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ARTICLE TYPE

# Surface-Enhanced Raman Scattering on a Zigzag Microfluidic Chip: towards High-Sensitivity Detection of As (III) Ions

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## ABSTRACT:

In the study, the microfluidic platform was combined with surface-enhanced Raman scattering (SERS) to implement the rapid quantitative detection of As (III) ions in a continuous flow. Silver nanoparticles (AgNPs) were used as SERS enhancement substrate, and glutathione (GSH) with 4-mercaptopyridine (4-MPY) were conjugated on the surface of AgNPs. When As (III) ions encountered GSH/4-MPY functionalized AgNPs, the original monodispersed probes would aggregate because As (III) ions had a strong affinity to the GSH. As a result, Raman signals of 4-MPY adsorbed on the surface of AgNPs were improved and the As (III) ions could be detected. Due to the advantages of microfluidics technology combining SERS detection, the highly sensitive and reproducible analysis of As (III) ions was realized in several minutes. The proposed method allowed the quantitative analysis of As (III) ions with a linear range (3 to 200 ppb), and the limit of detection (LOD) of As (III) ions was determined to be 0.67 ppb. The real water sample was also analyzed to confirm the practicability of the method and several microliter sample consumption was very friendly to the environment. This method also showed great potential in applying SERS combining lab-on-a-chip technique in the area of environmental monitoring with a high sensitivity and environment-friendly way.

**Keywords:** microfluidic chip, surface-enhanced Raman scattering, SERS, PDMS, arsenic ions

## 1. Introduction

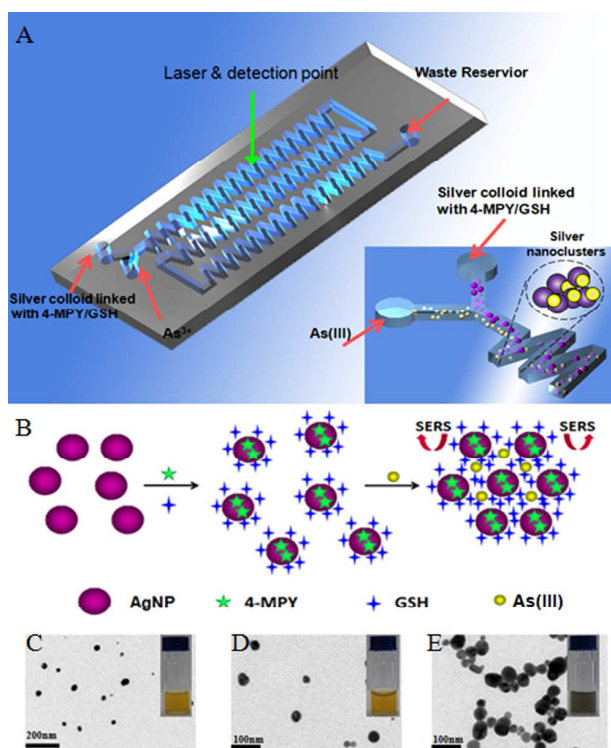
Arsenic is widespread in nature, and has been applied in agriculture, animal husbandry, electronics, industry, metallurgy and other fields. But this element is well known for its toxicity and carcinogenicity [1]. Arsenic can enter the body through the respiratory tract, digestive tract and skin. Many countries reported cases of acute and chronic arsenic poison [2]. There are inorganic and organic forms of arsenic in which inorganic arsenic is more toxic [3]. Due to the limitation of detection technology and the practical difficulties of arsenic removal from drinking water. Over the decades, many analytical techniques to detect As (III) ions at trace level have been developed, such as atomic absorption spectrometry (AAS), high-performance liquid chromatography (HPLC), inductively coupled plasma/atomic emission spectrometry (ICP/AES), and inductively coupled plasma/mass spectrometry (ICP/MS), etc [4]. Although these analysis methods can achieve low detection limit, some limitations such as costly, time-consuming and high skill requirements for operation still existed. It is very necessary to

develop a simple, fast and highly sensitive detection method.

