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Research paper

Absorbance-based detection of arsenic in a microfluidic system with push-and-pull pumping

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ABSTRACT

Rapid and portable analysis of arsenic (As) contamination in drinking water is very important due to its adverse health effects on humans. Available commercial detection kits have shown low sensitivity and selectivity in analysis, and also they can generate harmful by-products. Microfluidic-based approaches allow portable analysis with gold nanoparticles (AuNPs) as labels. However, they need complex surface modification steps that complicate detection protocols. Due to the lack of precise sensing and affordable solution, we focused on developing a microfluidic platform that uses a push-and-pull pumping method for sensitive detection of As. In this detection principle, a sample is introduced in the microfluidic channel modified with -SH functional groups where As can bind. Then, AuNPs are given in the channel and AuNPs bind on free -SH functional groups which are not allocated with As. Absorbance measurements are conducted to detect AuNPs absorbed on the surfaces and the resulting absorbance value is inversely proportional with As concentration. The method enables detection of As down to 2.2 μg/L concentration levels in drinking water, which is well-below the allowed maximum As concentration of 10 μg/L in the drinking waters by the World Health Organization (WHO). The paper reveals that multiple push-and-pull pumping of fixed volume of sample and AuNPs with a syringe pump can improve the binding efficiency in the microfluidic channel. With this technique, low amounts of sample (1 mL) and short total assay time (25 min) are sufficient to detect As.

1. Introduction

Heavy metals are very harmful due to their accumulation in nature and in the human body [1]. Heavy metals especially arsenic (As) are not biodegradable and have also carcinogenic and toxic effects even at low concentrations [2,3]. As(V), As(III), As(0) and As(-III), which are chemical species of As, are commonly found in groundwater [4]. Although a maximum contamination limit for As determined by the World Health Organization (WHO) and Occupational Safety and Health Administration (OSHA) is 10 μg/L, it is much higher than this value in some developing regions of the world, including Taiwan, Bangladesh, Chile, and India [5,6]. Considering poor reliable and cost-effective commercially available As detection methods, sensitive and rapid methods are needed to detect As on-site rapidly [7].

Existing laboratory-based methods, such as a silver diethyldithiocarbamate spectrophotometry, hydride generation atomic absorption spectrophotometry (HG-AAS), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma atomic emission spectrometry (ICP-AES), high performance liquid chromatography (HPLC) and flow injection analysis systems (FIAS) are high-sensitive methods for As detection [8–11]. However, these methods require high-cost and bulky equipment that cannot be used for rapid on-site testing.

As in drinking water can also be detected via colorimetric assays, but these colorimetric kits are mostly qualitative and not highly sensitive for the As concentration range determined by WHO [12]. In a study of colorimetric As detection, As was rapidly detected in approximately 3 min based on color changing from orange to blue using difluoroboron (BF_2)-curcumin down to 1.87 mg/L As concentration levels [13]. Moreover, As was detected down to 18 μg/L in 30 min on a paper strip using colorimetric assay [14]. Purple color was achieved in As samples using sulfanilic acid and N- (1-naphthyl) ethylene diamine dihydrochloride. In another rapid colorimetric-based As detection, arsine gas (AsH_3) generation was performed, and then AsH_3 was reacted with auric

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chloride on a Whatman filter paper that produce metallic gold color [15]. The intensity of color related with the concentration of As in water sample and 10 μg/L of As concentration can be detected in 10 min. An important problem of this method is the interference of As with phosphate that can create a problem in high phosphate concentrations [16]. Moreover, methylene blue was also used in colorimetric As detection assay [17]. As was detected down to 10–100 μg/L in 6 min with AsH_3 generation in the presence of silver nanoparticles/AuNPs. But, these methods suffer from toxic gas generation that can limit their usage on-site. Furthermore, As(V) was detected using molybdenum-based assay that formed microparticles in the presence of As and changed the color of the solution [18]. However, low sensitivity of this method (> 10 μg/L) for As detection in drinking water is the major problem. In another study, citrate-capped AuNPs were aggregated in the presence of As [19]. This method was used to detect As(III) colorimetrically down to 1.8 μg/L level.

