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Simultaneous detection of enrofloxacin and chloramphenicol antibiotics using surface-enhanced Raman spectroscopy combined with triangular silver nanoplates

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Abstract. *The emergence of antibiotic residues in the environment and food requires the development of sensitive and selective detection methods for monitoring these contaminants. Many different types of antibiotics will be used simultaneously to prevent diseases in livestock and aquatic animals, causing antibiotic residues in food and the environment. Rapid and accurate simultaneous analysis of multiple antibiotics at low concentrations remains a major challenge in the field of rapid detection. This study presents a sensitive and selective method for the simultaneous detection of two widely used antibiotics, enrofloxacin and chloramphenicol, by combining surface-enhanced Raman spectroscopy (SERS) with triangular silver nanoplates. Triangular silver nanoplates (TAgNPls) in the form of colloids were simply synthesized by chemical reduction method and then used as an effective SERS substrate, enhancing the Raman signals of the target antibiotics and enabling the detection of these antibiotics at trace levels. It was found that with a SERS substrate assembled from the above TAgNPls, the antibiotics enrofloxacin and chloramphenicol could be detected with detection limits of 2.6 μg/L and 4.3 μg/L, respectively. In addition, this SERS substrate also allows simultaneous detection of the above two antibiotics in one analytical sample with concentrations*

as low as 10 μg/L for both substances. The proposed method holds promise for addressing concerns related to antibiotic contamination in various environments and food sources, contributing to the advancement of analytical techniques for the trace detection of pharmaceutical residues.

Keywords: SERS; triangular silver nanoplates; antibiotics; enrofloxacin; chloramphenicol; simultaneous detection.

Classification numbers: 52.38.Bv; 82.80.Gk; 81.07.-b; 07.07.Df.

1. Introduction

Antibiotics play an important role in agriculture, contributing to the treatment and prevention of infections, and promoting growth in farmed species, thereby helping to bring economic efficiency. However, the indiscriminate use of these antibiotics and mixing multiple antibiotics have raised concerns about their presence in the environment, in food and their impact on public health. The monitoring of antibiotics in the environment and food has become urgent to minimize the risks associated with antibiotic residues.

Enrofloxacin and chloramphenicol, as widely utilized antibiotics in agriculture, have proven effective in treating various bacterial infections. Enrofloxacin (ENRO) is a chemically synthesized third-generation broad-spectrum quinolone antibacterial, an extremely important class of antibacterial moieties commonly used to treat skin infections, respiratory infections, and other diseases in animals [1]. Chloramphenicol (CAP) is an antibiotic originally isolated from streptomyces venezuelae and is effective against a variety of gram-positive and gram-negative bacteria in both humans and animals [2]. The use of antibiotics such as ENRO or CAP has significantly improved livestock and aquaculture productivity and reduced losses due to bacterial infections during the farming process. However, due to its long half-life and slow metabolism, they can negatively affect human health. Long-term consumption of foods with excessive ENRO residues can cause symptoms such as dizziness, vomiting, poor sleep, allergies, and even liver damage. Animal studies have shown that the use of antibiotics such as ENRO may increase the severity of collagen-induced arthritis [3]. Different countries or organizations have established maximum residue limits (MRLs) for ENRO. It is widely recognized that the ENRO's MRL is in the range of 100 μg/kg to 300 μg/kg, depending on the animal species and the food [4, 5]. In the case of CAP, this antibiotic has been shown to have harmful side effects in humans, such as gray syndrome and fatal aplastic anemia [6]. Many countries and regions (e.g. the EU, the USA, Canada, and China) have strict regulations on CAP, and do not allow it to be present in animal products [6]. However, both ENRO and CAP are still being abused in livestock and aquaculture in a variety of places around the world. These two antibiotics can be used alone or in combination, causing residues of these substances in livestock and aquatic products as well as in the environment. Therefore, it is essential to develop a method that allows rapid and accurate simultaneous detection of these antibiotics to strictly regulate their use.

