive pumps. We compared the fluid flow behaviour of two different

ionogels, which were drop-casted at the inlet section of $\mu PADs$, with the non-treated paper. Both ionogels highly affected the fluid flow by delaying the flow coming from the inlet. They reveal two distinctive liquid flow profiles due to their different physical and chemical properties and water holding capacities. Finally as a proof of concept, the mixing point of two fluids was selectively altered in position within the μPAD by the ionogel passive pumps.

2. Experimental

2.1. Reagents and Materials

Whatman Filter paper with Grades 1 and 595, Lumocolor Permanent Universal Black Ink (Staedtler Mars GmbH & Co. KG), ethanol and *n*-propanol (Sigma Aldrich, Spain), cyclic olefin copolymer (COP) (from Zeonex/Zeonor, Germany), Polydimethylsiloxane (PDMS, Sylgard) in monomer and curing agent (Sigma-Aldrich, Spain), the stone ink-pad (2" x 4" rectangle) (from HITT Marking Devices) were provided in order the fabricate the μPAD. For the synthesis of the ionogels, *N*-isopropylacrylamide, *N,N'*-methylene-bis(acrylamide),

2,2-Dimethoxy-2-phenylacetophenone photoinitiator and, 1-ethyl-3-methylimidazolium ethyl sulfate and trihexyltetradecyl-phosphonium dicyanamide ionic liquids (IL) were purchased from Sigma-Aldrich, Spain.

H₂SO₄ and NaOH solutions, and phenol red, which are used for the observation of the colour change (pH) on the μPAD, were provided by Sigma-Aldrich, Spain.

For visual observation, yellow food dye (McCormick, Sabadell, Spain) was used: 5 mL of water with 20 μ L of food dye (low concentration) or with 100 μ L of food dye (high concentration).

2.2. Fabrication of the Device

The microfluidic platform was fabricated using standard laboratory filter paper which absorbs the ink through its full thickness and defines the borders and so the flow channels of the microfluidic structure, Figure 1. As described before by Curto *et al.*, the main attractive characteristic of this ink is its hydrophobic nature when it is dry, and short drying time [21]. Moreover, ink viscosity was also reduced by using a solvent mixture made of a 1 : 1 v/v ethanol-n propanol, 10 : 1 ink-solvent mixture. The contact stamping is performed using PDMS stamps. The PDMS negative molds were fabricated using the Origami technique, in cyclic olefin copolymer (COP) material by Graphtec Cutting-plotter and subsequent thermocompression [22]. Then, PDMS with a content of 10 : 3 w/w monomer-curing agent, in the

mold, was cured at 60 °C for 8 h to obtain the PDMS stamp. The inking of PDMS is performed using the stone ink-pad which enables to control the volume of ink transferred from the PDMS stamp to the filter paper by providing a constant ink flow from the porous stone. The inking process was performed by gently pushing the PDMS stamp three times against the ink saturated stone pad and the PDMS stamp was placed in contact with the laboratory filter paper for three seconds, without the application of any force, this protocol was repeated in both sides of the paper. The μ PADs final structure (ink walls) was finalised manually by painting the openings (top and bottom figure 1d) with a pen.

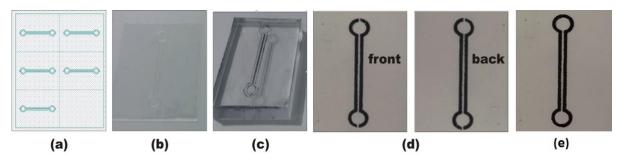


Figure 1: μ PAD fabrication: (a) mask design compatible with the origami technique, (b) COP negative mold fabricated by origami, (c) PDMS stamp, (d) front and back sides of the filter paper stamped with indelible ink (e) Picture of the final device.

