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Analytical Methods

Colorimetric and fluorescence quenching aptasensors for detection of streptomycin in blood serum and milk based on double-stranded DNA and gold nanoparticles

Ahmad Sarreshtehdar Emrani [a,1], Noor Mohammad Danesh [b,c,1], Parirokh Lavaee [d], Mohammad Ramezani [b], Khalil Abnous [e,*], Seyed Mohammad Taghdisi [f,*]

[a] Cardiovascular Research Center, Ghaem hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Nanotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Research Institute of Sciences and New Technology, Mashhad, Iran
[d] Department of Chemistry, Ferdowsi University of Mashhad, Mashhad, Iran
[e] Pharmaceutical Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Targeted Drug Delivery Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Antibiotic residues in animal foodstuffs are of great concern to consumers. In this study, fluorescence quenching and colorimetric aptasensors were designed for detection of streptomycin based on aqueous gold nanoparticles (AuNPs) and double-stranded DNA (dsDNA). In the absence of streptomycin, aptamer/FAM-labeled complementary strand dsDNA is stable, resulting in the aggregation of AuNPs by salt and an obvious color change from red to blue and strong emission of fluorescence. In the presence of streptomycin, aptamer binds to its target and FAM-labeled complementary strand adsorbs on the surface of AuNPs. So the well-dispersed AuNPs remain stable against salt-induced aggregation with a wine-red color and the fluorescence of FAM-labeled complimentary strand is efficiently quenched by AuNPs. The colorimetric and fluorescence quenching aptasensors showed excellent selectivity toward streptomycin with limit of detections as low as 73.1 and 47.6 nM, respectively. The presented aptasensors were successfully used to detect streptomycin in milk and serum.

1. Introduction

Streptomycin (Str) is an antibiotic obtained from Streptomyces grisens (de Oliveira, Rizzato Paschoal, Sismotto, da Silva Airoldi, & Reyes Reyes, 2009; Pendela, Hoogmartens, Van Schepdael, & Adams, 2009; Zhou et al., 2013). It has been broadly used in veterinary and human for treatment of gram-negative infectious disease (Granja et al., 2009; Zhou et al., 2013). Overdosage of streptomycin could result in the presence of this antibiotic in animal derived foods and serious side effects such as ototoxicity and nephrotoxicity (de Oliveira et al., 2009; Granja et al., 2009). Intoxication could occur at plasma concentration of 30–40 μg/ml or greater (Akaho, Maekawa, Uchinashi, & Kanamori, 2002). Based on European commission, safe maximum residue limit of streptomycin in milk is 200 μg/kg (Commission Regulation, 1990). Therefore, development of selective and sensitive sensors for detection of streptomycin in foodstuffs and serum are in great interest.

Different analytical methods have been applied for detection of streptomycin, including liquid chromatography–mass spectrometry (LC–MS) which detect streptomycin with high sensitivity but suffers from high cost and complicated sample preparation (Gremilogianni, Megoulas, & Koupparis, 2010; McLaughlin, Henion, & Kijak, 1994; Zhou et al., 2013), immunoassays such as fluorescence immunoassay (FIA), enzyme-linked immunosorbant assay (ELISA) and radio immunoassay (RIA) which have cross-reactions with other compounds in real sample analysis (Knecht et al., 2004; Pastor-Navarro, Maquieira, & Puchades, 2009; Zhou et al., 2013), high performance liquid chromatography (HPLC) which is highly-sensitive but requires post-column derivatization due to the lack of chromophore group in streptomycin (Edder, Cominoli, & Corvi, 1999; Viñas, Balsalobre, & Hernández-Córdoba, 2007; Zhou et al., 2013).

Aptamer-based sensors, aptasensors, have been widely applied to analytical methods. Aptamers are short single-stranded DNA

* Corresponding authors.
E-mail addresses: abnouskh@mums.ac.ir (K. Abnous), taghdisihm@mums.ac.ir (S.M. Taghdisi).
[1] These authors contributed equally to the work.