Conventional analytical methods for simultaneous detecting traces of antibiotics, including ENRO and CAP, are high-performance liquid chromatography (HPLC) [7, 8] and liquid chromatography-mass spectrometry (LC/MS) [9,10]. Although these methods provide results with high sensitivity, accuracy, and repeatability, they still contain some limitations such as requiring expensive equipment, as well as complex and time-consuming sample preparation. In recent years, surface-enhanced Raman spectroscopy (SERS) has emerged as a powerful technique

to enhance the sensitivity of molecular detection. The unique ability of SERS to amplify Raman signals by many orders of magnitude as well as its simplicity in sample preparation and analysis provide the opportunity to overcome the limitations of traditional analytical methods. With the advantage of high sensitivity and being able to provide "fingerprint" information about the chemical structure of the analyte, SERS allows the simultaneous analysis of many different analytes at trace concentrations. The characteristic peaks of different antibiotics can be easily used to differentiate each analyte in a mixture, enabling the detection of multiple antibiotics through a single SERS measurement. This can significantly reduce the detection time and improve analysis efficiency.

The key feature of SERS is its ability to enormously enhance the Raman scattering signals (up to hundreds of thousands of times or even more) and thereby provide detailed vibrational information of molecules. This enhancement occurs when molecules are placed very close to or on a noble metal surface that is rough at the nanoscale. The enhancement mechanism involves the excitation of the localized surface plasmon resonance, leading to an increase in the electromagnetic field near the nanostructured metal surface and, thus, an enhancement of the Raman scattering signal. The enhancement of SERS depends greatly on the morphology, size, and composition of the metal nanostructure (commonly known as the SERS substrate). SERS substrates are usually made from metal spherical nanoparticles, anisotropic non-spherical nanoparticles (e.g. triangular, cubic, hexagonal...) and branched nanostructures. Anisotropic or branched metal structures often contain many regions where the electric field is strongly increased (often called "hot spots"), thereby enhancing the Raman signals of molecules located in these regions. Among them, triangular silver nanoplates (TAgNPls) have attracted much attention due to their shape, sharp edges and vertices.

Many methods have been developed to synthesize TAgNPls, including chemical reduction [11–13], thermal synthesis [14], and templating process [15]. Among all these methods, chemical reduction is used most commonly due to its simplicity, low cost and good reproducibility [11–13]. A well-known procedure for the synthesis of AgTNPls was reported by Mirkin *et al.* in 2005 [11]. Accordingly, by reducing silver nitrate ($AgNO_3$) with sodium borohydride ($NaBH_4$) in the presence of trisodium citrate (Na_3CA), polyvinylpyrrolidone (PVP) and hydrogen peroxide (H_2O_2) at room temperature, the authors obtained TAgNPls with an average edge size of about 30 - 40 nm [11]. This is a simple and highly effective process. Therefore, several other groups have also fabricated TAgNPls according to the process of these authors [16–18]. In this report, we also prepared TAgNPls according to the procedure suggested by Mirkin *et al.* and then used them to make SERS substrates for the simultaneous detection of ENRO and CAP at low concentrations. The results obtained showed that SERS substrates which were made from TAgNPls allowed the detection of ENRO and CAP with detection limits of 2.6 μg/L and 4.3 μg/L, respectively. In addition, this SERS substrate also allows simultaneous detection of the above two antibiotics with concentrations as low as 10 μg/L for both substances.

Studies on the identification and quantification of ENRO or CAP by SERS have been reported [4–6, 19–27]. Specifically, Wang *et al.* used 6-Carboxyl-X-Rhodamine (ROX)-labeled aptamers and 4-mercaptobenzonitrile (4-MBN)-functionalized gold nanoparticles as SERS probes for the rapid detection and quantification of ENRO. Under optimal conditions, this SERS substrate achieved a limit of detection (LOD) of 0.12 nM (0.043 μg/L) [4]. Neng *et al.* combined SERS and molecularly imprinted polymers (MIPs) to detect ENRO and the LOD for ENRO they achieved was 0.25 ng/mL [5]. Xu *et al.* used amino-modified glycidyl methacrylate-ethylene dimethacrylate powdered porous material to detect ENRO in chicken muscles. With this SERS substrate,