2.3. Synthesis and Integration of the Ionogel

Two different ionogels were used for fluid manipulation. They were synthesised using *N*-isopropylacrylamide, *N*,*N'*-methylene-bis(acrylamide) and a photoinitiator (2,2-Dimethoxy-2-phenylacetophenone) dissolved in 1-ethyl-3-methylimidazolium ethyl sulfate (IL-1) or trihexyltetradecyl-phosphonium dicyanamide (IL-2) ionic liquids respectively, by mixing and heating at 80 °C for 30 min. The chemical structures of the ionogels are illustrated in Figure 2.

polymer gel

$$C_{14}^{\text{Ph}_3}$$
 $C_{14}^{\text{Ph}_3}$
 $C_{14}^{\text{P$

Figure 2: Chemical structure of the components of the ionogel. Left: polymer gel; top right: 1-ethyl-3-methylimidazolium ethyl sulfate IL (IL-1) and bottom right: trihexyltetradecyl-phosphonium dicyanamide IL (IL-2).

2.4. Integration of the Ionogel

5μL of IO-1 and IO-2 solutions were drop-casted at the inlet of the μPADs and rapidly UV-photopolymerised, in 10 s and 18 s (1600 mW cm⁻²) respectively, on the paper devices. For the proof of concept experiments, IO-2 was photopolymerised (in 18 s under 1600 mW cm⁻²) in the left side inlet of the Y-shaped μPAD which was fabricated by contact stamping. Then the ionogel μPADs were washed several times with deionised water (DI) to remove any unpolymerised material and excess of ionic liquid and let them dry at room temperature for 48 h. It was already demonstrated by us before that water soluble IL-1 remains on the structure of the ionogel after the washing and drying processes [20]. Moreover, all μPADs with ionogels were used under room temperature conditions. Therefore, the possible thermal responsiveness of the ionogel was avoided in this study.

2.5. Measurement Protocol

After obtaining three types of $\mu PADs$, (with IO-1, with IO-2 and with no ionogel), the same amount of coloured liquid (20 μL) was dropped on each device in order to compare the fluidic behaviour of the $\mu PADs$. During the proof of concept experiments, in order to observe fluid modulation, a 5 μL solution of NaOH (pH = 13) and a 5 μL solution of phenol red indicator and H_2SO_4 (pH = 2) were dropped onto the left and right inlets respectively, on both types of Y-shaped $\mu PADs$ (with and without ionogel). This action was repeated 19 times (95 μL in total). This slow fluid dropping method was adopted in order to control the amount of liquid added to the ionogel and to avoid any excess of liquid from getting into the main channel. The fluid flow was recorded by a Samsung Galaxy Note3 video camera. The photos of the fluid moving through the μPAD channels for different time values were extracted from the video. The distance of the running fluid from the inlet at different times was measured with a ruler.

The cross section and surface images of the papers with photopolymerised ionogels IO-1 and IO-2 were obtained by FEI Quanta 2000 low vacuum scanning electron microscope (SEM) system at an accelerating voltage of 10 kV, with magnification values of 263X and 140X.

3. Results and Discussion

3.1. Fabrication of the $\mu PADs$

The ink stamping method, firstly proposed by Vincenzo *et al.*, was considered in this publication due to its fast and cheap fabrication protocol for obtaining the µPADs [21]. Nevertheless this method has observed to be weak to generate large amount of devices since

the reproducibility was sometimes low. This was due to the non uniform penetration of the stamped ink through the back of the paper. Therefore it was decided to modify the protocol by using a simple double side stamping method of the paper. The ink barriers were successfully resolved after alignment of both stamps following the same stamping process than before [21]. The modified process is able to keep the fluid inside of the channel in the 100 % of the devices with an accurate ink transfer, just increasing a few seconds the fabrication time.

3.2. Integration of the Ionogel

The volume of the photopolymerised ionogel in the inlet, highly affects the degree of swelling of the ionogel, and consequently, the capability of the pump to provide more or less liquid to the μ PAD. Therefore, the ideal ionogel volume was decided by photopolymerising different volumes of ionogel solution in the inlet of the μ PAD. Volumes < 5 μ L are not enough to fill the whole inlet while volumes > 5 μ L swell too much during hydration and so the ionogel peels off of the μ PAD. Thus, a 5 μ L volume of ionogel solution is ideal for this μ PAD configuration. Ionogel were photopolymerised under UV light, as soon as they were drop-casted onto the paper surface. Using rapid photopolymerisation protocols, it was possible to avoid the spreading of the ionogel solution through all the thickness of the paper, ensuring a "sponge" structure of the ionogel on top of the paper. Several photopolymerisation times and ionogel solution volumes were investigated in order to generate a homogeneous, well spread and at the same time spongy structure at the inlet of the paper device. The ideal polymerisation times for each ionogel were 10 s and 18 s respectively for IO1 and IO2 with a volume of 5 μ L to cover a paper area of 6 mm².

