



Paper-based microfluidic sampling and separation of analytes for potentiometric ion sensing

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ABSTRACT

This work demonstrates a paper-based microfluidic sampling and separation platform that allows potentiometric sensing of chloride ions in presence of strongly interfering salicylate ions using a solid-contact ion-selective electrode as a detector. The device was composed of two pieces of paper with different shapes and pore sizes. A "T" shaped filter paper with a pore size of 12–25 μm was used as the detection zone. A filter paper with a pore size of 2.0 μm was modified with a complexing agent (Fe³⁺) and served as the separation zone. The two pieces of the paper were joined together just like a jigsaw. A solid-contact Cl⁻–selective electrode and a reference electrode were gently pressed onto the detection zone to create a direct contact between the electrodes and the solution absorbed in the paper. Utilizing the possibility to form stable complexes between Fe³⁺ and salicylate, the proposed platform enables the separation of salicylate and detection of chloride. This system offers a convenient platform for both sampling and separation of ions, in which sample pretreatment procedures can be simplified or avoided.

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1. Introduction

Potentiometry based on polymeric membrane ion-selective electrodes (ISEs) has long been regarded as a promising tool for the determination of ion activities [1,2]. With the introduction of better molecular receptors, new membrane materials and novel sensing concepts, the performance of ISEs has been dramatically improved during the past two decades [3,4]. A number of ISEs are available with high enough selectivity towards the target analyte to be applied in clinical-, process- and environmental analysis. However, the use of ISEs is sometimes restricted by interferences from the sample matrix [5,6].

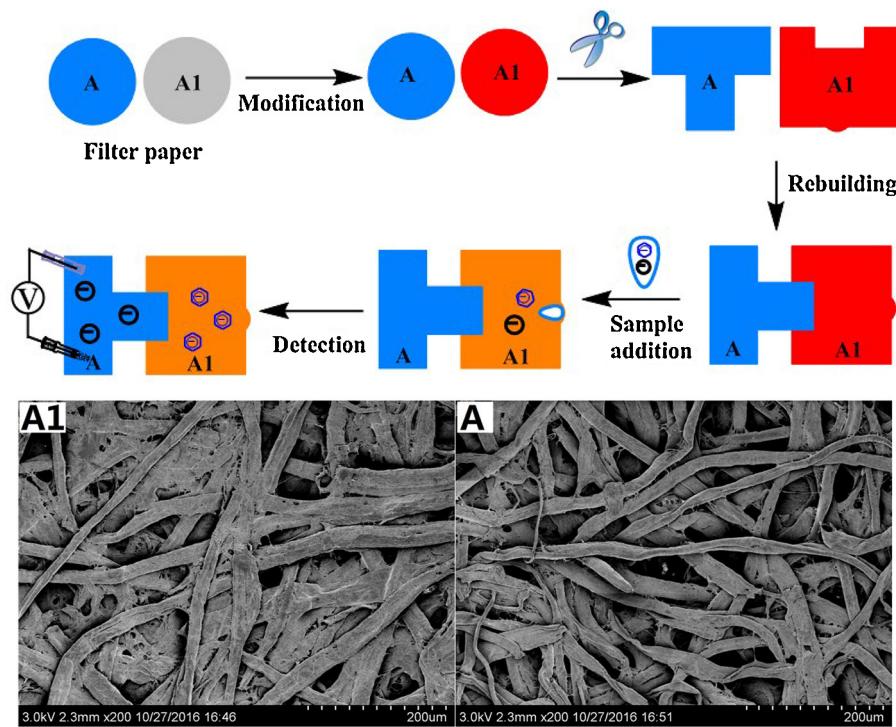
To reduce the sample matrix effects on potentiometric ion sensing, separation and pre-concentration of the target analyte has been adopted, e.g. by coupling the potentiometric detection with separation using liquid chromatography [7]. This approach, however, requires sophisticated and relatively expensive instrumentation. Furthermore, pre-concentration and matrix elimination procedures based on electrochemical accumulation, magnetic sep-

aration or paper-based filtration are alternative choices to enhance the performance of ISEs for potentiometric measurements [8–11]. In all these methods, medium exchange is an essential step for subsequent potentiometric detection, which has the drawbacks of tedious measurement protocols. Thus, there is a clear need to develop a convenient separation platform when using ISEs as a detector.