Microfluidic-based systems offers rapid, low-cost, and sensitive analysis of As using optical measurements. For instance, E.coli bacteria containing green fluorescent protein (GFP) was used to detect As(III) in a microfluidic device [20]. In the engineered strain, GFP formation was triggered when As(III) entered the bacteria. Intensity of GFP increased with As(III) concentration, and the method allowed to detect 50 μg/L As (III) concentration levels. In another microfluidic-based system, conventional hallow fiber membrane-based extraction system was used for As(V) detection down to 27 μg/L with spectrophotometric measurements by using dibutyl butylphosphonate and tributyl phosphate as selective agents and molybdenum blue as a colorimetric reagent [21]. As was also sensed down to 320 μg/L in 25 min using Leucomalachite green dye [22]. Furthermore, a commercial colorimetric kit was applied in a microfluidic system to detect As down to 5–20 μg/L with AsH_3 generation [23]. In this portable system, the detection was achieved in 60 min at in 22 °C or in 25 min at 50 °C. A portable microfluidic platform was also used for optical detection of As(III) from the soil down to 710 μg/L in 3 h [24]. In this smartphone integrated platform, As(III) bound on aptamers was destabilized AuNPs that resulted in aggregation of AuNPs. In another As(III) detection system, a paper-based microfluidic system was used to detect As(III) down to 1 μg/L in 5 min [25]. In this device, the amount of As(III) was determined with the aggregation of AuNPs functionalized with thioctic acid and thioguanine in the presence of As. However, the method requires complex surface functionalization steps for AuNPs.

Here, we present a new microfluidic-based method for sensitive As detection down to ~2.2 μg/L with bare AuNP labels. For this method, the number AuNPs captured on the -SH modified microfluidic surface is decreased with As concentration so that the change of the absorbance value on the channel measured with a handheld spectrometer reveals As concentration. Push-and-pull pumping of the As sample and AuNP solution in the microfluidic channel was also used in order to reduce sample volume and testing time for on-site As detection.

2. Materials and methods

2.1. Materials

(3-Mercaptopropyl) trimethoxysilane (3-MPS) (175617), 40 nm diameter AuNPs (741981), As standard solution (39436), and Tris(2-carboxyethyl) phosphine hydrochloride (TCEP) (C4706) were purchased from Sigma Aldrich (Missouri, USA). Acetone (20066) was obtained from VWR (Pennsylvania, USA). 200 proof Ethanol (K50690883 844) was purchased from Merck (Darmstadt, Germany). 24 × 50 mm^2 cover glasses with a thickness of 0.13–0.17 mm (I.075.00.006) were purchased from Interlab (Istanbul, Turkey). SYLGARD 184 Silicone Elastomer Kit (1673921) to prepare polydimethylsiloxane (PDMS) was bought from Dow Corning (Michigan, USA). The clear photoreactive resin (V2 FLGPCL04) was obtained from FormLabs (USA). Tygon® tubing (ND-100-80) that has 0.51 mm inner diameter and 1.52 mm outer diameter was acquired from Saint-Gobain (France). Syringes with a volume of 5 mL and 50 mL were acquired from BD (USA) and Beybi (Turkey), respectively. Drinking water having <5 μg/L aluminum, <0.05 mg/L ammonium, 13.8 mg/L chloride, <5 μg/L iron, 15 μg/L manganese, 3.1 mg/L sulphate and 17.3 mg/L sodium was purchased from OZSU (Izmir, Turkey).

2.2. Solutions

Distilled water with a resistance value of 0.5 MΩ was prepared using Sartorius Arium® (Germany). 70% Ethanol solution was made by diluting 70% (*v*/v) 200 proof Ethanol in distilled water. 3-MPS solution was prepared by diluting 2.5% (v/v) 3-MPS in Acetone. TCEP solution was made by diluting 0.3% (*w/v*) TCEP in distilled water. After AuNPs were centrifuged at 12000 rpm for 15 min, and the supernatant was removed, AuNPs solution was prepared by adding distilled water having the same volume of removed supernatant. Different concentrations of As solutions were prepared in distilled water and also drinking water.

2.3. Surface modification of glass substrates

Glass substrates (i.e., cover glasses) used for As detection surface were first cleaned with 70% Ethanol solution in an ultra sonicator (Isolab, Germany) for 10 min. After the glass substrates were dried with N_2, they were treated with air plasma (ZEPTO, Diener, Germany) at 0.5 mbar and 100 W for 4 min to activate surfaces. Then, glass substrates were silanized by incubating of 3-MPS solution for 2 h in a dark environment. After the glass substrates were cleaned with 70% Ethanol and dried with N_2, they were ready to be bonded to microfluidic chips. Contact angles were measured using Attension Theta Tensiometer (Biolin Scientific, Sweden), and Fourier Transform Infrared Spectroscopy (FTIR) was conducted using Spectrum Two FTIR Spectrometer (Perkin Elmer, USA).