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(ssDNA) or RNA sequences generated by an in vitro selection process called SELEX (systematic evolution of ligands by exponential enrichment) (Bai, Hou, Zhang, & Tang, 2014; Chen et al., 2014). Aptamers are able to specifically and selectively bind to their targets, ranging from small molecules to proteins and even cells (Gopinath, Lakshmipriya, & Awazu, 2014; Luo, Liu, Xia, Xu, & Xie, 2014). Aptamers offer advantages over antibodies, including simplicity of synthesis, low cost, excellent stability, no or low toxicity and immunogenicity (Chen, Yao, Xie, & Liu, 2014; Evtugyn et al., 2013; Luo et al., 2014; Yang et al., 2014). Owing to these advantages, aptamers have been broadly used in the fabrication of different biosensors (Luo et al., 2014; Taghdisi et al., 2014). Recently a ssDNA aptamer, STR1, that binds to streptomycin with high affinity was introduced (Zhou et al., 2013).

Gold nanoparticles (AuNPs) have widely used in the construction of fluorescence quenching and colorimetric aptasensors due to their unique features, such as high sensitivity, chemical stability, high absorption coefficient, ease of synthesis, and being an attractive energy acceptor (Gopinath et al., 2014; Liu et al., 2014; Tan et al., 2013; Zhang, Liu, Liu, Zhang, & Tan, 2013).

Colorimetry has commonly be applied for analytical applications since the readout requires only the naked eye (Gopinath et al., 2014; Yuan et al., 2014). Fluorescence is one of the most powerful signal transduction mechanisms which has been broadly used for design of aptasensors, owing to its high sensitivity, ease of application and simplicity (Kim et al., 2011; Zheng, Zou, & Lou, 2012).

Therefore, in this study for the first time, fluorescent and colorimetric sensors based on aptamer, its complimentary strand and AuNPs were designed for detection of streptomycin in milk and blood serum.

2. Materials and methods

2.1. Materials

The Streptomycin aptamer (Apt), 5′-TAG GGA ATT CGT CGA CGG ATC CGG GGT CTG GTG TTC TGC TTT GTT CTG TCG GGT CGT CTG CAG GTC GAC GCA TGC GCC G-3′, its complementary strand (Cs), 5′-C GGC GCA TGC GTC GAC CTG CAG ACG ACC CGA CAG AAC AAA GCA GAA CAC CAG ACC CCG GAT CCG TCG ACG AAT TCC CTA-3′, and FAM-labeled complimentary strand were obtained from Bioneer (South Korea). Plasma from rat, Streptomycin (STR), kanamycin, gentamicin, ciprofloxacin, amoxicillin and sodium tetrachloroaurate (III) ($HAuCl_4$) were purchased from Sigma (USA). Milk was purchased from Razavi (Iran).

2.2. Synthesis of water resuspended AuNPs

AuNPs were synthesized by the classical citrate reduction method, based on the previously published protocol (Storhoff, Elghanian, Mucic, Mirkin, & Letsinger, 1998). The synthesized AuNPs solution was centrifuged at 15,000*g* for 20 min at 4 °C. The supernatant was removed and AuNPs were resuspended in ultrapure water. Concentrations of AuNPs were estimated based on Extinction coefficient of $2.7 \times 10\ 8\ M^{-1}\ cm^{-1}$ at $\lambda = 520$ nm for 15 nm AuNPs.

The size and morphology of AuNPs were assessed by transmission electron microscopy (TEM) (LEO 912 AB, Germany).

2.3. Preparation of dsDNA

The Apt/Cs dsDNA was prepared by mixing Cs (4 μM final concentration) and Apt (4 μM final concentration) in binding buffer (20 mM Tris–HCl, pH 7.5). The mixture was incubated at room temperature for 60 min. Formation of dsDNA was investigated by 2.5% agarose gel electrophoresis (Fig. 1(a)).