Paper with its unique features such as low cost, feasible mass production, and pumpless liquid transport operation has been adopted as an attractive analytical and detection platform [12,13]. To date, microfluidic paper-based analytical devices (μPADs) with various readout principles and chemical functions have been designed [14–20]. Among those paper-based sensing platforms, μPADs coupled with potentiometric detection offer a selective and sensitive platform for ion sensing. Recently, our group provided a potentiometric ion sensing platform utilizing paper- and textile-based sampling [21–23]. Bühlmann, Whitesides et al. and our group designed μPADs into which a solid-state ISE and an all-solid-state reference electrode can be integrated for ion sensing and biosensing [24–27]. Furthermore, in situations where the ISE itself is not selective enough, paper-based pre-separation of the analyte from interfering ions can be a valuable option.

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Scheme 1. Schematic representation of the paper-based microfluidic sampling and separation system for potentiometric ion sensing. SEM images of the paper for separation zone (A1) and detection zone (A) are also shown.

Herein, a paper-based microfluidic sampling and separation system was exploited for potentiometric ion sensing (**Scheme 1**). The device was composed of two pieces of paper with different shapes and pore sizes. A “T” shaped filter paper with a pore size of 12–25 µm (“A” in **Scheme 1**) served as the detection zone, while a filter paper with a pore size of 2.0 µm (“A1” in **Scheme 1**) was modified with a complexing agent and served as the separation zone. Interfering ions present in the sample solution bind to the complexing agent to form a complex, which retards the migration of the interfering ions to the detection zone. On the contrary, the target ions were readily wicked into the detection zone, where potentiometric measurements took place.

Chloride (Cl⁻) is an important analyte in clinical analysis, while its detection with ISEs is challenging when salicylate (the major metabolite of aspirin) is present [28]. The therapeutic concentration of salicylate in plasma is up to 1–2 mM [29]. Furthermore, according to the Hofmeister series, the presence of high concentrations of salicylates can strongly interfere with the potentiometric detection of Cl⁻ [30]. As a proof of concept, the potentiometric detection of Cl⁻ in the presence of a high concentration of salicylate was therefore selected as a model system to develop and evaluate our paper-based sampling and separation system.

2. Experimental

2.1. Materials

Azulene (99%), Fe₂(SO₄)₃, and acetonitrile (ACN, 99.5%, anhydrous) were obtained from Aldrich and used without additional purification. Tetrabutylammonium hexafluorophosphate (TBAPF₆, 99%), 2-nitrophenyl octyl ether (*o*-NPOE), tridodecylmethylammonium chloride (TDMACl), high molecular weight poly(vinyl chloride) (PVC), and tetrahydrofuran (THF) were purchased from Fluka and used as received. Sodium chloride and sodium salicylate were obtained from Merck. Aqueous solutions were prepared with freshly deionized water (resistivity = 18.2 MΩ cm) obtained

with the ELGA purelab ultra water system (High Wycombe, United Kingdom). Calibration serum solutions with different ion composition were provided by Thermo Scientific. Black ribbon ashless filter paper (Whatman Grade 589/1, pore size = 12–25 µm) and Blue ribbon ashless filter paper (Whatman Grade 589/3, pore size = 2.0 µm) were obtained from Schleicher & Schuell GmbH (Dassel, Germany).

2.2. Electrode preparation

Glassy carbon (GC) disk electrodes with a diameter of 3.0 mm (inserted in a PVC housing with outer diameter = 1 cm) were polished and used for the construction of solid-contact ISEs for Cl⁻. In the three-electrode cell, a coiled Pt wire and an Ag/AgCl wire served as the counter and the reference electrode (calibrated versus ferrocene/ferrocenium, E_{redox} = 0.36 V), respectively. All polymerizations were done in ACN solutions containing 0.01 M azulene and 0.1 M TBAPF₆ by cycling the potential between -0.6 V and 1.2 V with the scan rate of 50 mV s⁻¹ (Autolab PGSTAT 30 potentiostat equipped with the GPES software) [31,32]. The number of polymerization cycles was 10. All solutions used for polymerization of the PAz films (3.0 mL) were purged with nitrogen for 5 min before the experiments and the TBAPF₆ salt was dried under vacuum at 80 °C for 30 min prior to use. The ion-selective membranes contained 34% PVC, 51% *o*-NPOE and 15% TDMACl. 40 µL membrane cocktail was applied per electrode by drop casting on the glassy carbon/PAz electrodes. All the electrodes were conditioned in 10⁻³ M NaCl overnight. When not in use, the electrodes were conditioned in 10⁻³ M NaCl.