SERS spectra can provide higher detection sensitivity and have been applied in many fields [5, 6]. SERS effect is a local physical phenomenon that happens on the holes or gaps in the rough metal surface. It is commonly regarded that SERS enhancement is mainly attribute to the electromagnetic field caused by the plasmon resonance on the metal surface [7]. Therefore, it is important to choose excellent substrate in SERS research. When the incident light is in the ultraviolet to visible light range, the Raman enhanced ability of Ag was stronger than other metals such as Cu and Au. In recent years, some applications of nanoparticles based SERS had been reported. Ren [8] *et al.* reported the detection of mercury ions with SERS technique based on the interaction between AgNPs and mercury ions. Li *et al.* developed a sensitive SERS sensor for determination of As (III) ions by using GSH/4-MPY functionalized AgNPs [9]. Bi *et al.* used gold nanoparticles as substrate and realized the sensitive SERS detection of DNA [10].

As a promising and powerful tool, microfluidics or lab-on-chip technique shows great potential in the past two decades [11-13]. It has many advantages such as fast speed [14, 15], low sample

consumption [16-18], easy for minimization [19, 20] and high throughput analysis [21, 22]. Moreover, combining the SERS detection on a microfluidic format will overcome some limitations of conventional SERS detection under static conditions [23, 24]. This is because the measurement under flowing conditions prevents problems of variable mixing times, scattering geometry, localized heating, and photo dissociation [25]. Therefore, there is growing interests in the study of coupling the microfluidic chip devices with SERS detection, and their applications for sensitive chemical and biological analysis [5, 26, 27]. In this work, we combined polydimethylsiloxane (PDMS) microfluidic platform with SERS to implement the rapid and sensitive SERS detection of As (III) ions in a continuous flow on a zigzag microfluidic chip.



**Fig. 1.** (A) The Schematic diagram of the microfluidic chip using for analyzing As (III) ions. The rapid fully mixing of As (III) ions and GSH/4-MPY functionalized AgNPs achieved in a zigzag (75° angles) microfluidic channel. (B) The analytical principle for As (III) ions. When As (III) ions couple with GSH/4-MPY functionalized AgNPs will aggregate and the Raman signals are improved when 4-MPY adsorbed on the surface of AgNPs. (C, D, E) The followings are TEM images and their visual color changes (shown in a glass bottle) corresponding to (C) non-aggregated AgNPs, (D) non-aggregated GSH/4-MPY functionalized AgNPs, and (E) aggregated GSH/4-MPY functionalized AgNPs in the presence of As (III) ions. The Scales bars are 200 nm, 100 nm, and 100 nm respectively.

## 2. Experiments

### 2.1 Reagents

Silver nitrate ( $\text{AgNO}_3$ , 99.8%) and sodium hydroxide (NaOH, 96%) were obtained from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China), hydroxylamine hydrochloride ( $\text{NH}_2\text{OH}\cdot\text{HCl}$ ) was purchased from Tianjin Kermel Chemical Reagent Co. Ltd.

(Tianjin, China). Glutathione (GSH, 99%), 4-mercaptopyridine (4-MPY, 95%) were obtained from Sigma-Aldrich (USA). The 1000 ppm concentration of As (III) ions standard stock solution was purchased from SCP Science Company (Beijing, China). Sylgard 184 PDMS and its curing agent were obtained from Dow Corning Company (Midland, MI, USA). All other solvents and reagents used were of analytical grade unless mentioned. The glasswares used to fabricate AgNPs were cleaned with aqua regia and doubly distilled water ( $\text{Mill-Q}$ ,  $18 \text{ M}\Omega\cdot\text{cm}^{-1}$  resistance) prior to use.

### 2.2 Instrumentation

Solutions were prepared by deionized water with  $18.2 \text{ M}\Omega$  specific resistances purified by a Cascada TM Ultrapure water system (Pall Corp., USA). All SERS spectra were recorded by a DXR Raman Microscope (Thermo Fisher, USA). A 632.8 nm He:Ne gas laser was focused by a 10× microscope objective with a power of 3.8 mW. The LSP04-1A syringe pump was purchased from Longer Precision Pump Company (Baoding, China).