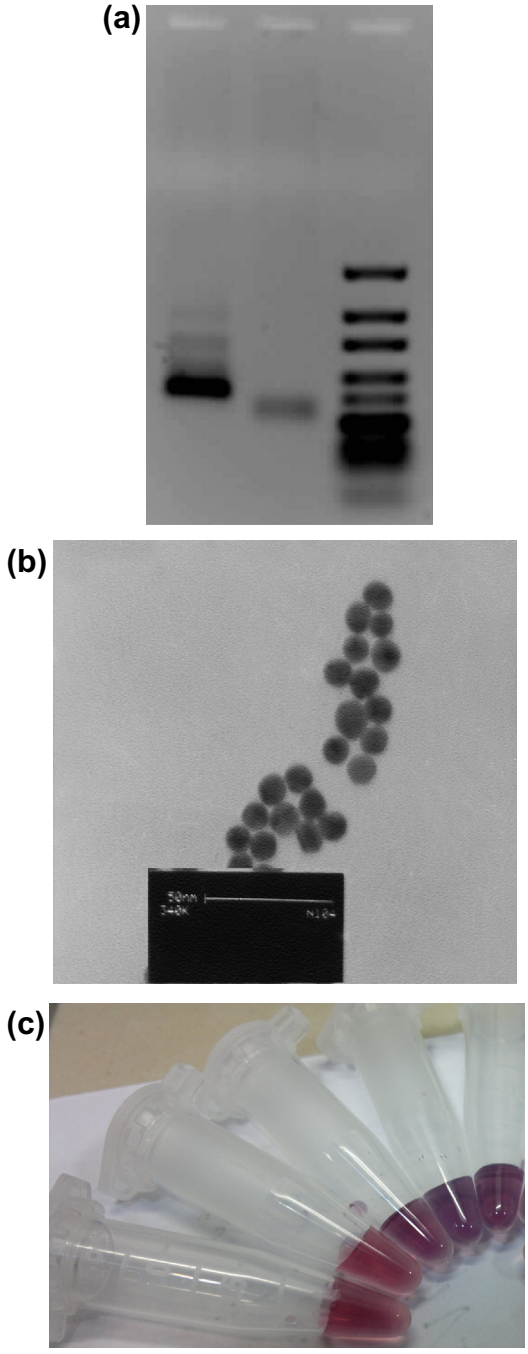


Fig. 1. (a) Agarose gel electrophoresis of Apt/Cs dsDNA. From left to right: Lane 1: Apt/Cs dsDNA, Lane 2: Apt, Lane 3: Ladder. (b) TEM image of AuNPs. (c) Visual color change upon treatment of AuNPs and dsDNA with different concentrations of streptomycin (0, 30, 300, 2000, 4000 nM, from right to left).

2.4. Streptomycin detection based on colorimetric technique

Increasing concentrations of streptomycin, 0–4000 nM final concentration, were added to dsDNA (2 μM final concentration) in 65 μl binding buffer. After 30 min, 5 nM AuNPs were added to the assay solution (final volume 200 μl). Mixtures were incubated for 30 min at room temperature. NaCl to final concentration of 100 mM was added to each well and after incubation for 5 min,

A_{520} was recorded using a Synergy H4 microplate reader (BioTek, USA). Data are means + SD, $n = 3$.

2.5. Streptomycin detection based on fluorescence quenching technique

A range of streptomycin concentrations, 0–4000 nM final concentration, were added to 2 μM FAM-labeled dsDNA in 65 μl binding buffer and incubated for 30 min. Then, 5 nM AuNPs were added to each well (final volume 200 μl). After incubation for 30 min at room temperature, fluorescence intensities, $\lambda_{Ex} = 494$ nm and $\lambda_{Em} = 520$ nm, were measured using the Synergy H4 microplate reader. Data are means + SD, $n = 3$.

2.6. Selectivity of the fluorescence quenching aptasensor

The selectivity was analyzed in the presence of 500 nM kanamycin, Streptomycin, gentamicin, amoxicillin and ciprofloxacin using the fluorescence method. Data are means + SD, $n = 3$.

