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Lateral flow test for visual detection of silver (I) based on cytosine-Ag(I)-cytosine interaction in C-rich oligonucleotides

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Abstract

The authors describe an oligonucleotide-based lateral flow test for visual detection of Ag(I). The assay is based on cytosine-Ag(I)-cytosine [C-Ag(I)-C] coordination chemistry to capture gold nanoparticle (AuNP) tags in the test zone. A thiolated C-rich oligonucleotide probe was immobilized on the AuNPs via gold-thiol chemistry, and a biotinylated C-rich oligonucleotide probe was immobilized on the test zone. The AuNPs labelled with C-rich oligonucleotides are captured by Ag(I) ions in the test zone through the C-Ag(I)-C coordination. The resulting accumulation of AuNPs produces a readily visible red band in the test zone. Under optimized conditions, the test is capable of visually detecting 1.0 ppb of Ag(I) which is 50 times lower than the maximum allowable concentration as defined by the US Environmental Protection Agency for drinking water. Hence, the test is inexpensive and highly sensitive. It was applied to the detection of Ag(I) in spiked samples of tap water and river water. In our perception, the test is a particularly valuable tool in limited resource settings.

Graphical abstract

We have developed a rapid and sensitive approach for visual detection of silver ions by using oligonucleotide-based lateral flow test strip. The approach relies on cytosine-Ag⁺-cytosine (C-Ag⁺-C) coordination chemistry to capture gold nanoparticles on the test zone of lateral flow device. This led to a novel and low-cost tool for rapid detection of silver ions.

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Keywords

silver ion; gold nanoparticles; oligonucleotide; visual detection; water analysis

1 Introduction

Environment contamination caused by heavy metal ions has been an important worldwide concern for decades.¹ Among them, silver ion (Ag^+) is one of the toxic heavy metal ions that can cause environmental pollution for water resources. In addition, Ag^+ is known to inhibit the activities of many bacteria, viruses, algae, and fungi, which is popular for the creation in various products, such as in food and clinical material.² It was reported that Ag^+ produced dose-dependent cytopathogenic effects on many kinds of cell types, including human gingival fibroblasts, keratinocytes, human tissue mast cells and endothelial cells, and so on, because it can bind with various metabolites and inactivate sulfhydryl enzymes.³⁻⁵ In addition, Ag^+ is associated with organ failure and reduction in mitochondrial function through the promotion of oxidative stress.⁶ Therefore, it is of great importance to develop sensitive and selective methods for detection of trace amounts of Ag^+ in environmental and food related samples.

Instrumental analysis methods including atomic absorption spectrometry (AAS),⁷ inductively coupled plasma mass spectrometry (ICP-MS)^{8,9} have been employed for Ag^+ detection. Although these methods exhibited high sensitivity and selectivity, most of the methods were time-consuming, complex or required expensive instrumentation and well-trained personals, which limited their practical applications. DNA base-metal ion interactions attract considerable attention because of their potential in sensing applications. Some metal ions can selectively bind to a few native or artificial bases in DNA duplexes to form metal-mediated base pairs.¹⁰ It was demonstrated that cytosine-cytosine (C-C) base pairs selectively bound Ag^+ ions to form C- Ag^+ -C in DNA duplexes.¹¹ It was shown that melting temperature of duplex DNA containing C-C mismatch increases upon addition of Ag^+ , also suggesting the stabilization of duplex formation by the Ag^+ .¹¹ Based on C- Ag^+ -C coordination, electrochemical methods¹²⁻¹⁴ colorimetric method^{15, 16}, and the fluorimetric

methods^{17,18} have been developed for the detection of Ag⁺. However, these methods required either sophisticated instruments or special reagents that were prepared by complicated organic synthesis. Therefore, the improved detection assay with simplified procedure, time-saving, high sensitivity and selectivity for the real-time detection of Ag⁺ is needed.

Paper based lab-on-chip devices have attracted an increasing attention because of the typical features including low-cost, one-step procedure, portability, disposability and small sample consumption.¹⁹ The lateral flow assay is considered as one of the most promising technologies with good stability and reproducibility.²⁰ Our group and others have successfully devised nucleic acid-based lateral flow biosensors using oligonucleotide-functionalized gold nanoparticles (AuNPs) for visual detection of nucleic acids²¹, proteins,²² gene mutations²³, cancer cells²⁴, organic compounds^{25, 26} and metal ions^{27, 28}. In this work, we describe a lateral flow assay based on Ag⁺-specific oligonucleotide conjugated AuNPs and cytosine–Ag⁺–cytosine (C–Ag⁺–C) coordination chemistry for visual detection of Ag⁺. The promising properties of the lateral flow assay are reported in the following sections.