ENRO in chicken muscles was successfully detected at a concentration as low as 0.01 mg/kg [19]. Jiang *et al.* used Ni-Zn-TiO_2 nanoparticles as SERS substrate to detect ENRO with a limit of detection (LOD) of 3×10^{-10} M (0.11 μg/L) [20]. Fu and co-authors fabricated a silver nanoparticles-modified microcavity fiber SERS probe to detect ENRO in milk and achieved a LOD of 10 μg/mL [21]. Zhou *et al.* developed the petal-like plasmonic nanoparticle clusters-based colloidal SERS method for ENRO detection and achieved a LOD of 1.15 μg/kg [22]. For CAP, Li *et al.* deposited flower-like silver nanoparticles on the hydrophobic region of the cellulose paper to detect CAP. The LOD of the proposed SERS substrate is 10^{-5} μg/mL [6]. Xie *et al.* fabricated the CAP–hybrid molecularly imprinted polymer–Au substrate to detect CAP in milk. The detection limit they achieved was 0.1 μg/ml [23]. Yu et al. presented an Ag-loaded system for SERS-based measurement of CAP with a LOD of 1.0×10^{-8} M (3.23 μg/L) [24]. Xiao et al. used silver nanoparticles as a SERS substrate for the rapid detection of CAP in honey and achieved a LOD of 4.0×10^{-9} $molL^{-1}$ (1.3 μg/L) [25]. Ha Anh *et al.* presented gold nanoparticles on aluminum as a SERS substrate for the detection of CAP with a LOD of 5.5×10^{-8} M (17.8 μg/L) [26]. Most recently, Chen *et al.* used a combination of Fe_3O_4@AuFe_3O_4@Au nanoflowers and Au@4-mercaptobenzoic acid@Ag nanoparticles for CAP detection. The LOD was determined to be 0.87 ng/L [27]. Publications on the use of SERS for the simultaneous analysis of multiple antibiotics are still quite few. To the best of our knowledge, there have been no publications on the use of SERS to simultaneously detect ENRO and CAP.

2. Experiment

TAgNPls were synthesized as follows. First, a mixture solution of 25 mL of silver nitrate ($AgNO_3$) (0.1 mM), 1.5 mL of trisodium citrate dihydrate ($Na_3C_6H_5O_7.2H_2O$) (30 mM) and 1.5 mL of polyvinylpyrrolidone (PVP) (0.7 mM) was magnetically stirred in a glass beaker for 2 minutes at room temperature. After that, 65 μL of hydrogen peroxide (H_2O_2) solution was added to the above mixture. Finally, 250 μl sodium borohydride ($NaBH_4$) (100 mM) solution was rapidly injected into the aforementioned solution. At this time, the solution immediately changed from colorless to light yellow. Over the next several minutes, the mixed solution continues to change color from light yellow to dark yellow, red, purple, and finally blue. The solution was then continuously stirred for 60 minutes and finally, a solution containing TAgNPls was obtained. After fabrication, the solution was centrifuged at 12000 rpm for 10 minutes, then washed twice in ethanol, redispersed in deionized water and kept in a refrigerator at 11^{o}C.

$AgNO_3$ (99.8%), $Na_3C_6H_5O_7.2H_2O$ (99%), H_2O_2 (30wt. %), and $NaBH_4$ (99,8%) were all of the analytical grade and were purchased from Xilong Chemical Co., Ltd. (Guangdong, China). PVP (average Mw ~55,000) was purchased from Sigma Aldrich. The deionized water was used throughout the experiment. The morphology of TAgNPls was characterized using an S-4800 field-emission scanning electron microscope (SEM) (Hitachi, Japan). The optical absorption of TAgNPls samples was identified by UV-Vis absorbance spectroscopy (Shimadzu UV1800, Japan) over the range 190–1100 nm.

ENRO (99%) and CAP (98%) were purchased from Sigma-Aldrich and used without further purification. The antibiotic solutions with different concentrations were prepared by sequential dilution. Specifically, ENRO powder was dissolved in methanol to form a stock standard solution with a concentration of 100 mg/L. This stock solution was then diluted with deionized water to produce ENRO solutions with different concentrations in the range of 50–0.01 mg/L.

CAP solutions with different concentrations in the range of 50–0.01 mg/L were similarly prepared in the same way as above. Antibiotic mixtures with different concentration ratios were prepared by mixing 10 mL of as-prepared ENRO and 10 mL of as-prepared CAP of different concentrations.

For collecting the SERS spectra of ENRO and CAP solution, 20 μL of TAgNPls colloid was mixed with 20 μL of ENRO or/and CAP containing solution followed by vortexing for 10 s. Then, 40 μL of the resulting solution was dripped onto a 5 mm × 5 mm silicon wafer. The sample was then allowed to dry naturally in the air. SERS spectra of ENRO and CAP solutions were recorded using a portable Raman spectrometer model BWS475-785H with a 785 nm excitation laser (B&W Tek, USA).