2.3. Design of the paper-based analytical devices

The device comprised of a separation zone (15 mm × 15 mm) with a pore size of 2.0 µm which contained Fe³⁺ and a detection zone (20 mm × 10 mm) equipped with a microfluidic channel (10 mm × 10 mm) in the form of a “T” shaped filter paper with a pore size of 12–25 µm. Before the measurements the two pieces of

the paper (separation and detection zones) were joined together just like a jigsaw. The bottom side of the connection area was covered with clear packing tape to ensure a close connection between the two pieces of paper, allowing the liquid (sample) to migrate from one piece of paper to the other via capillary forces (wicking). The structural feature of the paper was characterized by scanning electron microscopy (SEM, JSM5600 LV, operating at 5.0 KV).

2.4. Functionalization of filter paper

One piece of Whatman filter paper with a diameter 110 mm and pore size of 2.0 μm (blue ribbon) was dipped into 0.01 M $\text{Fe}_2(\text{SO}_4)_3$ solution for 1 h in order for iron(III) to absorb into the paper substrate. Then the Fe^{3+} -impregnated filter papers were washed with distilled water for 3 times to remove the excess (weakly adsorbed) iron(III), which was followed by drying the paper substrate in air at room temperature.

2.5. Potentiometric measurements with ISEs

Potentiometric measurements were performed using an EMF16 Interface (Lawson Labs Inc., USA). The activity coefficients were calculated by using the extended Debye-Hückel equation [33]. Measurements for selectivity coefficients were done using the electrode conditioned in 10⁻³ M NaCl. The selectivity of the GC/PAz/PVC-TDMACl (Cl^- -ISE) electrode was determined using the separate solution method to evaluate the influence of the interfering ions [34]. A single junction Ag/AgCl/3 M KCl reference electrode (6.0733.100, Herisau, Switzerland) was used here because it has its porous plug at the very end of the electrode, thereby giving a proper contact (liquid junction) to the sample/paper substrate when the electrode was gently pressed against the paper. The paper device was positioned horizontally on the support surface (Teflon plate), while the Cl^- -ISE and the reference electrode were positioned vertically to the detection zone (20 mm × 10 mm) of the paper device. The Cl^- -ISE had an outer diameter (=membrane diameter) of 1 cm. The electrodes were fixed in place by using a standard laboratory stand so that the distance between the working areas of the two electrodes was kept constant (ca 9 mm apart from each other). The physical separation of the two electrodes was applied to deal with the possible contamination (within 90 s measurement time) of the paper/sample by the 3 M KCl solution leaching out from the liquid junction of the reference electrode. A new piece of paper device was used for each standard and sample solution, thereby minimizing any contamination from chloride. The sample solution (150 μL) was added on top of the separation part ("A1" in Scheme 1) and then it wicked through the separation zone into the detection zone ("A" in Scheme 1). After the detection zone was completely wet (ca 60 s after sample addition), the indicator and the reference electrode were gently pressed onto the detection zone for potentiometric measurements. The time required for the manual fixation of the electrodes was ca 30 s. Thereafter, the EMF response was recorded for 90 s. The time (90 s) was a compromise between allowing sufficient time for stabilization of the potential on one hand and minimizing possible effects of sample evaporation on the other hand. After each measurement, the electrodes were rinsed with deionized water.