2.7. Streptomycin detection in serum and milk

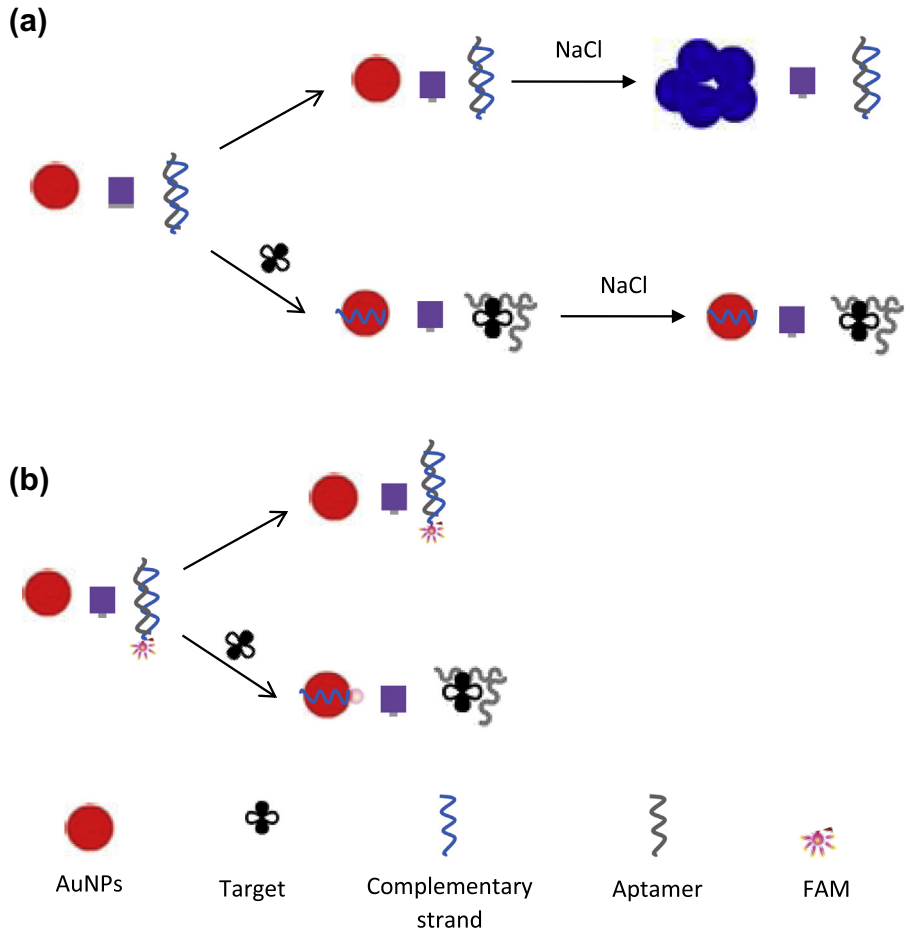
To investigate the application of the fabricated aptasensors in milk and serum samples, increasing concentrations of streptomycin (0–4000 nM) were spiked to milk and rat serum, and streptomycin concentrations were measured using the fluorescence quenching technique. For detection of streptomycin based on colorimetric technique, rat serum and milk were primarily diluted 1:50. Then, increasing concentrations of streptomycin were added to diluted serum and milk and streptomycin concentrations were recorded. Data are means + SD, $n = 3$.

3. Results and discussion

3.1. Sensing scheme

The presented colorimetric and fluorescence quenching aptasensors are based on target-induced release of complimentary strand from aptamer, strong interaction of ssDNA and water resuspended AuNPs and no or less interaction of dsDNA and AuNPs. It has been recently demonstrated that the removal of sodium citrate by water resuspention of AuNPs could enhance the sensitivity of both fluorescence quenching and colorimetric aptasensors (Liu et al., 2014).

For colorimetric aptasensor as shown in Scheme 1(a), in the absence of streptomycin, dsDNA is stable. dsDNA could not protect AuNPs against salt-induced aggregation, due to its rigid structure (Gopinath et al., 2014; Smith et al., 2014; Wei, Li, Li, Wang, & Dong, 2007). NaCl addition caps the repulsion between unmodified negatively AuNPs, leading to the aggregation of AuNPs. Upon the aggregation of these nanoparticles, the color of the reaction mixture obviously changes from wine-red to blue or light blue (Wen, Zheng, Shen, & Shi, 2013). Aptamer binds to its target with a greater binding constant compared to an ordinary DNA duplex (Ji et al., 2014; Yang, Wang, Xiang, Yuan, & Chai, 2014), so that upon the addition of streptomycin, the complementary strand



Scheme 1. Schematic description of streptomycin detection based on colorimetric (a) and fluorescence quenching (b) aptasensors.