2.4. Fabrication of microfluidic chips

PDMS-based microfluidic chip was produced using soft lithography method (Fig. S1) [26]. For this purpose, the mold of the microfluidic channels designed as 35 mm length × 5 mm width × 1 mm height was fabricated using 3D stereolithographic printer (Form2, Formlabs, USA). After a PDMS mixture prepared with a ratio of 10(polymeric base):1 (curing agent) was poured into the mold and it was degassed in a vacuum chamber, PDMS was cured overnight at 65 °C. The cured PDMS was removed from the mold. The fabricated channel had a length of 38.5 mm ± 0.1 mm, a width of 4.75 mm ± 0.2 mm and a height of 0.68 mm ± 0.2 mm. Inlets and outlets of the channel were opened using a blunt tip needle (TE series G14, Thomas Scientific, USA) with an inner diameter of 1.50 mm and an outer diameter of 1.82 mm. Fabricated open microfluidic channels on PDMS substrate were treated with 100 W air plasma for 3.5 min at 0.5 mbar, and then they were sealed on silanized glass substrates by clamping PDMS and glass substrates between two 3D printed pieces with screws (Fig. S1). The microfluidic chip contained two-microfluidic channels used as detection and reference channels to detect As levels.

2.5. Microfluidic protocols for arsenic detection

First, 100 μL of distilled water was injected to each channel on the microfluidic chip for 2 times for cleaning purposes. Then, 100 μL TCEP solution was incubated inside channels for 10 min to eliminate disulfide bonds on silanized surfaces [27], and then channels were washed with 100 μL of distilled water for 2 times. Afterwards, As sample was introduced in the detection channel and in the meantime, a reference solution (i.e., either distilled water or drinking water with 0 g/L As) was given in the reference channel. These samples were introduced using either pipetting or a syringe pump (NE 1600, New Era Pump Systems, USA).

100 μL of samples were used for pipetting. For the microfluidic protocol involving pumping steps, the microfluidic chip was connected to the syringe pump with tubings (Fig. S2). A flow rate of 10 mL/min was utilized to introduce 100 mL of sample for 10 min with a 50 mL syringe. At this sample introduction step, 10 mL/min flow rate could also be used for push-and-pull pumping of 1 mL sample for 10 min with a 50 mL syringe. After the channels were cleaned with 100 μL of distilled water, 100 μL of AuNP solution was given inside the channels and incubated for 2 h. At this step, 100 μL of AuNP solution could be also introduced using push-and-pull pumping at 1.5 mL/min flow rate with a 5 mL syringe for 10 min. After that, channels were washed with 100 μL of distilled water for 2 times.

2.6. Absorbance measurements

After completion of microfluidic protocols, absorbance values of the channels were measured using a handheld spectrometer (HR4000CG UV-NIR, Ocean Optics, USA). For these measurements, the spectrometer was connected to an inverted microscope (CKX41, Olympus, Japan) with a 3D printed adaptor through an eyepiece (Fig. S3). The channel was monitored under the microscope using 4× objective and measurements were conducted using OceanView software. After selecting the absorbance concentration model, scan average value of 5, boxcar width of 10 points and integration time of 5000 ms were set on the software. Absorbance values at 530 nm were utilized for As detection purposes since AuNPs were given peak absorbance value around at this wavelength (Fig. S4). Differences of absorbance values between reference and detection channels (i.e., called as absorbance difference) were then measured for each microfluidic chip to reveal the detection signal for different As concentrations.

2.7. Statistical analysis

All experiments were conducted three times using a new microfluidic chip. The data on the figures were shown as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) for multiple comparison with Tukey's post-hoc test was also conducted. The statistical significance threshold was set to 0.05 ($P < 0.05$). Mean values of experimental data were fitted using semi-log linear regression and coefficient of determination (R^2) values were presented on the figures. These analyses were conducted using GraphPad software (Prism 8 version, GraphPad, USA).