3. Results and discussion

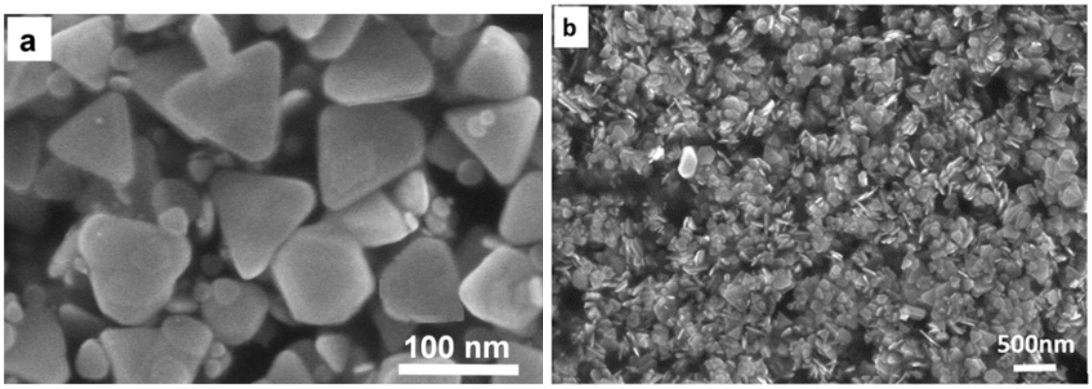

Fig. 1. SEM images with different magnifications of the TAgNPls obtained by the chemical reduction method.

Figure 1 is SEM images with two different magnifications of the fabricated TAgNPls. It can be seen the obtained sample is triangular silver nanoplates with an average edge size of about 80-90 nm (Fig. 1a). Besides the TAgNPls, some hexagonal and small spherical particles appeared in the obtained sample. Fig. 1b shows that the density of TAgNPls is very dense. With a special shape and when used in high density, an aggregation of TAgNPls when used as SERS substrate is certainly capable of providing a lot of hot spots from which a high SERS enhancement factor can be achieved.

The UV-Vis spectrum of a TAgNPls colloidal solution in Fig. 2 displays three peaks corresponding to different plasmon excitation modes of the triangular nanoplates. Specifically, the low sharp peak at about 335 nm is due to out-of-plane quadrupole resonance. The weak shoulder at around 415 nm can be attributed to the in-plane quadrupole resonance and the dominant peak at 520 nm represents the in-plane dipole resonance [12, 18].

To test the SERS sensitivity of the fabricated TAgNPls for simultaneous analysis of ENRO and CAP, the structures were first used as SERS substrates to detect ENRO and CAP as a single substance. Fig. 3 is the SERS spectra of ENRO with concentrations ranging from 50 mg/L to 0.01 mg/L recorded using TAgNPls SERS substrates. It can be seen that all the obtained SERS spectra show the characteristic Raman peaks of ENRO at 545, 745, 790, 1020, 1175, 1393, 1467

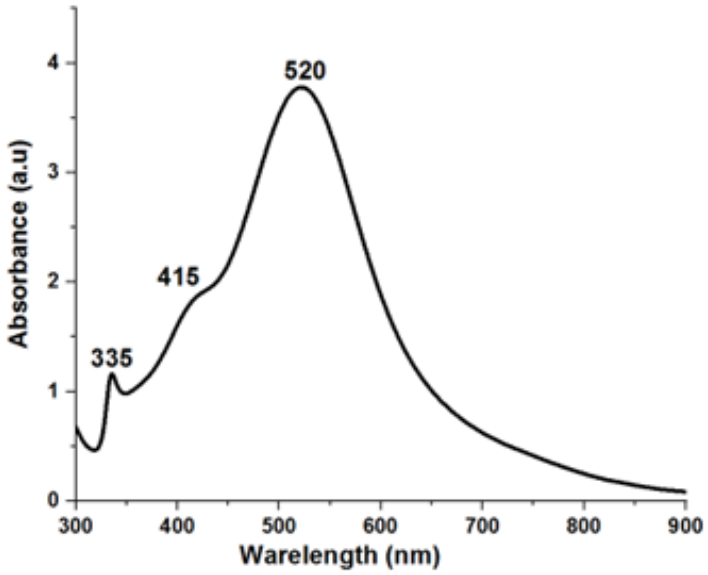

Fig. 2. UV-Vis absorption spectrum of a fabricated TAgNPls.