2 Experimental

2.1. Apparatus and reagents

The Airjet AJQ 3000 dispenser, Biojet BJQ 3000 dispenser, Clamshell Laminator, and the Guillotine cutting module CM 4000 were purchased from Biodot LTD (Irvine, CA, <https://www.biodot.com/>), Nikon COOLPIX S800c camera (Nikon, Japan, <http://www.nikon.com/>).

HAuCl₄, sucrose, sodium citrate, Tween 20, Triton X-100, trisodium citrate, deoxyadenosine triphosphate (dATP), bovine serum albumin (BSA), Streptavidin, PBS (pH 7.4), HEPES (pH 7.4), silver nitrate (AgNO₃) and the following metal salts: Cu(NO₃)₂, Mn(Ac)₂, Co(Ac)₂, Ni(NO₃)₂, Al(NO₃)₃, Cd(NO₃)₂, Zn(Ac)₂, Cr(NO₃)₃, Fe(NO₃)₃, Hg(Ac)₂, Ca(Ac)₂, Pb(NO₃)₂, and Mg(NO₃)₂ were purchased from Sigma-Aldrich (St. Louis, MO, <http://www.sigmaaldrich.com/>). Glass fibers (GFCP000800), cellulose fiber sample pads (CFSP001700), laminated cards (HF000MC100), and nitrocellulose membranes (HFB 18004 and HFB 24004) were purchased from Millipore (Billerica, MA, <http://www.emdmillipore.com/>).

All the chemicals used in this study were analytical reagent grade. Other solutions were prepared with ultrapure (18 MΩ•cm) water from Millipore Milli-Q water purification system (Billerica, MA, <http://www.emdmillipore.com/>). All the oligonucleotide probes used in this study were purchased from Integrated DNA Technologies, Inc. (Coralville, IA, <http://www.idtdna.com/>) and have the following sequence:

Detection probe: 5'-/5ThioMC6-D/TCA CCA CAA-3'

Capture probe: 5'-/5Biosg/TTC TCC TCA-3'

Control probe: 5'-/5Biosg/TTG TGG TGA-3'

2.2. Preparation of detection probe/AuNP conjugates

The AuNPs with an average diameter of 15 ± 3.5 nm were synthesized using the procedures reported previously.²⁹ Detection probe/AuNP conjugate was prepared according to the reported methods with slight modifications.²¹ Ten microliter of dATP was added into 1 mL of five-fold concentrated AuNP solution (the final concentration of dATP is 10 μ M). The mixture was incubated at room temperature for 20 minutes on shaker. Fifteen microliter of 1% of SDS was slowly added into the mixture, and incubated on shaker for another 10 minutes. Fifty microliter of 0.2 M of NaCl was dropped at the rate of 2 μ L every 3 minutes. Then 1 OD (optical density) of detection probe (Ag^+ -specific thiolated-oligonucleotide) was added and the mixture was incubated for 3 hours in water bath at 60°C. After the incubation, the mixture was centrifuged at 12000 rpm for 15 minutes, and the supernatant was discarded, then washed with 1 mL of PBS for 3 times, discard the supernatant and re-suspend the pellet in PBS. Repeat the above step 3 times and lastly re-suspend in 1 mL eluent buffer containing 20 mM Na_3PO_4 $12\text{H}_2\text{O}$, 5% BSA, 10% sucrose, and 0.25% Tween-20. The detection probe/AuNPs conjugate was stored at 4 °C before further use.

2.3. Preparation of streptavidin/biotinylated oligonucleotide complexes

One hundred nanomoles of biotinylated oligonucleotide probe (oligonucleotide capture probe or oligonucleotide control probe) was mixed with 2.5 mg mL^{-1} streptavidin and incubated at room temperature for 1 hour. After adding 500 μ L PBS to the mixture, the new solution was centrifuged using a centrifugal filter for 20 minutes at 6000 rpm at 4 °C to remove the unbound DNA. The above step was repeated for 3 times. The remaining solution in filter was diluted with PBS and used for dispensing.