Figure 3 shows two SEM images of the cross sections and surface of the papers with the photopolymerised ionogels IO-1 and IO-2 (dry), where it is possible to observe the ionogels-paper interfaces. The images present the physical interaction between the paper and the ionogel. The ionogels remain mainly on the surface of the paper and get absorbed in the superficial paper-fibers, allowing the liquid to flow from the ionogel into the paper easily when hydrated. The photopolymerisation process is therefore fast enough to retain the ionogel material at the surface of the paper but at the same time is able to anchor the ionogels strongly to the paper.

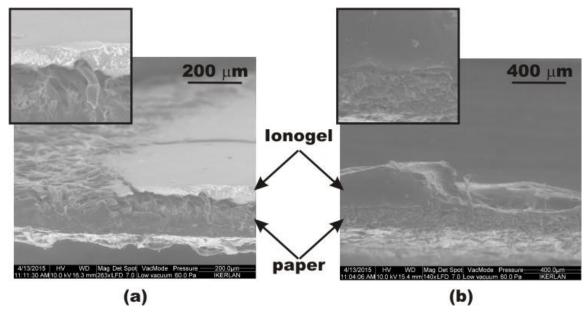


Figure 3: SEM images of the ionogels after photo-polymerisation on top of the paper, (a) IO-1 and (b) IO-2. Insertion pictures: zoom of the interface between ionogels and paper.

3.3 Ionogel Effect on Fluid Behaviour in µPADs

The fluid behaviour on the ionogel drop-casted $\mu PADs$ (with IO-1 and IO-2) were monitored and compared with the non-treated μPAD over time in order to understand the ionogel effect. Figure 4 shows the fluidic profile of a coloured liquid while flowing through the $\mu PADs$ over time. It can be clearly seen that the ionogel highly affects the fluid behaviour on paper by delaying the fluid flow, behaving as passive pumps in the $\mu PADs$. The ionogel acts as a sponge at the inlet of the $\mu PADs$, therefore the liquid has first to overtake the negative pressure generated by the ionogel, which absorbs the liquid into its gel matrix preventing the liquid from reaching the paper and so running through the channel. In addition, when the liquid reaches the paper and capillary action through the paper takes place (wicking of the paper), this effect is delayed, due to the hydration action of the ionogels.

This effect depends on the chemical characteristics and the swelling rate of the different ionogels. For instance, parameters such as the type of ionic liquid which highly determines the swelling behaviour of the ionogel (hydrophobicity or hydrophilicity), the porosity level of the gel structure, and the geometry of the gel are essential to explain the fluid behaviour in these hybrid devices [23].

During the swelling process of the gel, water intake, the k_{sw} of IO-1was calculated to be 3.1 \pm 0.6 \times 10⁻³ s⁻¹ [20], while the k_{sw} of IO-2 was 4.5 \pm 0.3 \times 10⁻² s⁻¹, being IO-1 around 15 times faster, see previous publications [23]. This could be explained due to their differences in

hydrophobicity. In our case, IO-1 contains a hydrophilic IL (1-ethyl-3-methylimidazolium ethyl sulphate) with elevated water swelling capacity while IO-2 has a more hydrophobic IL (trihexyltetradecyl-phosphonium dicyanamide ionic liquids) which interferes with the water intake of the ionogel. Therefore IO-1 reaches swelled equilibrium earlier than IO-2 and so starting the wicking process of paper much earlier than with IO-2.

Another parameter that needs to be considered is the porosity of the ionogels. Both ionogels are porous and able to accommodate larger volumes of water. Nevertheless the Dicyanamide anion of the IL of IO-2 strongly bonds with water molecules as demonstrated by Gallagher *et al.* [24]. Therefore as the absorbed water is retained and the swollen structure of IO-2 is more stable than IO-1. The wicking of the paper in the IO-2 μ PAD occurs later and with less volume available. Therefore both parameters could explain the difference in performance of the two μ PADs.