2.6. Fe^{3+} determination by UV-Vis spectroscopy

Fe^{3+} was determined according to a previous report with some modification [35]. Briefly, a functionalized filter paper with a diameter of 69 mm was immersed into 4.5 mL 0.5 M HCl and incubated overnight at room temperature. 100 μL acidified sample aliquots were reacted with ferrozine reagent (0.1 wt-% ferrozinein, 200 mmol L⁻¹ HEPES buffer, pH 7.0), and the ferrozine-Fe(II) com-

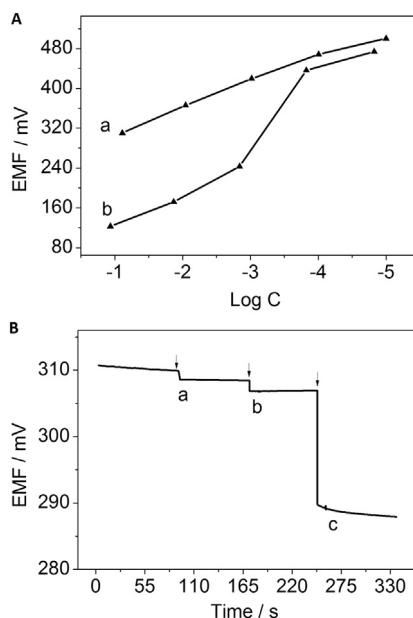


Fig. 1. (A) EMF responses (beaker-based measurements) of the ISEs toward (a) NaCl and (b) salicylate. (B) EMF responses of the ISEs to 0.1 M NaCl in the presence of (a) 1.5×10^{-5} M, (b) 1.5×10^{-4} M and (c) 1.5×10^{-3} M salicylate.

plex was quantified at 562 nm by UV-vis spectrophotometry (Thermo Scientific, Genesys 10 s UV-vis, USA).

3. Results and discussion

3.1. Solid-contact ISEs for Cl^-

As a proof-of-concept experiment, solid-contact ISEs for Cl^- were prepared by using electrosynthesized polyazulene (PAz) as the solid-contact [31,32], coated with a plasticized PVC-based membrane containing TDMACl as ion exchanger for Cl^- [36]. The resulting electrodes are denoted as GC/PAz/PVC-TDMACl. Beaker-based measurements were carried out first. Fig. 1A (curve a) shows that the electrode exhibited a linear response ($r^2 = 0.997$) over the Cl^- activities from 1.0^{-1} to 1.0^{-4} M with a slope of 54.7 mV/pCl⁻ and a detection limit of approximately 10^{-5} M in pure chloride (NaCl) standard solutions. A super-Nernstian response to salicylate was observed (Fig. 1A, curve b) when the electrode was initially conditioned in 10^{-3} M NaCl, which may due to the non-equilibrium response toward the lipophilic salicylate ion. The selectivity coefficient (in logarithmic scale) for chloride over salicylate and SO_4^{2-} were determined to be $+3.4 \pm 0.04$ and -2.5 ± 0.05 , respectively, which is in good agreement with those reported earlier [30]. Such a low selectivity for chloride over salicylate is demonstrated in Fig. 1B that shows the response of the Cl^- ISE to the added salicylate. Even small additions of salicylate to the chloride ion solution change the EMF of the electrode (a, b), which is followed by the dramatic drop of EMF after addition of 1.5×10^{-3} M salicylate (c). Therefore, the presence of lipophilic salicylate in the solution would make the direct determination of Cl^- virtually impossible in clinical samples with this particular Cl^- ISE.

Indeed, the presence of high concentration of salicylate in human serum caused an elevation of the measured chloride level [37]. Although the introduction of new ionophores, epoxy resin-based anion-responsive polymers and asymmetric two-layer membrane structures have shown remarkable reduction of the interferences from salicylate and made the sensing membrane feasible for practical applications and even available in commercial blood analyzers [38–41], cost-effective and simple-to-use methods