2.4. Preparation of oligonucleotide-based lateral flow test strips

The test strip consists of four components: sample application pad, conjugate pad, nitrocellulose membrane, and absorbent pad (Scheme 1). All components were laminated into a sheet of plastic orderly using the Clamshell Laminator. The sample application pad (17 mm $\times$ 30 cm) was made from glass fiber and saturated with a buffer (pH 8.0) containing 0.05 M Tris-HAc, 0.25% Triton X-100, 2.5% Tween-20 and 0.15m M NaNO_3 . Then, the pad was dried at 37 °C for 3 h and stored in desiccators at room temperature. Nitrocellulose membranes were pretreated with detergents or surfactants by the membrane manufacturer (Millipore (Billerica, MA, <http://www.emdmillipore.com/>)), so no more treatment was needed before use. The test zone and control zone on the nitrocellulose membrane (25 mm $\times$ 30 cm) were prepared by dispensing a desired volume of streptavidin/capture probe (test zone) and streptavidin/control probe (control zone) solutions on the designed area with a “BioJet” dispensing platform (Biodot LTD, Irvine, CA, <https://www.biodot.com/>), respectively. The dispense volumes were quantitatively controlled, and the test/control zones was precisely adjusted at the exact position. The distance between the test zone and control zone was 3 mm. The control/test zone width was adjusted to 1 mm. The membrane was then dried at 37°C for 1 h and stored at 4°C in a dry state. The detection probe/AuNP conjugate was dispensed on the conjugate pad. Finally, the sample application pad, conjugate pad, nitrocellulose membrane, and absorption pad were assembled on a plastic adhesive backing (60 mm $\times$ 30 cm) using the clamshell laminator. Each part overlapped 2 mm to ensure that

the solution can migrate through the strip during the assay. Test strips with a 3 mm width were cut using the Guillotin CM 4000 cutting module.

2.5. Analytical procedure

Sample solutions containing various concentrations of Ag^+ were prepared in running buffer (HEPES, 100 mM). The maximum loading volume of a sample solution on a test was around 100 μL (0.1 mL) (see the details in Electronic Supporting Material). In a typical test, 100 μL of sample solution was applied to the sample pad. During the assay process, the solution migrated up by capillary force. The test line and control line were evaluated visually within 15 min. For quantitative measurements, the optical intensity of the test line was read using Imagine J software.

2.6. Analysis of tap water and river water samples

Tap water sample was obtained from the tap of the laboratory (Department of Chemistry and Biochemistry, NDSU, Fargo, ND). River water sample was obtained from the Red River (Fargo, ND). All samples were first filtered through a 0.22 μm filter membrane to remove insoluble substances. In the case of detecting Ag^+ in tap and river water, 20 μL of running buffer (200 mM HEPES) was mixed with 80 μL of water sample. Other procedures were the same as that described in Section 2.5. The results were compared with that obtained by ICP-MS (PerkinElmer Inc., <http://www.perkinelmer.com/>) using the reported methods with slight modification.⁸

3 Results and discussion

3.1. Principle of Ag^+ detection with lateral flow test strip

The principle of Ag^+ detection with the lateral flow test strip is based on cytosine- Ag^+ -cytosine (C- Ag^+ -C) coordination chemistry to form oligonucleotide duplexes on the AuNP surface. The accumulation of the AuNP tags on the test zone of lateral flow test strip is occurred associated with the formation of oligonucleotide duplexes. The configuration and measurement principle are illustrated in Scheme 1. In this study, three oligonucleotide probes were used: one thiolated oligonucleotide probe (detection probe) and two biotinylated oligonucleotide probes (capture probe and control probe). The thiolated probe was immobilized on the AuNP surface and the resulting detection probe/AuNPs conjugate was loaded on the conjugate pad. Typically, the sample solution containing certain amount of Ag^+ was added onto the sample application pad. Subsequently, the sample solution migrated by capillary action and passed the conjugate pad to rehydrate the detection probe/AuNPs conjugates while Ag^+ bound with the cytosine of the detection probe on the AuNP surface. The formed Ag^+ -detection probe/AuNP complexes continued to migrate along the strip. The complexes were captured by the capture probe immobilized on the test zone due to the formation of capture probe- Ag^+ -detection probe/AuNP. The accumulation of AuNPs produced a characteristic red band on the test zone. The excess detection probe/AuNP conjugates continued to migrate through the control zone and were captured by control probe (complementary with the detection probe). Finally, two red bands were shown (Scheme 1A). In the absence of Ag^+ , only one red band was observed in the control zone (Scheme 1B). In this case, the red band in the control zone shows that the test strip works

properly. Qualitative analysis was simply performed by observing the color change of the test zone, and quantitative analysis was realized by recording the optical intensities of the red bands with the Image J software.