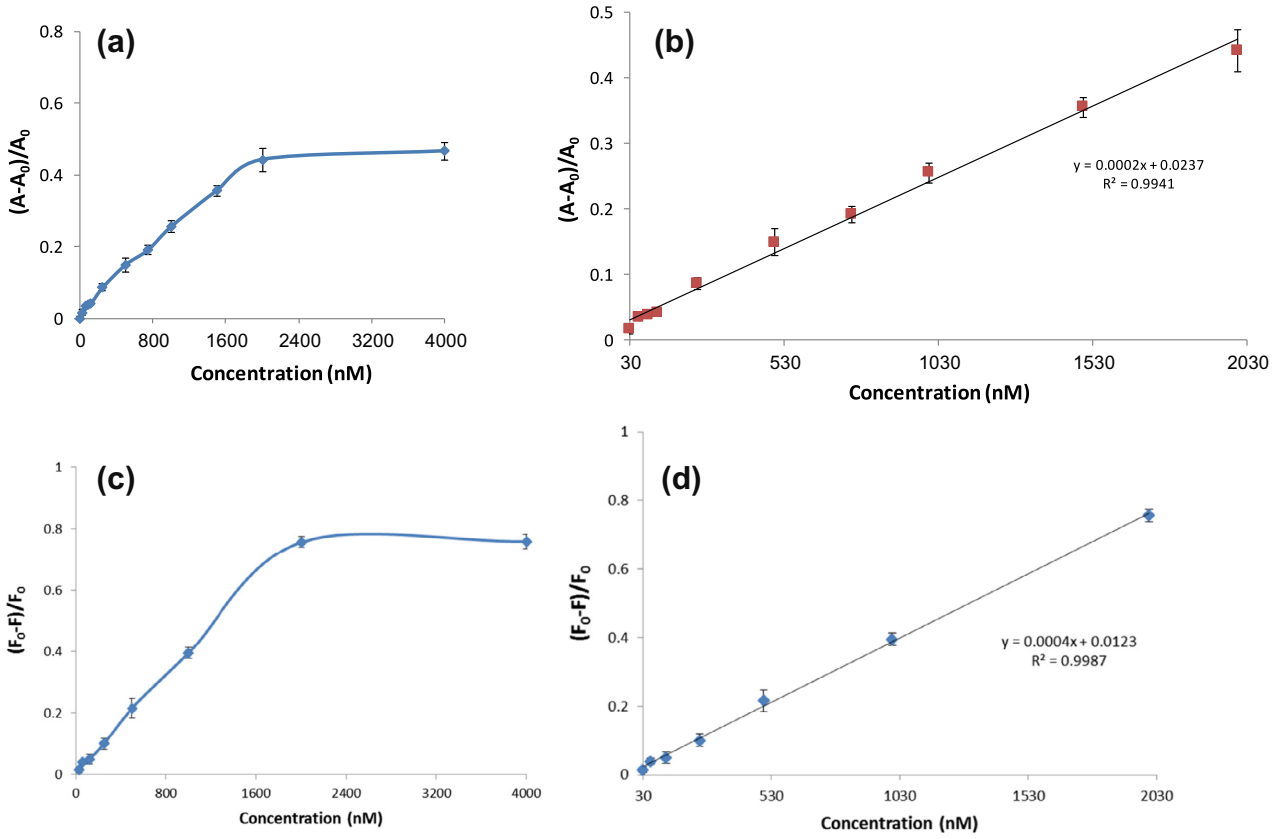


Fig. 2. (a) Relative absorbance of AuNPs as a function of streptomycin concentration. (b) Streptomycin standard curve. A_0 and A are the absorbance at 520 nm before and after addition of various concentrations of streptomycin, respectively. (c) Relative fluorescence intensity of FAM-labeled dsDNA as a function of streptomycin concentration. (d) Streptomycin standard curve. F_0 and F are the fluorescence intensities at 520 nm before and after addition of various concentrations of streptomycin, respectively.

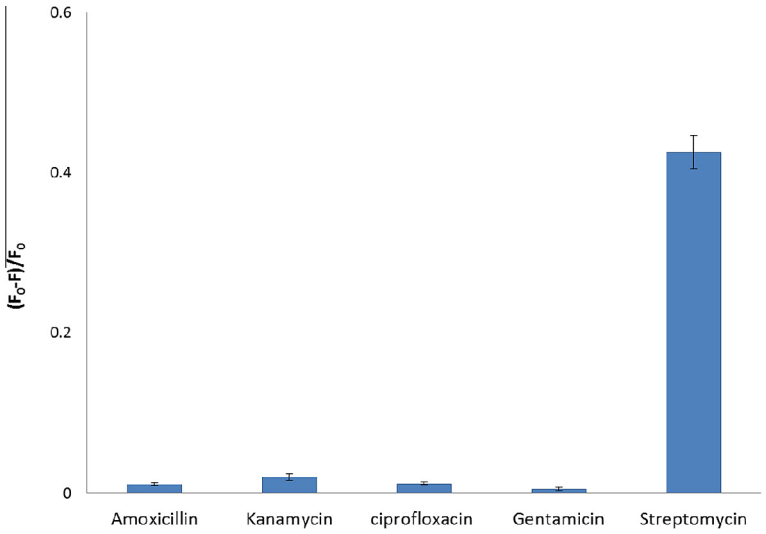


Fig. 3. Efficiency of fluorescence in the presence of various antibiotics.

leaves the aptamer and aptamer/streptomycin conjugate forms. The released complementary strand adsorbs on the surface of AuNPs by electrostatic interaction between the negatively charged AuNPs and positively charged bases of complementary strand (Chang, Wei, Wu, Lee, & Lin, 2013; Liu et al., 2014). So that AuNPs are stabilized by the complimentary strand against salt-induced aggregation.