3. Results and discussion

Arsenic detection procedure in a microfluidic chip with reference and detection channels was presented in Fig. 1. As solution and reference solution with 0 g/mL As were introduced in the microfluidic channels. As molecules were bound on the glass substrate having thiol groups. Then, the bare AuNPs delivered to the channels were bound to the remaining surface thiol groups. The number of AuNPs was decreased on the surface with a higher concentration of As presented in the detection channel since the available thiol groups on the glass surface were decreased with As concentration. The amount of As could be perceived with absorbance value differences between reference and detection channels at 530 nm wavelength, which gives peak absorbance value for AuNPs (Fig. S4).

3.1. Surface functionalization protocol

The success of silanization process was controlled using surface contact angle measurements. The silanized glass surface showed higher contact angle than the air plasma threated glass surface (Fig. S5) due to the deposition of 3-MPS [28]. To evaluate success of functionalization

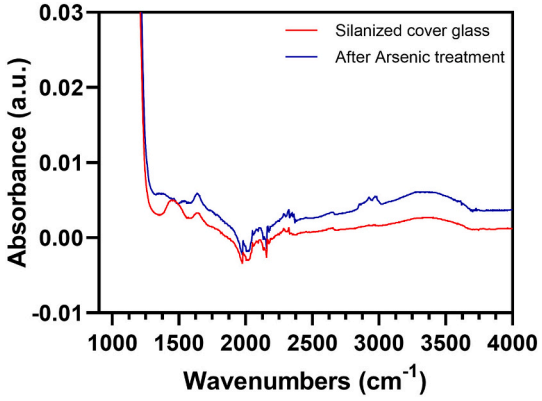

Fig. 2. The FTIR results on glass substrates after silanization and As incubation steps.

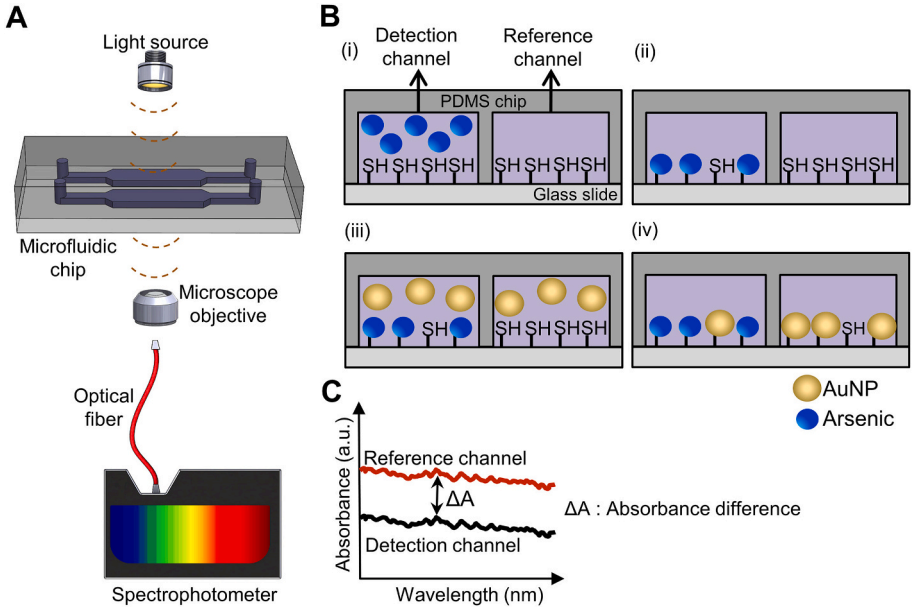

Fig. 1. Arsenic detection procedure in a microfluidic chip having detection and reference channels with thiol groups on their surface. (A) 3D illustration of As detection setup. (B) Microfluidic protocols for As detection. (i) As and reference solutions were injected in the detection and reference channels, respectively. (ii) After the channels were washed with distilled water, (iii) AuNPs were introduced in the microfluidic channels. (iv) After a washing step with distilled water, the absorbance measurements were conducted in each channel. (C) Represented absorbance measurements from detection and reference channels. The absorbance difference between reference and detection channels was correlated with As concentration presented in the sample.

processes, glass surfaces were analyzed with FTIR (Fig. 2). 3-MPS has OH, CH and C = O bonds in its molecular structure [29]. Hence, peaks of 3-MPS were seen at absorption valuesof 1643, 2932, and 2983 cm^{-1}, respectively. Peaks for acetone, that was used to prepare 3-MPS solution, were seen at absorption values of 1456, 2940, and 2966 cm^{-1} [30]. Peaks for As bound on the cover glass were observed at 1465, 2829, and 2956 cm^{-1} [31,32]. Based on the FTIR measurement results, it was concluded that the glass surface was successfully coated with 3-MPS and As could attach on this surface.