Therefore IO-1 and IO-2 highly affect the fluidic behaviour of the μ PADs by both delaying the flow and decreasing the available sample volume at the inlet. Moreover they reveal two distinctive and reproducible liquid flow profiles: IO-2 >> IO-1 >> Paper (flow delay).

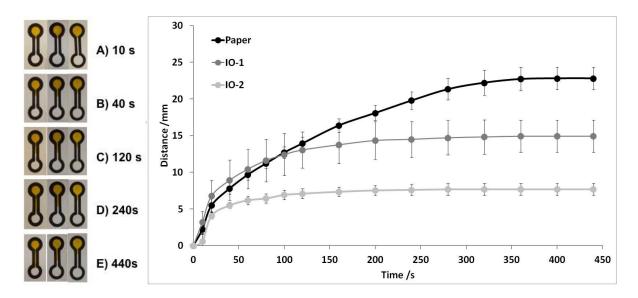


Figure 4: Fluid flow performance of three type of $\mu PADs$: Left μPAD : bared paper, middle μPAD : IO-1, right μPAD : IO-2, 10 s (A), and 40s (B), 120s (C), 240s (D) and 440s (E) after injecting 50 μL of a yellow dye to each device simultaneously, (n = 3).(20 μL of the yellow dye solution (0.4 % v:v) were used to study the performance of these devices; this amount was not enough to reach the outlet in this particular μPAD configuration).

These experiments were performed using both, a low (0.4 % v:v) and a high (2.0 % v:v) concentration solution of yellow food dye and pure water. It was observed that the concentration of the dye did not significantly influence the performance of the ionogel passive pumps. Nevertheless, in each particular application of this methodology, the compatibility of

the ionogel with the chemical and physical characteristics of the sample must be investigated in order to obtain the best performing pumps.

3.4. Application

As a proof of concept, the fluid flow delay capability of the ionogel passive pumps and the subsequent effective mixing behaviour of two fluids on a Y-shaped µPAD were investigated. The IO-2 ionogel was photopolymerised in the left side inlet of the µPAD and the mixing behaviour on the IO-2 µPAD was compared to the behaviour on a bared µPAD with no ionogel (Figure 5). Two different solutions were injected in the µPAD inlets at the same time. On the left side inlet, a solution of NaOH (colourless, pH: 13), while on the right side inlet, a solution containing phenol red pH indicator and H₂SO₄ solution (yellow, pH: 2) Figure 5a. No significant effect on the ionogel passive pumps' performance was observed at those pHs when comparing them to the results obtained for the same experiments carried out with deionised water. After that, the yellow solution starts wetting the paper channel a runs to the channel intersection while the solution dropped on the IO-2 does not move from the inlet, Figure 5b. The mixing process was observed by the formation of a pink colour line at the interface of both solutions due to an abrupt change of pH expressed by the pH indicator. In the case of the µPAD with the IO-2 ionogel, due to the fluid flow delay in the left side channel promoted by the swelling of the IO-2, the mixing process occurs in the middle of the left fluidic channel (Figure 5c), where the two fluids first met. Then, the mixing point of the fluids shifted towards to the middle point of the µPAD due to the continuous flow of the NaOH solution coming from the IO-2 ionogel after the ionogel reached swelling equilibrium. (Figure 5d).

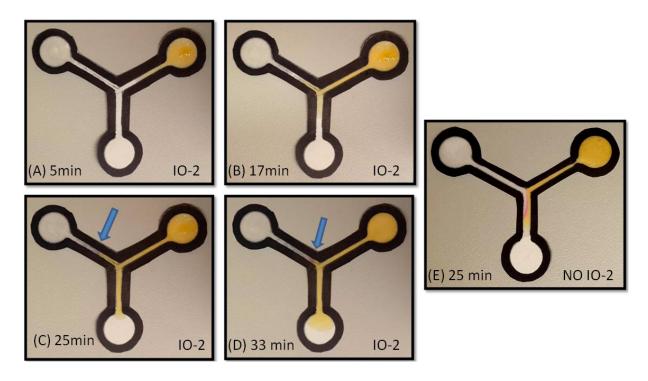


Figure 5: A Y-shaped μ PAD with photopolymerised IO-2 in the left side inlet, 5min (A), 17 min (B), 25 min (C), 33 min (D), while injecting NaOH solution (pH = 13) into the left inlet (purple arrow) and phenol red pH indicator and H_2SO_4 solution (pH = 2) (yellow arrow) into the right inlet. Phenol red gives a pink colour change in an basic environment.) (E) a Y-shaped μ PAD with no ionogel.