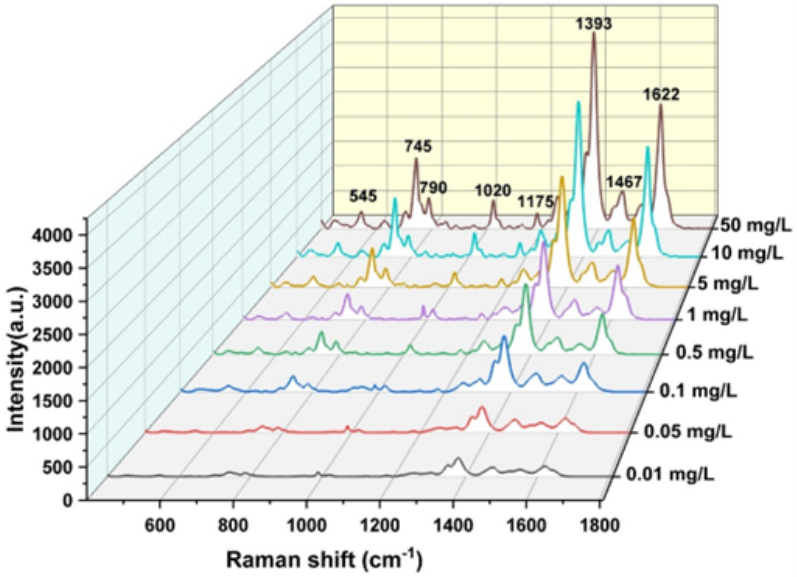

Fig. 3. SERS spectra of ENRO at different concentrations in the range of 0.01–50 mg/L which were recorded with similar TAgNPls SERS substrate.

and 1622 cm^{-1}. Specifically, the bands at 545 and 1175 cm^{-1} are attributed to the C-C bending or stretching modes. The band at 745cm^{-1} is assigned to the methylene rocking mode. The bands at 790 and 1467 cm^{-1} represent the benzene ring vibrations. The symmetric C-O-C stretching, O-C-O symmetric stretching, and C=O stretching vibrations are observed at 1020, 1393 and 1622 cm^{-1},

respectively [4, 5, 19–22]. We can see that the intensity of the main peaks of ENRO gradually decreases as its concentration decreases from 50 mg/L to 0.01 mg/L. When the ENRO concentration is only 0.01 mg/L, the main characteristic peaks of ENRO are still clearly visible. This demonstrates that by using TAgNPls SERS substrate, we can detect ENRO at concentrations as low as 0.01 mg/L.

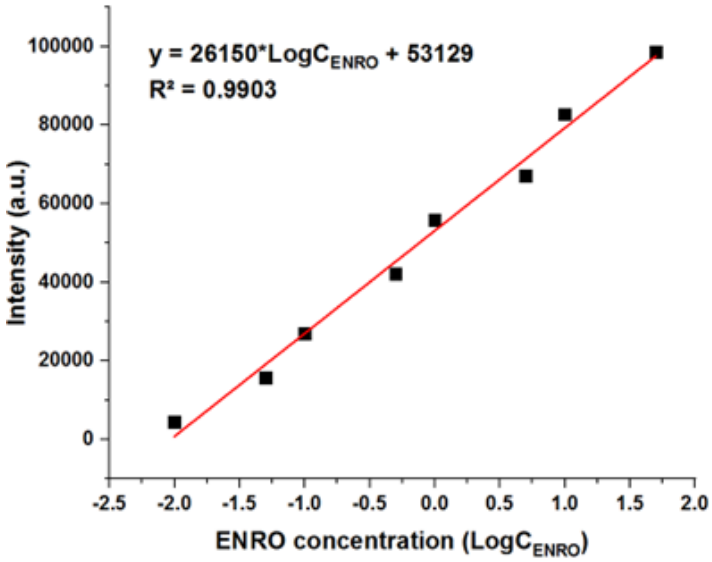

Fig. 4. Relationship between the intensity of the ENRO's 1393 cm^{-1} peak and ENRO concentration in the range of 0.01–50 mg/L.

The calibration curve representing the relationship between the intensity of the SERS band at 1393 cm^{-1} of ENRO and its concentration (in the range of 0.01–50 mg/L) was established and shown in Fig. 4. It can be seen the dependence of the intensity of ENRO's 1393 cm^{-1} peak on the ENRO concentration in the analytical solution in the range of 0.01–50 mg/L shows a good linear relationship. The regression equation is y = 26150*Log C_{ENRO} +53129 with $R^2 = 0.9903$, where y is the SERS intensity of the 1393 cm^{-1} peak of ENRO and C_{ENRO} represents the concentration of ENRO in the analytical solution. The LOD value of ENRO was 2.6 μg/L, estimated using a signal-to-noise ratio of 3 ($S/N = 3$). These results are similar to those of some other reports [5, 20, 22].