3.2. Optimization of arsenic detection protocol

In the As detection protocol, we optimized pH of AuNPs solution and the incubation time of AuNPs and As sample to enhance the detection signal. Here, As sample was prepared in distilled water. Following the protocol using pipetting of 1000 mg/L of As concentration with 10 min incubation and then 120 min AuNPs incubation, it was observed that the highest absorbance difference was reached for 6.5 pH value of AuNPs solutions (Fig. 3A). The reason for the negative absorbance difference results for other pH values can be due to unspecific binding of AuNPs on As treated surfaces. Moreover, the effect of incubation time of AuNPs on the absorbance difference was examined using pipetting of 100 mg/L of As solution followed by 10 min As incubation. As shown in Fig. 3B, the maximum absorbance difference was obtained for 120 min AuNPs incubation. This absorbance difference was statistically different than the absorbance difference values of 10 and 30 min of AuNPs incubation. Lastly, the absorbance difference was investigated for 100 mg/L of As concentration with different As incubation times followed with 120 min AuNPs incubation. It was observed that absorbance differences were increased with the incubation time and saturated after 10 min (Fig. 3C). Hence, 10 min of As incubation and 120 min incubation of AuNPs prepared in 6.5 pH value were applied as optimum conditions in As detection experiments for obtaining maximum absorbance difference for As sample.

3.3. Arsenic detection

Different concentrations of As spiked in 100 µL distilled water were introduced into the detection channel with pipetting and then incubated for 10 min. In the meantime, reference solution was introduced in the reference channels in each chip. The absorbance difference between reference and detection channels was increased with As concentration (Fig. 4A). Increasing As concentration increases the amount of As bound to -SH bonds on the glass surface, and therefore, fewer AuNPs adhere on the surface. The limit of detection (LOD) concentration was obtained by intersecting the linear fit curve of experimental data with the LOD signal, which equals to mean plus three standard deviation of the absorbance difference signal for 0 g/mL As [33]. LOD was found as 1.3 mg/L for 100 µL distilled water sample introduced with pipetting (Fig. 4B). In order to improve the sensitivity of the assay by capturing more As molecules on the chip surface, sample volume was increased to 100 mL and introduced by a syringe pump. We observed that LOD was reached 2.2 µg/L for 100 mL of drinking water (Fig. 5). Therefore, increasing sample volume by 1000-fold with syringe pumping help to improve LOD for more than 550-fold in the microfluidic chip even in drinking water. The limit of quantification (LOQ) concentration was calculated by intersecting linear fit curve of experimental data with the LOQ signal, which equals to mean plus ten standard deviations of the absorbance difference signal for 0 g/mL As [34]. LOQ concentration was found as 1.33 mg/L. There are lots of minerals in the drinking water, such as chloride (13.8 mg/L), iron (<5 µg/L), manganese (15 µg/L), sulphate (3.1 mg/L), and sodium (17.3 mg/L) that can bind to thiol groups also [35–39]. The absorbance values of microfluidic channels treated with AuNPs after incubation of distilled and drinking water containing no As were compared, and no statistical difference was observed between the channels (Fig. S6). This observation can indicate other minerals presented in the drinking water cannot interact with the thiol groups as efficient as As. On the other hand, the thiol group can be linked with other heavy metals, such as chromium (Cr), cadmium (Cd), lead (Pb), mercury (Hg) and copper (Cu) [40,41]. But, these heavy metals should be presented as low as (<3 µg/L for Cd, <10 µg/L for Pb, and < 6 µg/L for Hg) As concentration permitted in the drinking water according to WHO standards [42]. For different As concentrations spiked in drinking water, measured absorbance signal, relative standard deviation (RSD) and recovery rate were presented in Table S1 to evaluate reproducibility and accuracy. The experiments were conducted at different time intervals on different microfluidic chips. The RSD was found 27.7–59.2% and the recovery rate was 72.3–120.94% for As concentration of 10–10,000 µg/L. Recovery rates were adequate with respect to Standard Method Performance Requirements (SMPRs) of Association of Official Analytical Collaboration (AOAC) [43] in certain As concentrations. Although RSDs are above AOAC's SMPRs, the reproducibility can be improved with increased in As concentration. Based on the results, we believe that our method would be more suitable for qualitative detection of As.