This behaviour is compared to the μ PAD with no ionogel, Figure 5e, where both solutions flow through the channel with a laminar flow regime and mix at the interface of both flows generating the characteristic pink colour from the mixing point toward the end of the main channel. This is therefore an unconventional way of fluid flow manipulation from what it should be expected from two liquids that were dropped at the same time in the inlets of the Y-shaped μ PAD. Here the mixing and reaction point of two liquids on a μ PAD can be modulated on desired by applying the fluidic flow delaying capabilities of the ionogels passive pumps in a simple manner. This investigation opens the use of ionogel passive pumps in μ PADs for other applications and they will be investigated in the near future. For instance, the delaying effect, the key point of controlling fluid flow, opens the possibility of selectively or sequentially introducing reagents or samples into a μ PAD sensing zone. Moreover, ionogels could be used as delay barriers in the μ PAD main channel to promote chemical reactions.

The ionogel passive pumps presented here do not need of any external force in order to release fluid to the μPAD main channel unlike other previously published pumps, which use chemicals, temperature and external pressure forces, among others.

For instance, the work of B. Lutz *et al.*[14] uses dissolvable sugar delay barriers for programming multistep assays. Although it is a very smart solution, sucrose is dissolved in the sample, which can cause interferences during detection in some applications. Our ionogel pumps do not add any chemical component to the sample. The work of T. Kokalj *et al.* [25] uses the wicking capabilities of paper and a liquid column stored on a chip to drive the sample into the main microfluidic channel. This system needs external pressure, finger force, to start the wicking process and therefore control the fluid. The ionogel passive pumps do not need of any manual/external manipulation to control the flow, it is just necessary to know the chemical characteristics of the ionogel. An interesting paper from R. R. Niedl and C. Beta [26] uses a thermo-responsive hydrogel as a fluid reservoir. When temperature increases, the hydrogel collapses and releases fluid into the structured paper substrate. The main disadvantage of this method is that the hydrogel is not integrated into the μPAD as in our case, and that hydrogel dehydrates very fast so fluidic control is very difficult. In our case the ionic liquid in the ionogels acts as plasticizer, generating a more robust structure.[20]

4. Conclusions

 $\mu PADs$ are the new generation, low cost, equipment free platforms for fluid handling and analysis with wide range of applications due to the impressive properties of paper. Nevertheless, the transition of μPAD from the laboratory to consumers' hands has not been accomplished yet due to the lack of effective handling and control of fluids on paper. Therefore, in our work we are proposing a solution to this problem by providing a new concept for fluid flow manipulation in $\mu PADs$ by introducing ionogel materials as passive pumps.

It has been clearly demonstrated that ionogels highly affect the fluid flow on paper by fluid delaying, behaving as passive pumps in $\mu PADs$. Two type of ionogels, with different chemical and physical properties, were drop-casted at the inlet of the $\mu PADs$ which were obtained by ink-stamping paper with PDMS stamps, and leaded to two distinctive liquid flow profiles when compared to the bared paper. The photopolymerised ionogels remain mainly on the surface of the paper and get absorbed in the superficial paper-fibers allowing for the liquid to flow from the ionogel into the paper easily. The delaying effect of the ionogels depends on the characteristics (chemical and dimensions) of the ionogel which determine the swelling degree of the gel. Moreover, as a proof of concept, the fluid delay capability of the ionogel

was applied to a Y-shaped μPAD , showing a completely different fluid mixing behaviour compared to the bared μPAD .

5. Acknowledgements

The project was carried out with the support of the Ramón y Cajal programme (Ministerio de Economía y Competitividad). FBL and JS thank to the European Union's Seventh Framework Programme (FP7) for Research, Technological Development and Demonstration under grant agreement no. 604241 for economical support. JE acknowledges the Gobierno Vasco, Dpto. Industria, Innovación, Comercio y Turismo under ETORTEK IE14-391. Authors personally acknowledge Marian M. De Pancorbo for letting them to use her laboratory facilities at UPV/EHU.

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