### 2.3 Fabrication of PDMS microfluidic chip

The microfluidic device was fabricated in PDMS by standard soft lithography methods as previously reported [28-30]. A zigzag-shaped PDMS microfluidic channel was designed to obtain efficient and rapid mixing of two confluent streams (As displayed in Fig. 1A). The width of channel was  $350 \mu\text{m}$  and the depth of channel was  $50 \mu\text{m}$ . To fabricate PDMS chip, a mixture of PDMS prepolymer and its curing agent was prepared in the ratio 10:1 of weight. After pouring into the mold master and baking for 30 min at  $80^\circ\text{C}$ , the fluidic access holes at the end of each channel were punched by a sharp needle. The residue of drilled PDMS was removed by ethanol before the chip baked 20 min at  $80^\circ\text{C}$  in the oven. Finally, the surfaces of PDMS were activated with oxygen plasma and then bonded with glass substrate irreversibly.

### 2.4 Preparation of AgNPs

It had been well known that the SERS substrates are very important for the SERS enhancement [5, 6]. Silver colloids were synthesized by different reducing agent existing differences in particle size and surface roughness. AgNPs were synthesized by reducing silver nitrate with hydroxylamine hydrochloride according to Leopold's method [31]. In brief, 10.44 mg  $\text{NH}_2\text{OH}\cdot\text{HCl}$  was dissolved in 89 mL  $\text{H}_2\text{O}$  and 1 mL of 0.30 M NaOH solution. Then, 10 mL of 0.01 M  $\text{AgNO}_3$  solution was added to the above solution under vigorous stirring. The reaction mixtures were continuously stirred for another 0.5 hour. The prepared silver colloid was stored at room temperature.

### 2.5 Functionalization of AgNPs with GSH and 4-MPY

10  $\mu\text{L}$  of 100  $\mu\text{M}$  GSH and 10  $\mu\text{L}$  of 400  $\mu\text{M}$  4-MPY were added to 2 mL of prepared AgNPs with stirring for 0.5 hour. The mixtures were AgNPs modified by GSH and 4-MPY.

### 2.6 SERS Detection of As (III) ions in the zigzag microfluidic chip

Various concentrations of As (III) ions (6 – 400 ppb) were prepared using 1000 ppm As (III) ions standard solution to test the SERS signal strength of aggregation of 4-MPY functionalized AgNPs caused by As (III) ions in the PDMS microfluidic

channels.

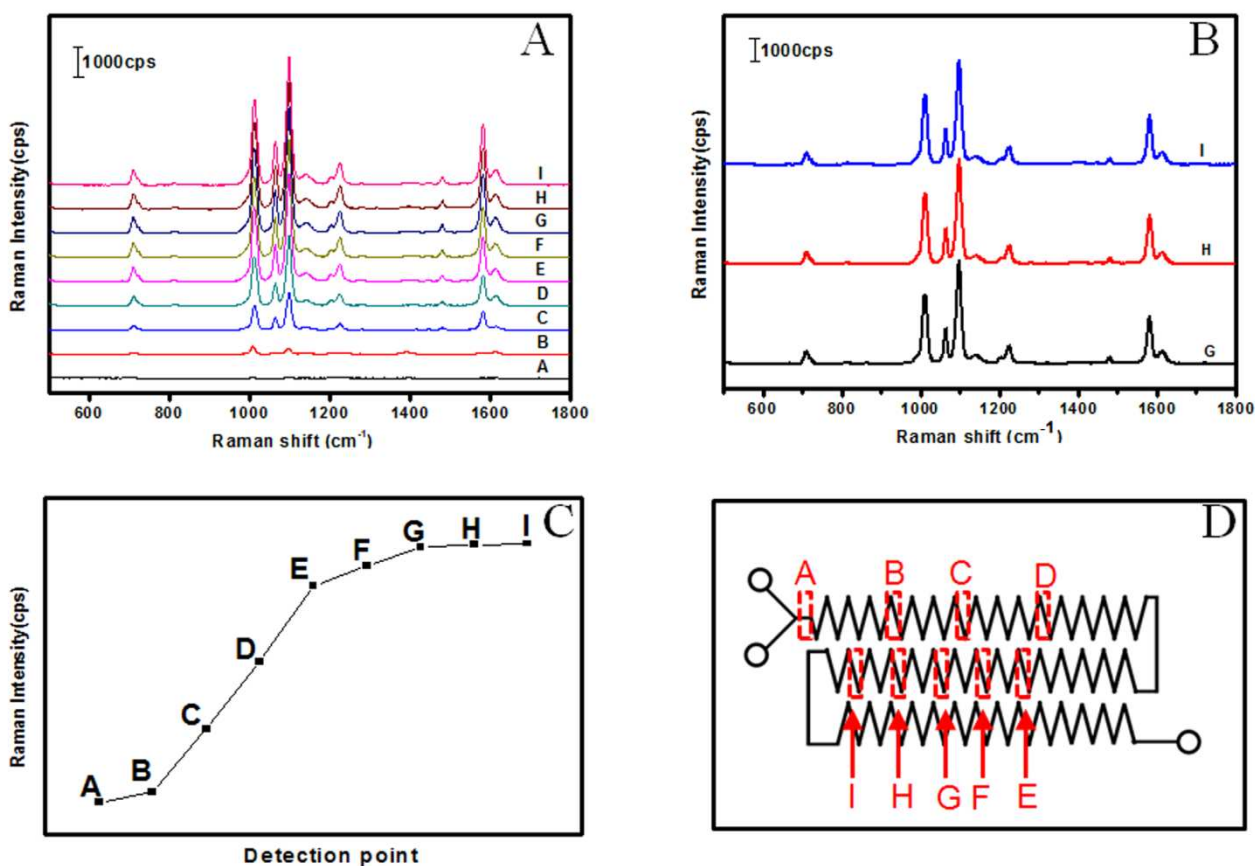
At room temperature, the PDMS microfluidic chip was set on confocal micro Raman spectrometer detection platform. The same volume of GSH/4-MPY functionalized AgNPs solution and different concentrations of As (III) ions in aqueous samples were injected into PDMS microfluidic chip in certain velocity at the same time.