Sequential push-and-pull pumping, which can improve molecular binding on microfluidic surfaces [44], was used to reduce the sample volume of As detection. For this purpose, 1 mL of sample was pumped through the channel 100-times with sequential push-and-pull operations for 10 min. This strategy revealed that reference signal obtained for reference sample with 0 g/mL As concentration prepared in distilled water was statistically different than the sample signal obtained for 10

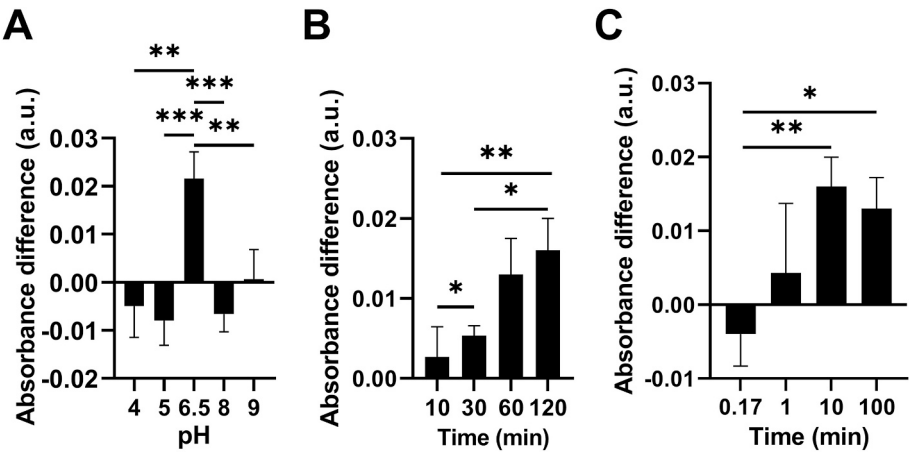

Fig. 3. Optimization of the As detection procedure. The comparison of absorbance difference values between reference and detection channels for (A) different pH values of AuNPs solution, and different incubation times of (B) AuNPs, and (C) As solution. *, ** and *** represent $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