Figure 2 presents the typical photo images of strips in the absence of Ag^+ and presence of 20 ppb Ag^+ . One can see that two bright red bands appeared in the presence of 20 ppb Ag^+ , whereas only one red band was observed in the absence of Ag^+ (see photo images of fully assembled test strips in Electronic Supporting Material, Fig. S1). It should be mentioned that the sequences of detection oligonucleotide probe and capture oligonucleotide probe had strong effect on the control signal (in the absence of Ag^+). In current study, both detection oligonucleotide probe and capture oligonucleotide probe have 9 bases including 4 cytosine (C) and the melting temperature of the duplex (detection probe-capture probe) with 4 C-C mismatches is below 20 °C in the absence of Ag^+ . Therefore, detection probe and capture probe didn't hybridize or partially hybridized at room temperature in the absence of Ag^+ , resulting in no AuNP was captured on the test zone. The presence of Ag^+ stabilized the duplex formation by forming C- Ag^+ -C base pairs in oligonucleotide duplexes. In addition, the oligo dC sequences were used as both detection and capture probes in the lateral flow assay of Ag^+ . There was no signal observed on the test zone in the presence of 50 ppb Ag^+ . The reason was that the detection oligo dC probes on the AuNPs self-hybridized in the presence of Ag^+ during the migration along the membrane, and the hybridization efficiency was reduced significantly when the AuNP-labeled detection oligo dC probes reached the test zone. Future work will aim to improve the sensitivity of the lateral flow assay by optimizing the number and the positions of C-C mismatches in oligonucleotide sequences.

3.2. Optimization of analytical parameters

To obtain the best sensitivity and reproducibility of the assay, the following parameters were optimized: (a) type of nitrocellulose membranes; (b) the concentration of the detection probe used to prepare the detection probe/AuNP conjugate; (c) the volume of detection probe/AuNP conjugate loaded on the conjugate pad; (d) the components of the running buffer; and (e) the amount of the capture probe on the test zone. The optimizations were performed by varying one experimental condition and keeping constant conditions for other parameters. The signal-to-noise (S/N) ratio was used to evaluate the analytical performances. Respective data and Figures are given in the Electronic Supporting Material (Fig. S2). The following experimental conditions were found to give best results: (a) HFB 24004 nitrocellulose membrane; (b) using 1.0 OD (11.3 nmoles) of detection oligonucleotide probe to prepare detection probe-AuNP conjugates; (c) using 4.0 μL of detection probe-AuNP conjugates per assay; (d) a running buffer of HEPES (200 mM); (e) dispensing streptavidin- biotinylated capture oligonucleotide probe twice on the test zone.

3.3. Analytical performance

Under optimal experimental conditions, sample solutions containing different concentrations of Ag^+ were tested on the test strips. Fig. 3A presents the typical photo images of test strips in the presence of different of Ag^+ concentrations ranging from 0 ppb to 2000 ppb. There was no distinct red band observed on the test strips test zone in the absence of Ag^+ (0 ppb Ag^+ , control). The red band on the test zone was quite visible even at 1 ppb Ag^+ , which can

be used as the threshold for the visual determination of Ag^+ without instrumentation. In addition, quantitative detection was performed by recording the intensities of the test lines with Imagine J software. It was observed that the intensities of the test line increased with the increase of Ag^+ concentration. The resulting calibration plot (Fig. 3B) of the intensities versus Ag^+ concentration is linear over the 0 to 100 ppb range and is suitable for quantitative work. The detection limit of 0.6 ppb (based on $S/N=3$) was estimated in connection with the 15-min assay time. The comparison of different silver ion detection methods was summarized in Table 1. The lateral flow assay possesses good sensitivity. The detection limit is comparable with some of the reported methods. Besides, the lateral flow assay exhibited superior characteristics including non-enzymatic reaction, single-step testing and bare-eye detection at 1 ppb. The maximum contamination level of Ag^+ in drinking water defined by the World Health Organization (WHO) and the USA Environmental Protection Agency (EPA) is 50 ppb and 100 ppb, respectively. The presented LFA thus offers a promising tool for on-site monitoring of Ag^+ in real sample.