### 3. Results and discussion

#### 3.1 Analytical principle

The analytical principle of SERS sensing As (III) ions based on aggregation of the GSH/4-MPY functionalized AgNPs on the PDMS microfluidic chip was shown in Fig. 1B. GSH molecule contains active sulfhydryl (-SH) that can bind to AgNPs through the Ag-S bonds [32, 33]. 4-MPY combines with AgNPs through three different ways, i.e., the lone pair electrons of the sulfur (S)

or nitrogen (N) atom, and via the aromatic  $\pi$  electrons [34]. It can be concluded that the 4-MPY molecules adsorbed on the AgNPs surface mainly by means of the sulfur atom, and the Ag-N interaction acts as a supporting role in the adsorption process [35]. When As (III) ions encountered the GSH/4-MPY functionalized AgNPs in the PDMS microfluidic channel, AgNPs aggregated because As (III) ions had a strong affinity to the GSH and each As (III) ion could bind three GSH-modified AgNPs through As-O linkage [36]. The As (III) ions could be detected by Raman signal enhancement of 4-MPY reporters due to the aggregation that induced generation of hotspots. To prove this phenomenon, we made the TEM and their visual color change pictures for the non-aggregated AgNPs (Fig. 1C), non-aggregated GSH/4-MPY functionalized AgNPs (Fig. 1D), and aggregated GSH/4-MPY functionalized AgNPs in the presence of As (III) ions (Fig. 1E), respectively. The aggregated GSH/4-MPY functionalized AgNPs cluster could be clearly observed and the solution color changed from yellow to light gray.



**Fig. 2.** (A) Raman spectra along nine different points in a zigzag channel. (B) The Raman intensity at the location (G), (H) and (I) in the enlarged picture. (C, D) SERS intensity curves at the different locations and its corresponding position in the microchannel

#### 3.2 The optimization of the flow rate

There are many strategies to realize the rapid mixing in microfluidic channel by their different geometries [37, 38], but in some strategy such as three-dimensional serpentine-shaped structure [39] or pillar obstruction [40] the fabrication process are very difficult. Herein, a zigzag-shaped PDMS microfluidic channel was designed to obtain efficient and rapid mixing. After optimization, the V-shaped channel's angles was designed as  $75^\circ$ .