Similarly, SERS measurements of CAP on TAgNPls SERS substrates were also performed and the results are shown in Figs. 5 and 6. It can be seen all the obtained SERS spectra in Fig. 5 show the characteristic Raman peaks of CAP at 630, 865, 995, 1108, 1350 and 1598 cm^{-1} [6, 23–27]. Specifically, the peak at 630 cm^{-1} is assigned to ring breathing mode. The band at 865 cm^{-1} represents the stretching mode of C-H on the phenyl group. The band at 995 cm^{-1} is attributed to the C-O stretching mode. The band at about 1108 cm^{-1} can be attributed to the C-O bending and C-H stretching vibrations. The band at 1350 cm^{-1} is assigned to the NO_2 symmetric stretching mode, and 1598 cm^{-1} represents ring stretching vibration [6, 23–27]. As the concentration of CAP decreased, the intensity of these characteristic Raman peaks also decreased. When the CAP concentration in the analytical solution dropped to just 0.01 mg/L, these characteristic Raman peaks were still observed quite clearly.

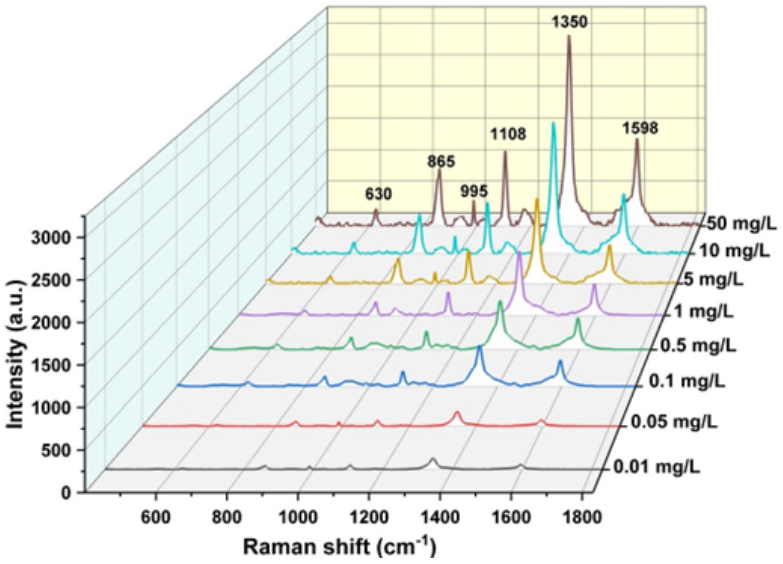

Fig. 5. SERS spectra of CAP at different concentrations in the range of 0.01–50 mg/L which were recorded with similar TAgNPls SERS substrates.

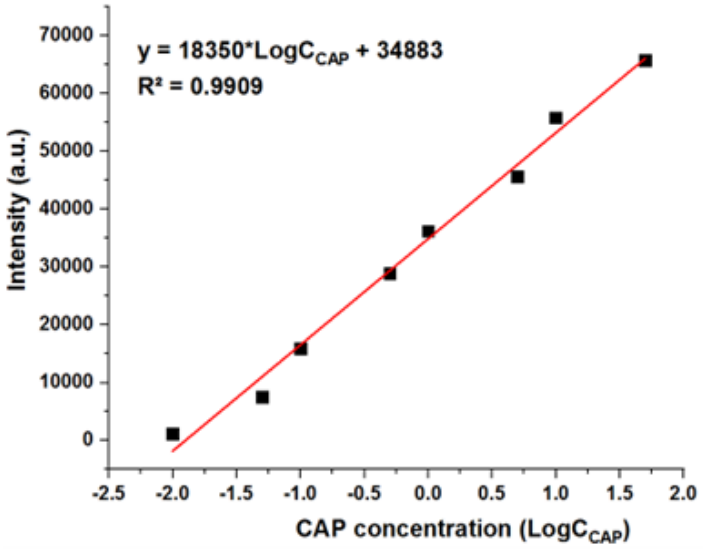

Fig. 6. Relationship between the intensity of the CAP's 1350 cm^{-1} peak and CAP concentration in the range of 0.01–50 mg/L.