3.4. Specificity of the detection

To validate the specificity of the LFA for Ag^+ analysis, several 10 ppm of other metal ions including Cu^{2+} , Mn^{2+} , Co^{2+} , Ni^{2+} , Al^{3+} , Cd^{2+} , Zn^{2+} , Cr^{3+} , Fe^{3+} , Hg^{2+} , Ca^{2+} , Pb^{2+} and Mg^{2+} have been tested on the test strips, compared with the mixtures of Ag^+ (100 ppb) and each individual metal ion (10 ppm) (Fig. 4). Red bars and blue bars represent the responses of individual metal ion and the mixture of Ag^+ and individual metal ion on the test strips, respectively. One can see that there is no interference from other metal ions even the concentrations of other metal ions are 100 times higher than that of Ag^+ . The above results indicate that our strategy exhibits high specificity for the detection of Ag^+ .

3.5. Analysis of tap water and river water samples

The practical application of the LFA was demonstrated by applying it to detect Ag^+ in tap water and river water samples. In parallel, inductively coupled plasma mass spectrometry (ICP-MS) analysis was performed as a confirmatory method for the quantitation of Ag^+ . The water samples were spiked with Ag^+ at different concentrations (5 ppb, 10 ppb, 20 ppb and 50 ppb) and the results are summarized in Table 2. As presented in Table 2, the analytical results of the test were in good agreement with the results obtained from ICP-MS, indicating that the LFA had good reliability to quantify Ag^+ in environmental samples.

4 Conclusions

In conclusion, we have successfully developed a rapid and sensitive method for the detection of Ag^+ based on the LFA. Under optimal conditions, a visual detection limit of 1 ppb was obtained within 15 min without multiple operation steps and expensive instrumentations. The detection limit for Ag^+ was 0.6 ppb (equals to 3.5 nM) with a linear range of 1-100 ppb. The presence of other metal ions showed no interference on Ag^+ detection. Test results from the spiked tap water and river water samples verified the efficiency of our assay, which holds great potential in practical applications. Future work aims to develop the LFA for visual detection of multiple toxic metal ions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Schematic illustration of visual detection of Ag^+ on oligonucleotide-based lateral flow test strip. (A) in the presence of Ag^+ ; (B) in the absence of Ag^+ .

Figure 2.
Typical photo images of oligonucleotide-based lateral flow test strips in the absence of Ag^+ (0 ppb, control) and presence of 20 ppb Ag^+ .

Figure 3.

Photo images (left) of the test strips with different concentrations of Ag^+ and the resulting calibration curve (right). The photo images of the test strips were recorded with a digital camera, and the intensities of the red bands on the test lines were read by the Image J software. Each data point represents the average value obtained from three different measurements. Assay time: 15 min. Running buffer: 200 mM HEPES.

Figure 4.

The intensities of the test zone in the presence of 100 ppb Ag⁺ and 10 ppm of other metal ions. Red bar: 10 ppm individual metal ions in the sample solution; Blue bar: the mixture of Ag⁺ (100 ppb) and a corresponding metal ion. Each data point represents the average value obtained from three different measurements.

Table 1

An overview on recently reported nanomaterial-based methods for determination of Ag(I).

Materials used	Methods applied	LOD	Reference
Furfuryl alcohol modified gold nanoparticles	Colorimetric assay	12 nM	30
Prussian blue nanoparticles	Colorimetric assay	5 nM	31
DNA based gold nanoparticles	Colorimetric assay	0.59 nM	32
Graphene oxide and exonuclease III-assisted signal amplification	Fluorescence	0.1 nM	33
Silver(I) ion imprinted polymeric nanoparticles	Electrochemistry	0.088 nM (0.015 ppb)	34
Silver-specific DNA and Rodamine B	Fluorescence	15.9 nM (2.73 ppb)	35
Silver-specific oligonucleotides modified gold nanoparticles	Lateral flow assay	3.5 nM (0.6 ppb)	This work

Table 2
Determination of Ag⁺ in water samples using LFNAB and ICP-MS methods

sample	Ag ⁺ spiked (ppb)	LFNAB method (ppb) ^a	ICP-MS method (ppb) ^a
tap water	5.0	4.91±0.22	4.95±0.19
tap water	10.0	9.87±0.37	9.91±0.42
river water	20.0	19.55±0.46	19.78±0.38
river water	50.0	48.85±0.61	49.21±0.62

^a Values represent averages of triplicate determinations ± SD.