For the fluorescence quenching aptasensor (Scheme 1(b)), addition of streptomycin induces formation of aptamer/streptomycin conjugate and release of FAM-labeled complementary strand. Since AuNPs are known as strong quenchers (Shi et al., 2013; Sun, Guo, Zhang, Guo, & Xie, 2011), the adsorption of FAM-labeled complementary on the surface of AuNPs, results in fluorescence energy transfer and quenching by the AuNPs through

fluorescent resonance energy transfer (FRET). In the absence of streptomycin a strong fluorescence emission is observed.

3.2. Water resuspended AuNPs characterization

The synthesized AuNPs were characterized using TEM. The results showed well-dispersed AuNPs with diameter of 15 nm (Fig. 1(b)).

3.3. Streptomycin analysis

In the colorimetric method, an obvious color change from blue to wine-red could be observed as streptomycin concentrations increased (Fig. 1(c)).

Fig. 2(a) shows the absorbance of AuNPs at different concentrations of streptomycin. The assay showed a well linear response over the wide range of nanomolar concentrations of streptomycin.

The limit of detection (LOD), as described by the International Union of Pure and Applied Chemistry (IUPAC) (Eq. (1)), was calculated to be 73.1 nM (53.3 μg/kg).

$$\text{LOD} = 3 \times \text{Standard deviation/Slope} \quad (1)$$

Fluorescence intensity of FAM-labeled Apt/Cs dsDNA at different concentrations of streptomycin was plotted in Fig. 2(c). The result indicated that the fluorescence intensity increased and reached to plateau at concentration of 2000 nM. LOD was measured to be 47.6 nM (34.7 μg/kg), which was lower than the obtained LOD by colorimetric method.

Reported detection limits of streptomycin in other studies were as following: 7.5 μg/kg for HPLC (Viñas et al., 2007), 4.7 μg/kg for LC-MS (Granja et al., 2009), 10 μg/kg for Immunochemical screening (Heering, Usleber, Dietrich, & Märtlbauer, 1998) and 30 μg/kg for optical biosensor (Ferguson et al., 2002). Compared to the designed aptasensors, generally these methods need expensive and sophisticated instruments and require lengthy turnaround time.

Selectivity is one of the most important characteristics of a practical sensor. To assess the selectivity of the presented aptasensor, other antibiotics including ciprofloxacin, kanamycin, amoxicillin, streptomycin and gentamicin were analyzed by fluorescence method. As shown in Fig. 3 the fluorescence intensity for streptomycin was significantly higher than other antibiotics. This result showed excellent selectivity of the designed aptasensor for detection of streptomycin.

3.4. Streptomycin analysis in biological samples

The fabricated aptasensors were applied to measure streptomycin concentration in milk and rat serum. Different concentrations of streptomycin were spiked into serum and LODs