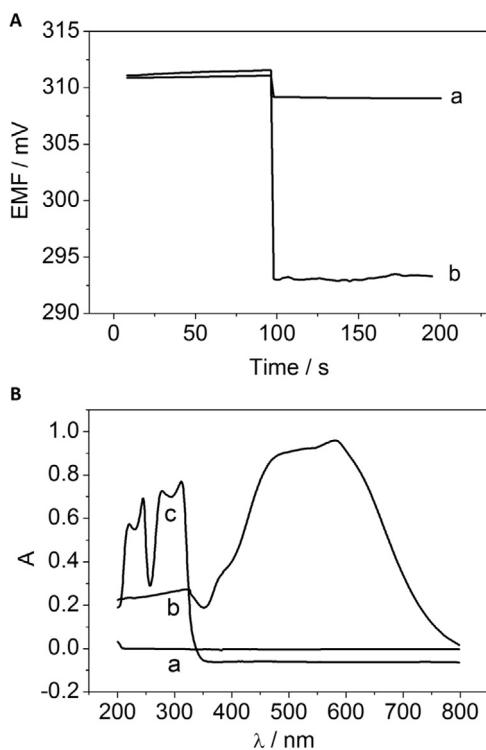


Fig. 2. (A) EMF responses (beaker-based measurements) of the ISEs toward 0.1 M NaCl containing 1.5 mM salicylate in the presence (a) and absence (b) of Fe³⁺. (B) UV-vis spectra of 0.1 M NaCl (a), 0.1 M NaCl containing 1.5 mM salicylate in the presence (b) and absence (c) of 1.0 mM Fe³⁺.

for determination of chloride ions in the presence of interfering ions are still required.

3.2. Interactions between Fe³⁺ and salicylate

It has been found that salicylate can bind Fe³⁺ into a purple-violet complex that can be monitored spectrophotometrically [42]. Beaker-based measurements were first carried out to investigate the interactions between Fe³⁺ and salicylate. As can be seen from Fig. 2A, a large potential decrease of Cl⁻ ISE can be observed in the presence of 1.5 mM salicylate compared to the potential of the electrode for the pure 0.1 M NaCl solution. On the contrary, salicylate causes only a slight potential difference in the presence of Fe³⁺, which is due to the formation of a complex of salicylate and Fe (III) ions. Since the binding constant between Fe³⁺ and salicylate is ca 2.73×10^{17} , salicylate in the complex cannot be extracted into the membrane to produce a potential response [43]. Furthermore, the absorption spectrum of salicylate is suppressed in the presence

of Fe³⁺, assuring complexation of salicylate by iron(III). Instead, a new broad absorption band with a maximum around 580 nm arises owing to the presence of the Fe(III)-salicylate complex (Fig. 2B) [28]. Although a high concentration of stable complexes may lead to a slight potential change in beaker-based measurements (Fig. 2A), Fe³⁺ can be used as a shielding reagent and adsorbed on the filter paper for determination of chloride ions in the presence of salicylate.

3.3. Paper-based microfluidic sampling and separation platform

Previous research has shown that the properties of the filter paper determine the wicking speed and could affect the contact time between the sample and the reagents [44]. Thus, the differences in properties for each paper may be useful in microfluidic sampling and separation of analytes. In this work, two paper substrates with different pore size and wicking speed were used. Whatman grade 1 filter paper (pore size = 2.0 μm) with a relatively low wicking speed could prolong the contact time between the sample and the reagents and was selected for the separation zone to facilitate the separation of the interfering ions from the sample. Conversely, a filter paper with a pore size of 12–25 μm was used for the detection zone, because it provides a much higher flow rate, which allows rapid measurements and reduces the effect of water evaporation (Scheme 1). The SEM images in Scheme 1 show the differences in pore size and fiber thickness between the filter papers used for the separation zone (A1) and the detection zone (A).

Utilizing the possibility to form stable complexes between Fe(III) and salicylate, we describe herein a paper-based microfluidic platform consisting of a separation unit (paper containing Fe³⁺) for the separation of salicylate and detection of chloride (Fig. 3A). The functionalization of the separation zone by Fe³⁺ was done utilizing paper, where cellulose and Fe³⁺ interact strongly with each other through electrostatic adsorption and hydrogen bonding [45]. To confirm functionalization, the absorbed Fe³⁺ was extracted and quantified by UV-vis spectroscopy resulting in 0.85 μmol Fe³⁺ absorbed in a filter paper of size 15 \times 15 mm², which is the size of the separation zone used ("A1" in Scheme 1). In this work, 150 μL of sample solution was added on the separation zone, and if all of the absorbed Fe³⁺ dissolved in this volume, then the concentration of Fe³⁺ was $5.6 \pm 0.9 \text{ mM}$ ($n = 3$). Since the predominant stoichiometry of the Fe(III)-salicylate coordination complex formed is 1:1, the concentration of Fe(III) on the paper substrate was enough to eliminate salicylate interferences under the experimental conditions used here [43].