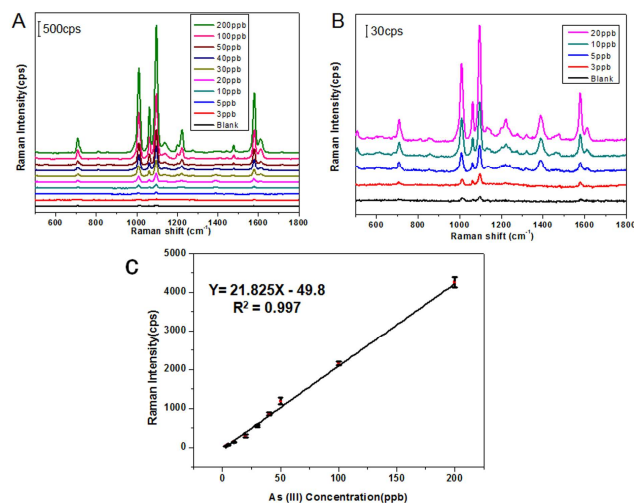
Regarding the hydrodynamic study, the *Péclet* number is defined as  $Pe = UL/D$ , in which  $U$  is the flow velocity,  $L$  is the length, and  $D$  is the diffusion coefficient, respectively. According to this equation, the *Péclet* number achieved 9813 that could realize the fully mixing in our chip. The typical geometry is schematically represented in Fig. 1. The same volume of GSH/4-MPY functionalized AgNPs and As (III) ions aqueous solution were injected into the PDMS microfluidic chip simultaneously from



two separately sample inlets by the same syringe pump. The long serpentine V-shape channel contributes to the rapid mixing. At a lower flow rate, the adhesion of nanoparticles on the channel walls would cause “memory effects” that will lead to the difficulty of quantitative analysis. Moreover, according to the observations, when the speed was too low (40  $\mu\text{L}/\text{min}$ ), the AgNPs was easy to make the accumulation and cause the channel clogging. On the other hand, the high pumping speed (80  $\mu\text{L}/\text{min}$ ) would lead to incompletely reaction even the cracking of PDMS chip due to high pressure. Therefore, the 60  $\mu\text{L}/\text{min}$  was chosen as the suitable flow rate for the subsequent experiments.

### 3.3 The effect of the detection position on SERS signal intensity

In this study, the SERS signals obtained from the mixtures of analytes and aggregated colloids were measured in the microfluidic channel. As illustrated in Fig. 2, in order to guarantee the completely mixing in the microchannel, nine different locations (spot (A) to (I)) along the channel were chosen to test its mixing efficiency by their Raman spectra. Fig. 2A and 2C depicted the plot of the Raman intensity of 1098  $\text{cm}^{-1}$  band measured at different locations with Raman spectra and its corresponding signal curve. Clearly, the intensity showed a monotonic increase from location (A) to (F). But when the detection spots were set on the (G), (H) and (I), the SERS signal strength reached a plateau. Fig. 2B was the enlarged picture for the Raman intensity at the location (G), (H) and (I). There were no obvious differences between their Raman intensities, revealing that two kinds of reagents had made fully mixing reaction and kept a steady state when the positions were placed behind the location (G) in the microchannel. Therefore, the detection spot was set the location (I) for the all subsequent experiments. We tested the Raman intensity of the same concentration As (III) ions in the channel and tubes with fully mixing conditions, respectively. The mixing efficiency can obtain as 96.2% after calculation, in our system. In addition, the mixing behaviour and process also can be monitored on the microfluidic scheme.



**Fig. 3.** (A) SERS spectra changes upon GSH/4-MPY functionalized AgNPs with various amount of As (III) ions concentrations in the PDMS microfluidic channel. (B) SERS spectra changes of GSH/4-MPY functionalized AgNPs at lower concentrations of As (III) ions in the PDMS microfluidic channel. (C) Calibration curve of As (III) ions at 1098  $\text{cm}^{-1}$  for the detection of linear range on the three different chips, respectively ( $n=3$ ). The error bars represent standard deviations based on

three independent measurements

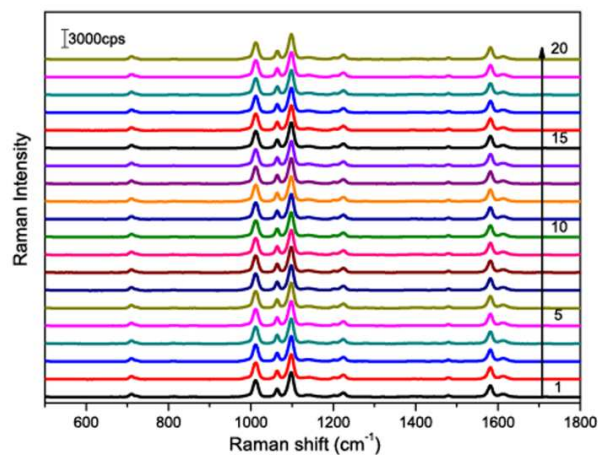
### 3.4 The detection sensitivity and linear range of SERS microfluidic sensors