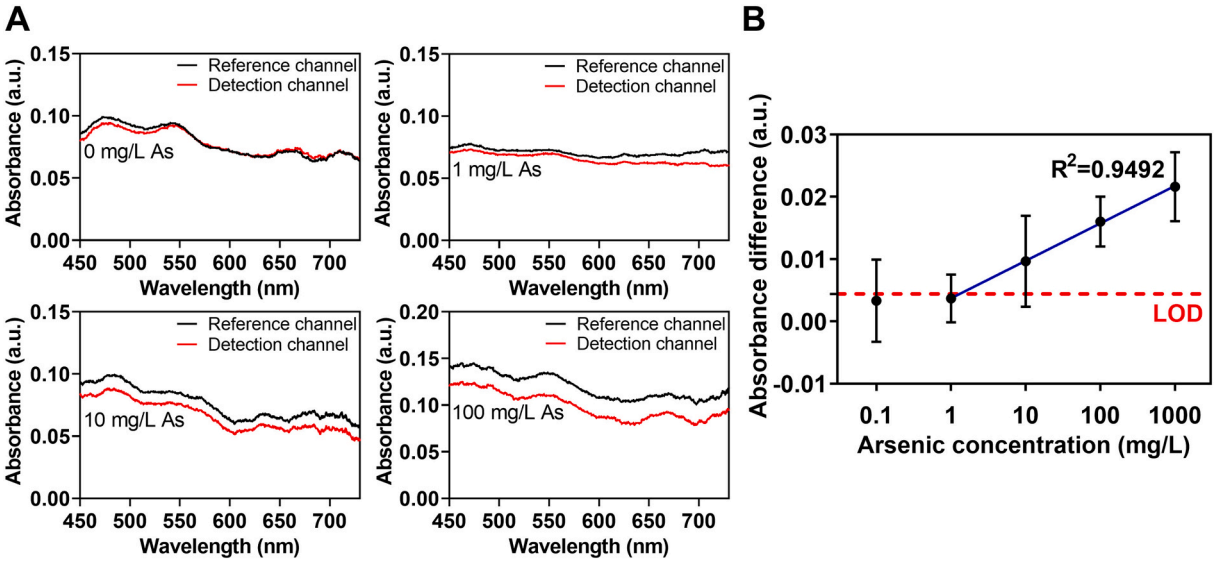

Fig. 4. Absorbance values of different As concentrations prepared in distilled water and introduced in the microfluidic channels with pipetting. (A) Absorbance values obtained on the microfluidic chips for different As samples. (B) Correlation of absorbance difference with As concentrations. Data are represented as mean of three replicates with standard deviation. Linear fit is presented on the graph as a solid line with coefficient of determination (R^2). LOD signal is shown as a dot line.

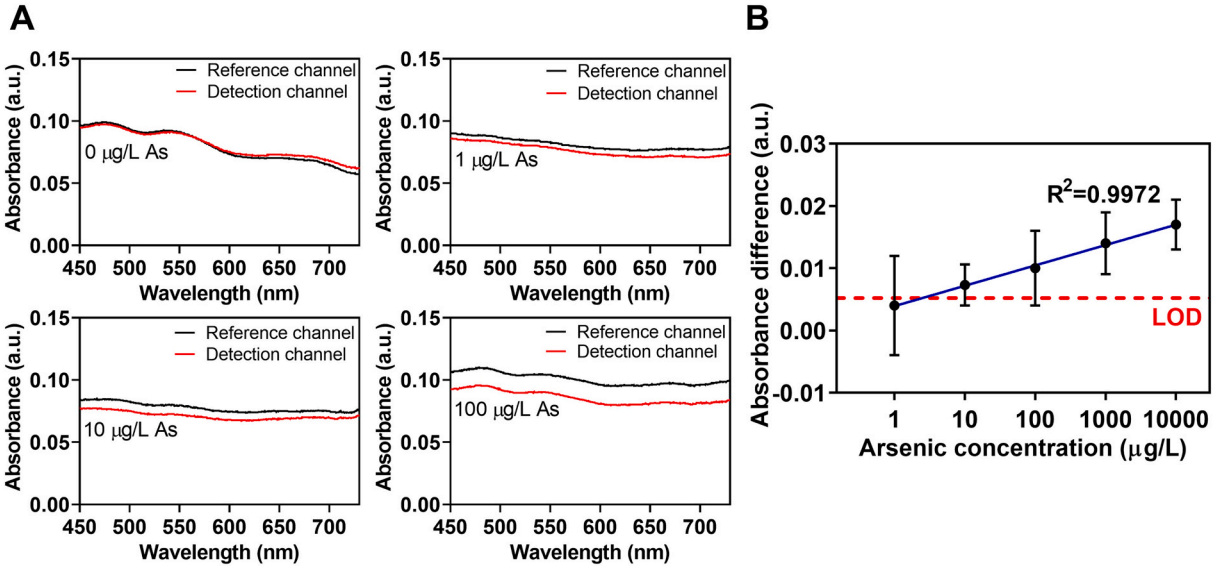

Fig. 5. Absorbance values of different As concentrations prepared in drinking water and introduced in the microfluidic channels with pumping. (A) Absorbance values obtained on the microfluidic chips for different As samples. (B) Correlation of absorbance difference with As concentrations. Data are represented as mean of three replicates with standard deviation. Linear fit is presented on the graph as a solid line with coefficient of determination (R^2). LOD signal is shown as a dot line.

µg/mL As sample prepared in distilled water (Fig. 6). Moreover, neither background signal nor sample signal was statistically indifferent than the signals obtained with continuous pumping of 100 mL. This shows that the sequential push-and-pull pumping can decrease sample consumption without sacrificing assay sensitivity.

Sequential push-and-pull pumping method was also applied for introducing AuNPs to decrease necessary incubation time of AuNPs. For this purpose, As sample prepared in distilled water with a concentration of 10 mg/mL and distilled water as a reference sample (0 g/mL As) were pipetted inside the channel and waited for 10 min. Afterwards, AuNPs with a volume of 100 µL were pumped into the channels for 150 times with 10 min of sequential push-and-pull operations. Statistical difference was observed between reference and As samples for sequential push-and-pull pumping of AuNPs and also for 2 h incubation of AuNPs (Fig. 7). Moreover, background and sample signals of different AuNP incubation methods were statistically indifferent. Hence, the As analysis could be reduced to 25 min with push-and-pull pumping.