Interestingly, the operation and effectiveness of the device can be observed by the naked eye. As the solution passed through the separation zone, salicylate in the solution was largely retained by Fe³⁺ ions. The color of the separation zone thus changed from light

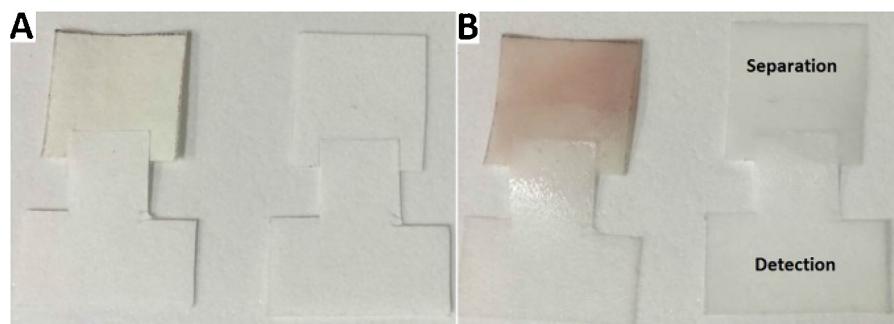


Fig. 3. (A) Photographs of the device with (left) and without (right) Fe³⁺ functionalization. (B) Photographs of the device in the presence (left) and absence (right) of salicylate in the sample solution.

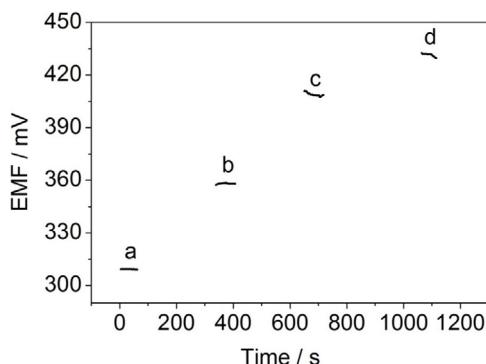


Fig. 4. Potentiometric response of the solid-contact Cl^- -ISE utilizing the proposed paper-based analytical device for sampling of standard solutions of 10^{-1} (a), 10^{-2} (b), 10^{-3} (c) and 10^{-4} M NaCl (d).

yellow (Fig. 3A left) to purple-violet (Fig. 3B left) due to the formation of the Fe(III)-salicylate complex.

Due to the small volume of sample solution ($150 \mu\text{L}$) and its evaporation, the EMF responses were recorded for only 90 s. EMF measurements utilizing the paper-based device were carried out for determination of standard solutions and the results are shown in Fig. 4. A linear response can be observed for the Cl^- -ISEs when the measurement was run in decreasing Cl^- activity from 10^{-1} to 10^{-3} . A slope of 52.4 ± 0.7 was obtained, which is slightly lower than that observed in beaker-based measurement (Fig. 1A). For the proposed Cl^- -ISE the lower detection limit is higher using paper-based sampling than in beaker-based measurements. This phenomenon has also been observed in textile-based sampling for Cl^- [23].

To evaluate the measurement time on the potential response, the potentiometric measurement was run for more than 600 s in each solution. As shown in Fig. 5, the potential responses of the Cl^- -ISE are similar for both paper- and beaker-based measurements. Moreover, the paper containing Fe(III) behaved similarly to the paper substrate without Fe(III) when detecting Cl^- in absence of salicylate. There was a clear potential drift in paper-based measurements and the potential drift was more obvious at low concentrations of Cl^- (as can be seen from Fig. 4). During the first 90 s, the drift was in the range $0.01\text{--}0.03 \text{ mV s}^{-1}$ for the detection of low concentrations of Cl^- . Since the drift was most obvious for low chloride concentrations, and slightly higher for paper-based sampling than beaker-measurements, it can tentatively be related to chloride-interference from the reference electrode and/or evaporation. The overall potential drift in absence (Fig. 5 curve b) and presence of Fe^{3+} (Fig. 5, curve c) are similar for the paper-based sampling, indicating that the presence of Fe^{3+} does not signifi-

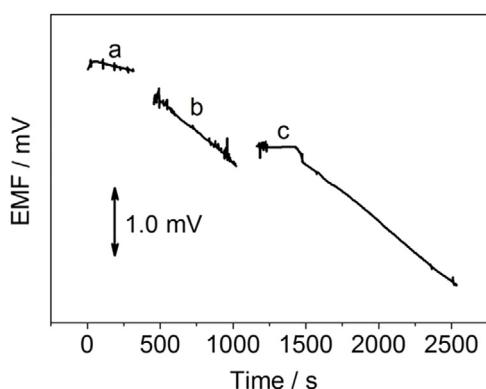


Fig. 5. Potentiometric response of the solid-contact Cl^- -ISE for 0.1 M NaCl in beaker-(a) and paper-based measurements without (b) and with (c) modification by Fe^{3+} .