#### The choice of Raman characteristic peak

Confocal SERS spectra of AgNPs modified by GSH/4-MPY with different As (III) ions concentrations in the PDMS microfluidic channel were displayed in Fig. 3. Characteristic peaks of 4-MPY such as 710, 1011, 1062, 1098, 1224 and 1579  $\text{cm}^{-1}$  were observed. The characteristic peak at 1098  $\text{cm}^{-1}$  corresponding to the ring-breathing/C–S stretching mode indicated that 4-MPY was bound to the surface of AgNPs through the sulfur atom [41]. Fig. 3A revealed that all the intensity of Raman characteristic peak were enhanced with the increase of the concentration of As (III) ions and 1098  $\text{cm}^{-1}$  was the most significant peak to As (III) ions. Therefore the SERS peak at 1098  $\text{cm}^{-1}$  was selected as an instructive peak for the quantitative analysis of As (III) ions.

#### Sensitivity and linearity analysis

In order to investigate the minimum concentration of As (III) ions in aqueous solution detected by the presence of GSH/4-MPY functionalized AgNPs in PDMS microfluidic channels, the same volume of GSH/4-MPY functionalized AgNPs solution and different concentrations (6–400 ppb) of As (III) ions solution were introduced into PDMS microfluidic chip simultaneously. Therefore, the final concentration of As (III) ions was 3–200 ppb for SERS detection after completely mixing. The measurement was repeated three times on different chips, and the relative intensity and the error bar were shown in the calibration curves in Fig. 3C. Under the optimal condition, it could be seen that the detection linear range was obtained from 3 to 200 ppb ( $R^2=0.997$ ). Fig. 3B demonstrated the SERS signals of GSH/4-MPY functionalized AgNPs with different As (III) concentrations (3, 5, 10, 20 ppb) and there were significant differences between these signals. According to the minimum signal-to-noise ratio of 3, the limit of detection (LOD) of As (III) ions was determined to 0.67 ppb which was lower than the WHO defined limit (10 ppb). The results indicated that SERS microfluidic sensors could be used as a rapid and highly sensitive tool for As (III) ions detection.



**Fig. 4.** SERS spectra of GSH/4-MPY functionalized AgNPs with 200 ppb of As (III) ions concentrations in the PDMS microfluidic channel

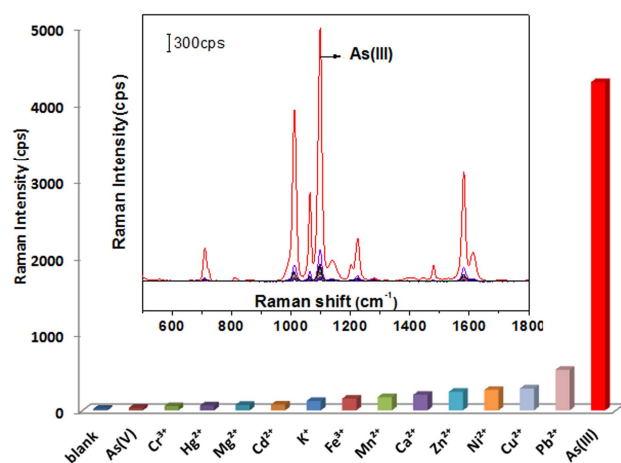
( $n=20$ ).

### 3.5 Stability and reproducibility of the SERS microfluidic sensors

For obtaining the good sensitivity and reproducibility, some optimization has been implemented as mentioned above. At optimal condition, As (III) ions and GSH/4-MPY functionalized AgNPs were mixed on three different chips respectively, and the Raman intensity was recorded to study the signal stability acquiring from PDMS microfluidic chip. As shown in Fig. 3C, there was good linear relationship between Raman intensity at 1098  $\text{cm}^{-1}$  and As (III) ions concentration within 3 – 200 ppb, the correlation coefficient was above 0.99. In addition, the reproducibility of Raman performance on a microfluidic format was also evaluated. As displayed in Fig. 4, we obtained 20 SERS spectra curves of GSH/4-MPY functionalized AgNPs mixed with As (III) ions (200 ppb) in the PDMS microfluidic channel. No significant difference among 20 curves and the relative standard deviations were 1.21%. It indicated that the proposed method for As (III) ions detection had good reproducibility and reliability.