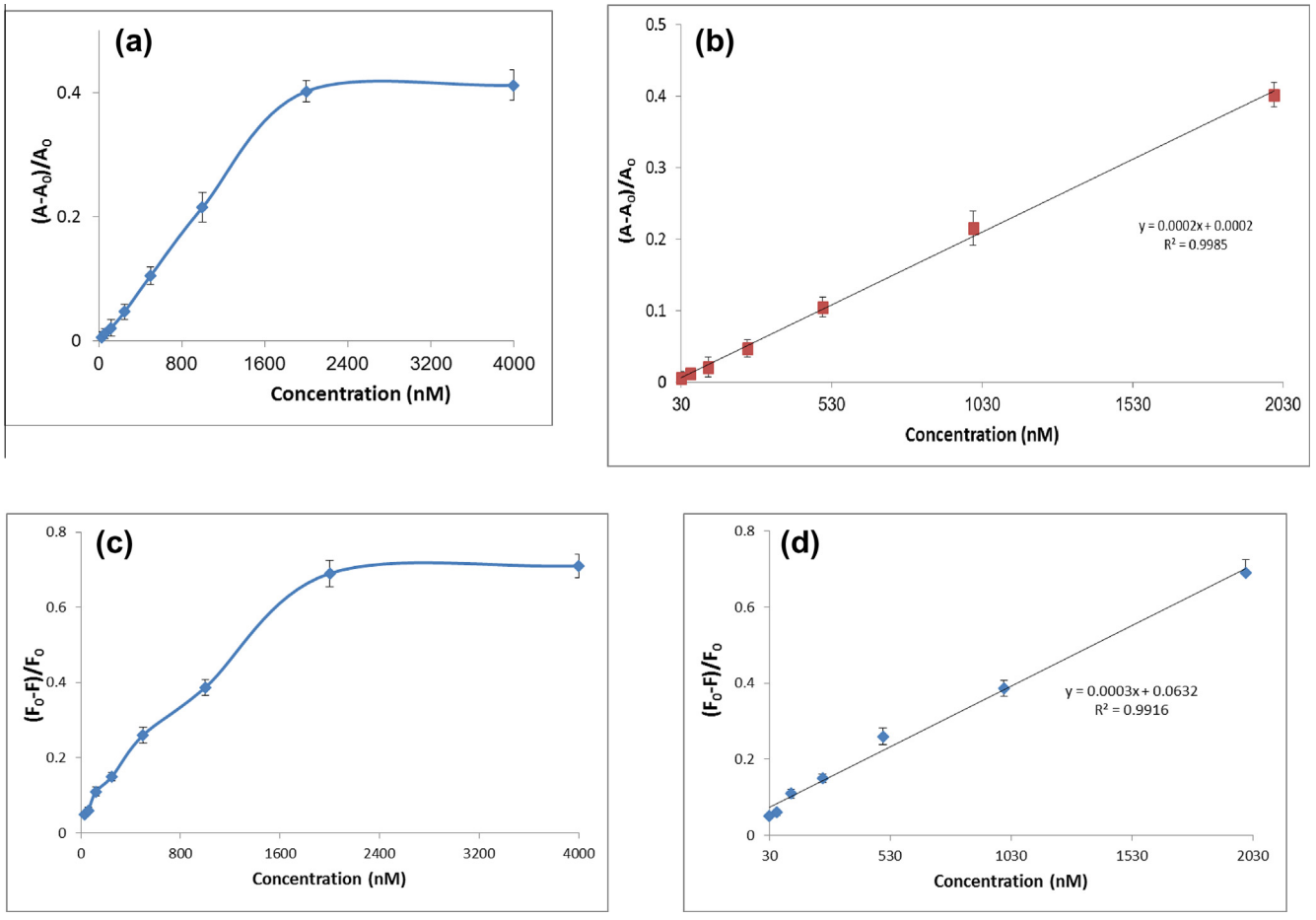


Fig. 4. (a) Relative absorbance of AuNPs upon the addition of various concentrations of streptomycin in serum. (b) Streptomycin standard curve in serum. A_0 and A are the absorbance at 520 nm before and after addition of various concentrations of streptomycin, respectively. (c) Relative fluorescence intensity of FAM-labeled dsDNA upon the addition of various concentrations of streptomycin in serum. (d) Streptomycin standard curve in serum. F_0 and F are the fluorescence intensities at 520 nm before and after addition of various concentrations of streptomycin, respectively.