4. Conclusion

The permissible limits for As in drinking water are set by various organizations such as WHO, American Public Health Association (APHA), Indian Standard Institution (ISI), Central Pollution Control Board (CPCB) and Indian Council of Medical Research (ICMR) [45]. Due to the negative effects of As on human health, many countries have accepted the WHO standard of 10 µg/L as the maximum level [45]. Especially in European countries, it is recommended in national guidelines to reduce As concentration in drinking water to 1 µg/L [46]. It has been shown that deaths caused by As related diseases decrease with the decrease in the permissible level [45,46]. The maximum allowed As

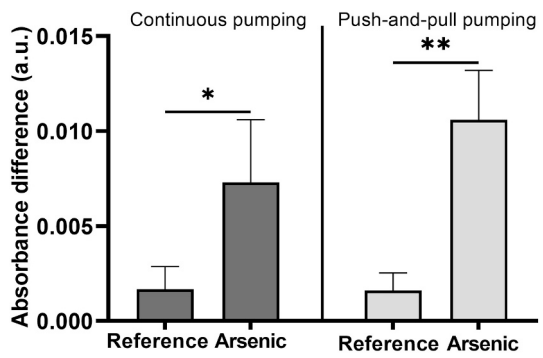

Fig. 6. Absorbance difference values of reference sample with 0 g/mL As and 10 μg/L As sample introduced with continuous and sequential push-and-pull pumping methods. Data are shown as mean of three replicates with standard deviation. * and ** represent $P < 0.05$ and $P < 0.01$, respectively.

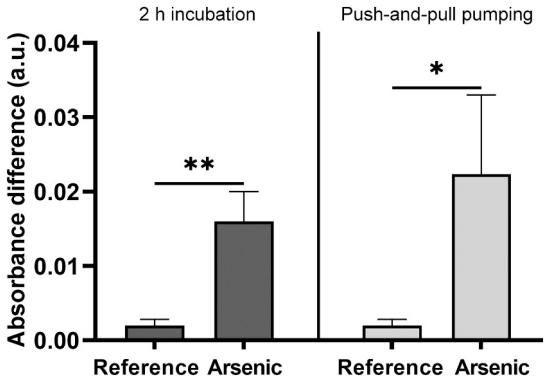

Fig. 7. Absorbance difference values of reference sample with 0 g/mL As and 10 mg/L As sample by using either 2 h incubation of AuNPs or sequential push-and-pull pumping of AuNPs. Data are shown as mean of three replicates with standard deviation. * and ** represent $P < 0.05$ and $P < 0.01$, respectively.

contamination level determined by WHO standards (10 μg/L) cannot be easily detected with available low-cost kits [5]. Moreover, reaction and AuNPs based As detection systems involve complex chemical functionalization steps that need precise processing [25,47]. Microfluidic-based As detection using optical measurements offer portable, rapid, and sensitive As detection (Table S2). However, most of these methods could not reach detection limits meeting WHO standards. Moreover, they can either produce toxic gases or require complex surface functionalization steps. Here, we presented a new microfluidic device with push-and-pull pumping strategy to detect As down to 10 μg/L concentration levels in a minute amount of sample (1 mL). Furthermore, analysis time could be less than 30 min by this pumping strategy in all assay steps. We utilized PDMS-based microfluidic device and surface functionalized glass coverslip for detection, and the detection was conducted with bare AuNPs used as labels. Hence, the cost of a single test is about $ 1.5, which is comparable with low-cost As detection kits ($ 0.4–2 per test) [5,48]. Moreover, the utilization of bare AuNPs facilitates the storage of these detection labels and also the detection protocols by eliminating complex AuNPs functionalization procedures and sample preprocessing steps [49]. As detection measurements were also conducted using a portable spectrometer, that could also be applied for on-site testing. Pumps could be integrated in the microfluidic platform for automated analysis for the future. Therefore, we believe that our microfluidic detection technique could potentially provide low-cost and portable As detection in the field, and by doing so it could disseminate the usage of on-site As tests for rapid assessment of As contamination levels to reduce related health problems.

Author contributions

H.C.T. conceived and designed the study; Y.G. designed and fabricated the microfluidic platform; B.K and Y.G. performed experiments; all authors analyzed the data; B.K. and H.C.T. wrote the manuscript.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mee.2021.111583.

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