### 3.6 Selectivity of As (III) ions for the SERS microfluidic sensors

In order to prove that the method was robust and selective to As (III) ions, different kinds of metal ions were respectively injected into the PDMS microfluidic chip with GSH/4-MPY functionalized AgNPs under the optimal conditions. The As (III) ions concentration was selected as 2.68  $\mu\text{M}$  (200 ppb), and concentration for As (V),  $\text{Cd}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Ni}^{2+}$ , and  $\text{Fe}^{3+}$  ions were selected as the same concentration 2.68  $\mu\text{M}$ . The concentration for  $\text{K}^+$ ,  $\text{Hg}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Ca}^{2+}$ , and  $\text{Mn}^{2+}$  ions were 10 fold higher than As (III) ions. As shown in Fig. 5, it was clear that only As (III) ions could induce the aggregation of AgNPs through the bond of GSH and lead to a significant increase in the SERS signal. Contrarily, there was no apparent SERS signal for other metal ions and it implied that the SERS microfluidic sensor had high selectivity to As (III) ions.



**Fig. 5.** SERS intensity changes of the aggregated GSH/4-MPY functionalized AgNPs in the presence of different metal ions at 1098  $\text{cm}^{-1}$ . Inset showed the SERS spectra changes influenced by the different kinds of metal ions. The concentration of As (III), As (V),  $\text{Cd}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Ni}^{2+}$  and  $\text{Fe}^{3+}$  ions were 2.68  $\mu\text{M}$  and other metal ions concentrations were 10 fold higher than As (III) ions

### 3.7 The analysis of practical samples

The practical performance of the proposed method was further identified by samples of local drinking water. Series concentration of As (III) ions was added into tap water without any treatment. The experiment was determined three times respectively by adding the standard As (III) ions into the samples. As shown in Table.1, the recoveries of samples spiked with As (III) ions of 30 – 100 ppb were 98.1% – 105.5%, with the relative standard deviations of 1.5% – 3.6%, respectively. To verify the reliability of the method, we analyzed the same samples by ICP-MS method. The recoveries of samples spiked with As (III) ions of 30 – 100 ppb were 101.2% – 110.9% and relative standard deviations were 1.2% – 2.9%. There was no apparent difference between these two methods. It suggested the method had good precision and repeatability to detect real samples.

Table 1. The recovery of spiked As (III) ions in the tap water and the standard deviation of the samples were detected three measurements by our method and ICP-MS.

Sample	Added ppb	Our method		ICP-MS	
		Found (ppb, $n=3$ )	Recovery	Found (ppb, $n=3$ )	Recovery
1	30	29.43±1.06	98.1%	33.27±0.93	110.9%
2	50	52.74±1.78	105.5%	50.61±0.6	101.2%
3	100	100.75±1.5	100.8%	101.21±2.9	101.2%

## 4. Conclusions

In summary, this study provided a feasible approach for the highly sensitive SERS detection As (III) ions on the microfluidic platform. Experimental results demonstrated that the proposed method had a wide linear range with high sensitivity. The device facilitated the interaction of the analyte molecules and the Ag nanoparticles, and the diffusion limitations of confluent laminar flow were effectively solved by a chaotic advection in a zigzag microfluidic channel. Combining the promising power of microfluidics and SERS technology, the ultrasensitive detection of As (III) ions was realized in several minutes with very low-consumption that is very friendly to the environment because Arsenic element is well known for its toxicity and carcinogenicity. Moreover, its characteristics of fastness, simplicity and sensitivity with good reproducibility will make it potentially be environment-friendly used in various chemical and environmental pollutant sensing applications.

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## Notes and references

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## Graphic Abstract

A quantitatively sensitivity analysis for trace As(III) ions was proposed based on the SERS technique on a zigzag microfluidic chip.