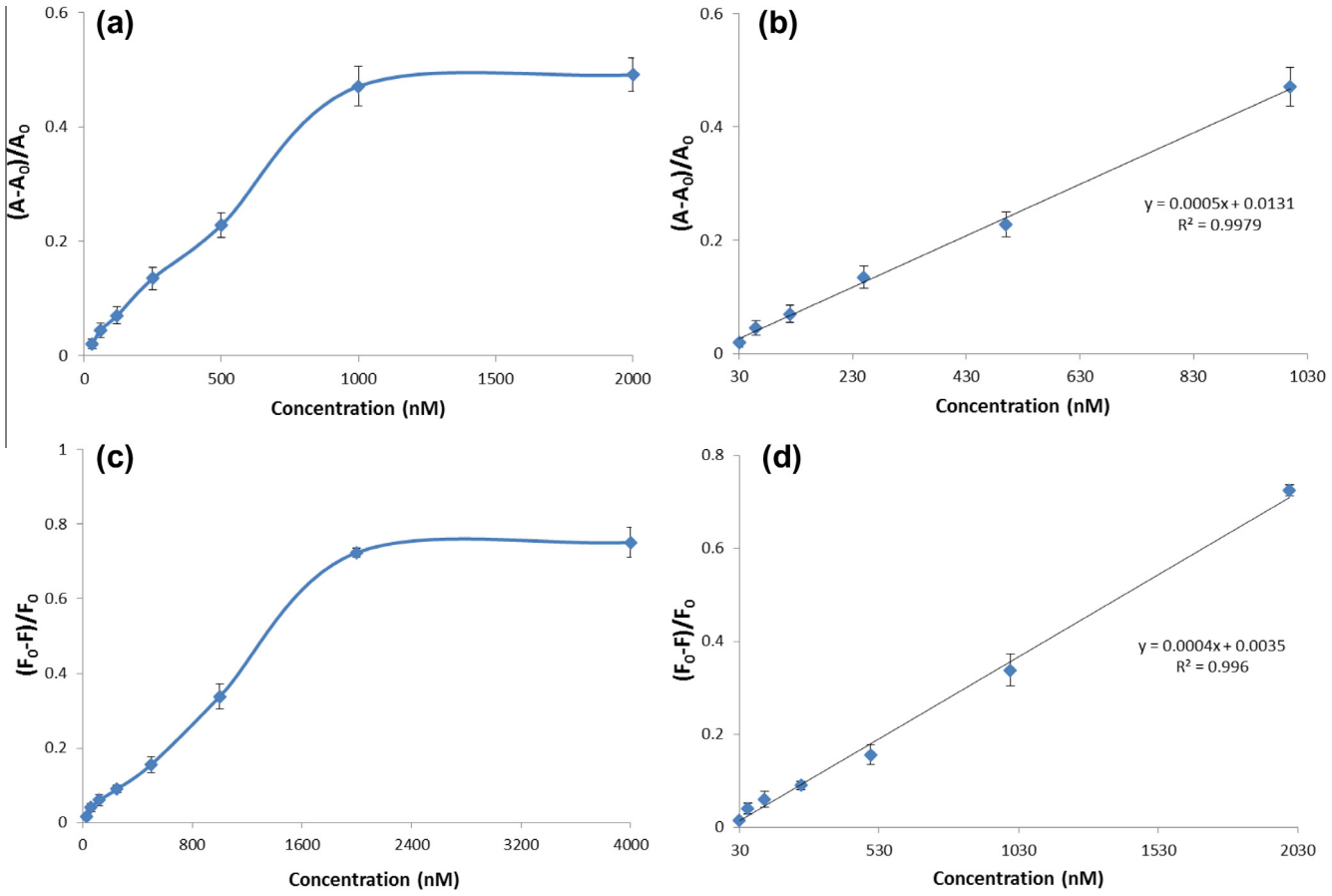


Fig. 5. (a) Relative absorbance of AuNPs upon the addition of various concentrations of streptomycin in milk. (b) Streptomycin standard curve in milk. A_0 and A are the absorbance at 520 nm before and after addition of various concentrations of streptomycin, respectively. (c) Relative fluorescence intensity of FAM-labeled dsDNA upon the addition of various concentrations of streptomycin in milk. (d) Streptomycin standard curve in milk. F_0 and F are the fluorescence intensities at 520 nm before and after addition of various concentrations of streptomycin, respectively.

were determined to be 58.2 nM (0.041 μg/ml) and 102.4 nM (0.072 μg/ml) for fluorescence quenching and colorimetric aptasensors, respectively (Fig. 4). Known concentrations of streptomycin were added into milk and LODs were calculated to be 56.2 nM (40.94 μg/kg) and 108.7 nM (72.19 μg/kg) for fluorescence quenching and colorimetric aptasensors, respectively (Fig. 5). The determined LODs were much lower than the permitted level of streptomycin in milk (200 μg/kg) and the streptomycin toxicity level in blood (35–40 μg/ml) (Akaho et al., 2002; Commission Regulation, 1990).

These results indicated the designed aptasensors could successfully be used for detection of streptomycin in milk and serum.

4. Conclusion

In summary, we presented an easy-to-build fluorescence quenching and colorimetric aptasensors based on AuNPs and dsDNA for the sensitive and simple detection of streptomycin. The designed sensors showed high selectivity toward streptomycin. The limit of detection for colorimetric and fluorescence quenching aptasensors were determined as low as 73.1 and 47.6 nM, respectively. Moreover, both aptasensors could well detect streptomycin in milk and serum.

Conflict of interest

There is no conflict of interest about this article.

Acknowledgment

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