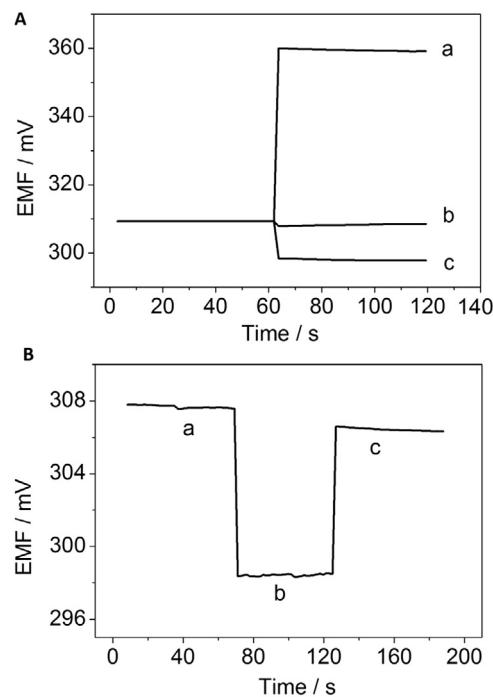


Fig. 6. (A) EMF responses of the device with (a,b) and without (c) Fe^{3+} functionalization toward 0.01 M NaCl (a) and 0.1 M NaCl containing 1.5 mM salicylate (b,c) (B) EMF responses of the device with (a,c) and without (b) Fe^{3+} functionalization toward serum alone (a) and serum containing 1.5 mM salicylate (b,c).

cantly influence the potential drift. A slight potential drift due to the solid-contact ISE cannot be excluded [23].

3.4. Paper-based microfluidic sampling and separation of salicylate

To demonstrate the feasibility of the device for potentiometric ion sensing, 0.1 M NaCl sample solution in the absence and presence of 1.5 mM salicylate were measured (Fig. 6A). For the paper device without Fe(III), the recorded potential showed a large decrease in the presence of 1.5 mM salicylate (Fig. 6A, curve c). However, only a small potential change was observed for the paper device containing Fe(III) (Fig. 6A, curve b). These results indicate that the salicylate is indeed capable of being separated by complexation with Fe(III). Moreover, the separation process may be facilitated also by non-specific adsorption of the lipophilic ions on the filter paper.

The analytical feasibility of this paper-based device was evaluated also in serum samples. The matrix effect of human serum was first evaluated via potentiometric sensing. As illustrated in Fig. 6B, spiking serum with 1.5 mM salicylate resulted in about 10 mV potential decrease for the paper device without Fe^{3+} . On the contrary, the paper device containing Fe^{3+} showed a potential change of only ca. 1 mV, which could even be attributed to the potential drift of the electrode in the complex sample matrix. The result is encouraging, but extensive optimization of the paper-based analytical procedure would still be required in order to achieve the extremely high accuracy, repeatability and reproducibility that would be required for clinical analysis. However, the results presented in this work demonstrate the feasibility of paper-based microfluidic sampling and separation of analytes combined with potentiometric sensing.

4. Conclusions

In conclusion, a low-cost, simple, disposable paper-based microfluidic sampling and separation platform for potentiometric sensing was demonstrated. The advantage of this system is in the use of paper for both sampling and separation of ions. Thus, any complex pretreatment procedures can be simplified or avoided. It should be noted that many pieces of separation zones with different shielding reagents can in principle be designed and connected together just like a jigsaw. In that way, different types of interferences can be eliminated to facilitate the subsequent potentiometric detection. We also anticipate that this strategy potentially broadens the range of analytes that can be measured by potentiometric ion sensors.

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