The calibration curve representing the relationship between the intensity of a typical CAP SERS band at 1350 cm^{-1} on its concentration in the range of 0.005–10 mg/L represents a good linear relationship (Fig. 6). The regression equation is $y = 18350 * \mathrm{Log}C_{\mathrm{CAP}} + 348831$ and $R^2 = 0.9909$, where y is the SERS intensity of the peak at 1350 cm^{-1} of CAP, and C_{CAP} represents CAP

concentration in the analytical solution. The limit of detection (LOD) value of CAP is 4.3 μg/L, estimated by the signal-to-noise ratio of 3 ($S/N = 3$). This LOD value is like the LOD values obtained by some research groups ([24, 25] for example).

To protect livestock and aquatic animals from diseases, several different antibiotics will be mixed to be used simultaneously for livestock and aquatic animals. In this study, to investigate the ability of TAgNPls SERS substrate to detect multiple antibiotics simultaneously, we mixed two antibiotics ENRO and CAP in different ratios and recorded the SERS spectrum of this mixture. Fig. 7 shows the SERS spectrum of the ENRO-CAP mixture sample with the concentrations of ENRO and CAP both being 50 mg/L. Comparing with the SERS spectra of ENRO and CAP in Figs. 3 and 5, it can be seen that the SERS spectrum of the ENRO-CAP mixture sample displays peaks at 745, 1020, 1393, 1467, 1622 cm^{-1} of ENRO and peaks at 865, 995, 1108, 1350, 1598 cm^{-1} of CAP.

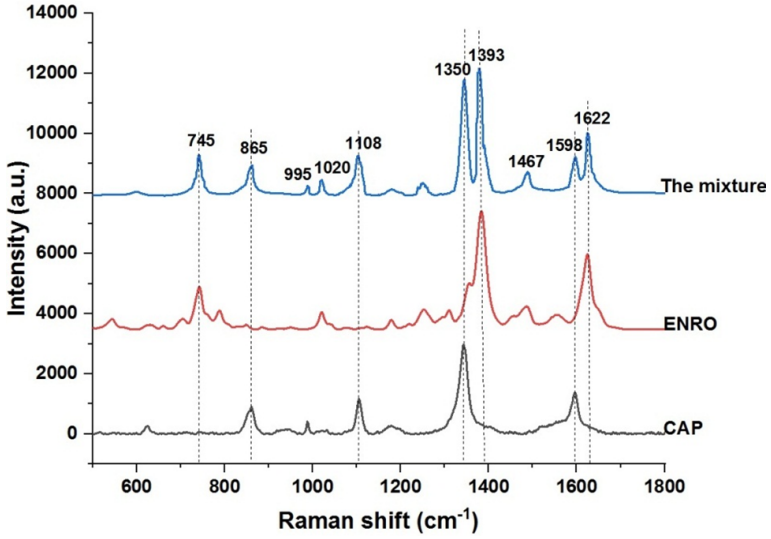

Fig. 7. SERS spectra of ENRO, CAP and ENRO-CAP mixture with the same concentration of each substance of 50 mg/L obtained using similar TAgNPls SERS substrate.

Figure 8 shows the SERS spectra of ENRO-CAP antibiotic mixtures with the concentration of each antibiotic in the mixture being 50, 10, 5, 1, 0.5, 0.1, 0.05 and 0.01 mg/L, respectively. As the concentration of ENRO-CAP in the mixture decreases, the intensity of the characteristic peaks of the mixture also gradually decreases. When the concentration of ENRO and CAP in the mixture was only 0.01 mg/L, characteristic peaks of ENO and CAP were still clearly observed. This result shows that, by using SERS combined with AgTNPls, we can simultaneously analyze ENRO and CAP at concentrations as low as 0.01 mg/L. This positive result opens up great potential for applying SERS as a multi-substance analysis method in food and the environment.

The reproducibility of the TAgNPls SERS substrate was tested and the results are illustrated in Fig. 9. Fig. 9 shows the SERS spectrum of the ENRO-CAP mixture with a concentration of both antibiotics of 1 mg/L which were recorded using SERS TAgNPls substrates synthesized in three different batches. It can be seen the three obtained SERS spectra have a quite good overlap.

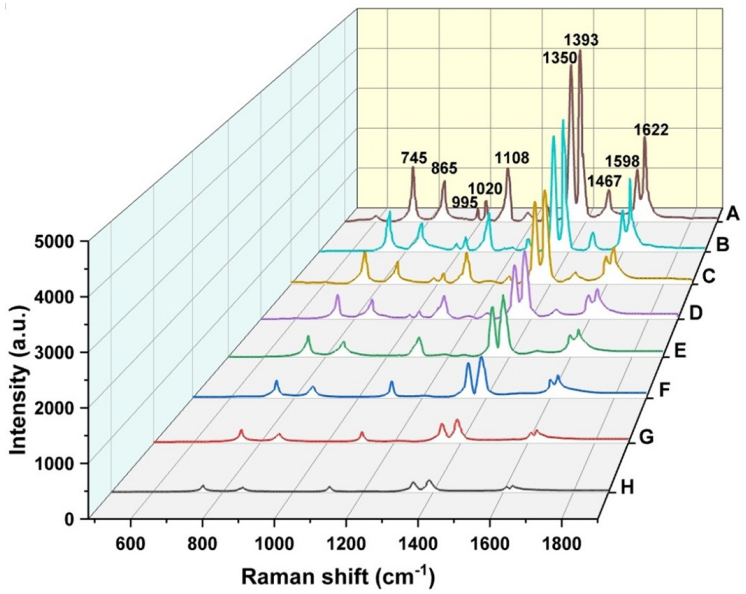

Fig. 8. SERS spectrum of ENRO-CAP mixture with the concentration of both antibiotics of 50 mg/L (curve A), 10 mg/L (curve B), 5 mg/L (curve C), 1 mg/L (curve D), 0.5 mg/L (curve E), 0.1 mg/L (curve F), 0.05 mg/L (curve G) and 0.01 mg/L (curve H), obtained using similar TAgNPls SERS substrate.

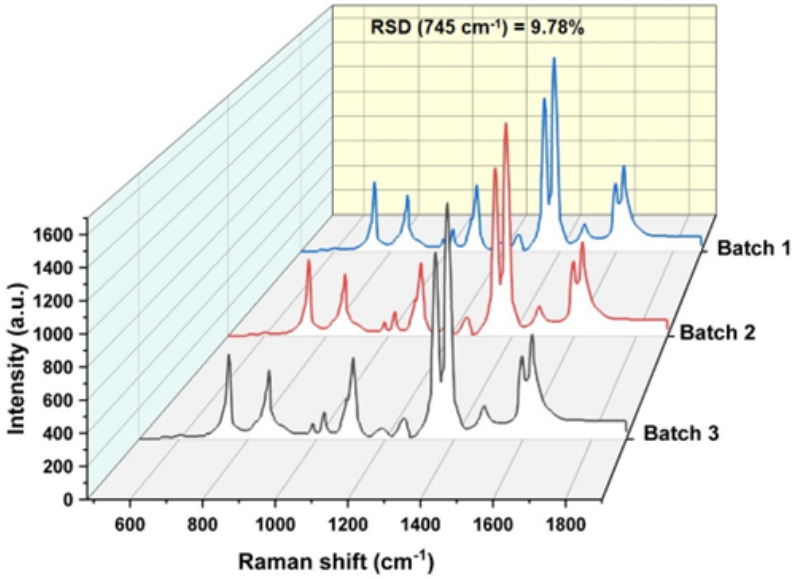

Fig. 9. SERS spectrum of ENRO-CAP mixture with the concentration of both antibiotics of 1 mg/L obtained using three SERS substrates that were assembled from TAgNPls fabricated in three different batches.

The intensities of all Raman peaks of these three SERS spectra are almost equal. Furthermore, to quantitatively evaluate a SERS substrate for reproducibility for a specific analyte, one or more SERS bands of this analyte are selected, and then the Raman signal intensity change of these bands is determined. The change in intensity of the Raman signal is usually expressed as a relative standard deviation (RSD) value. It is generally accepted that an RSD value of less than 20% for the change in Raman signal intensity is an indicator of a well-reproducible SERS substrate [28]. In the present study, the characteristic band of the ENRO-CAP mixture at 745 cm^{-1} was chosen to examine the change in Raman signal intensity. Calculations show that for TAgNPls synthesized in three different batches the RSD value of the intensity of the band at 745 cm^{-1} was only 9.78%. This result demonstrates the good reproducibility of the TAgNPls SERS substrate.

4. Conclusions

In summary, using TAgNPls prepared very simply by the chemical reduction method, we succeeded in simultaneously detecting traces of the antibiotics enrofloxacin and chloramphenicol. When used alone, enrofloxacin was detected with an LOD of 2.6 μg/L, while chloramphenicol was detected with an LOD of 4.3 μg/L. Meanwhile, when used together, enrofloxacin and chloramphenicol could be simultaneously detected at concentrations as low as 10 μg/L. The above results demonstrate the great potential of SERS in the simultaneous detection of traces of multiple contaminants in food and the environment.

Acknowledgments

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