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Adsorptive stripping voltammetric technique for the rapid determination of tobramycin on the hanging mercury electrode

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Abstract

A linear sweep adsorptive stripping voltammetric method (AdS-LSV) for the determination of tobramycin (TOB) has been proposed for the first time. The method is based on the formation of the voltammetrically active *iso*-butyraldehyde derivative of TOB and the electrochemical behavior of TOB *iso*-butyraldehyde derivative has been studied. TOB *iso*-butyraldehyde derivative exhibits a sensitive cathodic peak at −1.40 V (versus SCE) in a medium of B-R buffer (pH 9.8) with a scan rate of 90 mV s^{-1} after a preconcentration period of 120 s at −1.10 V (versus SCE). The linear concentration range of application was 6.87×10^{-9}–3.44×10^{-7} mol L^{-1} of TOB, with a relative standard deviation of 4.4% (for a level of 1.0×10^{-7} mol L^{-1}) and a detection limit of 3.44×10^{-9} mol L^{-1}. The method was applied to the direct determination of TOB in injectable formulations and spiked urine and serum samples.

Keywords: Linear sweep adsorptive stripping voltammetry; Tobramycin; *iso*-Butyraldehyde derivative

1. Introduction

Tobramycin (Scheme 1) produced by *Streptomyces tenebrarius* is a broad-spectrum aminoglycoside antibiotic against Gram-positive and some aerobic Gram-negative bacteria [1]. Like all other aminoglycosides, tobramycin (TOB) has a comparably narrow safety margin because of its oto- and nephrotoxicity especially in a long-term therapy. This drug has a high urine excretion ratio (more than 85% of the administered dosage) in unaltered form over 24 h [2]. For these reasons, a rapid and highly sensitive analytical method is essential for the evaluation of this substance in biological fluids.

A variety of methods including liquid chromatography (LC) [3–18], immunoassays [19–24], microbiological assays [25], spectrophotometry [26,27] and capillary zone electrophoresis (CE) [28,29] have been introduced for the measurement of TOB in pharmaceutical preparations and biological matrices. Among these methods, LC and immunoassays are preferred. Direct LC for TOB determination is not feasible because there is no significant UV chromophore in the TOB molecule. Therefore, precolumn or post-column chemical derivatization steps are necessary for UV detector. These derivatizing reagents include 3,5-dinitrobenzoyl chloride [3], 1-fluoro-2,4-dinitrobenze [4–7], 2,4,6-trinitrobenze sulfonic acid [8,9], *o*-phthalaldehyde [10–12], 1-naphthyl isothiocyanate [13]. But the procedures of these methods are complicated and time-consuming due to requiring extensive clean-up and extraction steps. In addition, some special detectors such as fluorescence [14,15], tandem mass spectrometry [16] or electrochemical detectors [17,18] are used with liquid chromatographic methods. These instruments are expensive and impractical for routine use. Immunoassays, which become increasingly popular, sometimes show inaccuracy because of variable interference between individuals. Moreover, the reagents used in immunoassays are expensive.

Polarographic and voltammetric methods have proved to be very sensitive analytical methods to determine organic molecules. Now they are widely used in the fields of pharmaceutical analysis, forensic analysis and environmental

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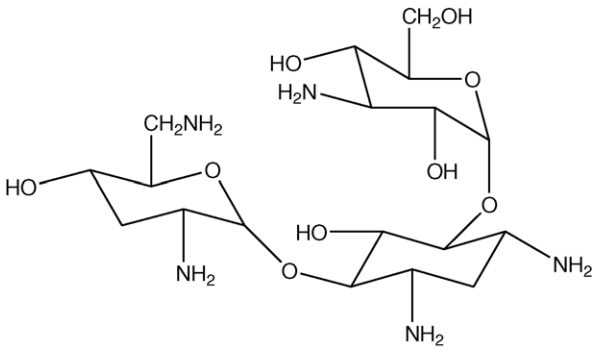


Scheme 1. Chemical structure of TOB.

analysis due to their high sensitivity, low detection limit, easy operation and simple instrumentation [30]. Some polarographic methods have been introduced to determine aminoglycosides. Perruchon and Caullet [31] used differential pulse polarography to determine Gentamicin, Netilmicin and Sisomicin after hydrolysis of these aminoglycosides with sulphuric acid. Ayad and Yousef [32] used d.c. polarography to determine Kanamycin, Gentamicin and Amikacin after reaction of these aminoglycosides with nitrous acid to form nitroso derivatives. Fang et al. [33] described a single sweep oscillopolarographic method to determine Kanamycin after forming its formaldehyde derivative. But all the above polarographic methods could not be applied to biological fluids due to their high detection limits or complicated derivatization procedures.

Up to date, no polarographic or voltammetric methods for the determination of TOB were reported in literatures. Like other aminoglycosides, a direct polarographic or voltammetric determination of TOB is not feasible because it does not contain an electroactive functional group. There are five primary amino groups in the TOB molecule. Owing to the facts that the primary amino group can react with formyl group to form a schiff bond which is an electroreducible species, and that the reaction can take place in mild conditions, we used aldehyde as the derivatizing agent in this work. The aim of the present work is to develop a rapid, sensitive electroanalytical procedure for the determination of TOB in pharmaceutical preparations and biological fluids using linear sweep adsorptive stripping voltammetric method (AdS-LSV). The proposed method avoided the time-consuming extraction step and was easy to be applied in routine determination.

2. Experimental

2.1. Apparatus

All voltammetric measurements were carried out employing a model CHI660 electrochemical workstation (CH Instruments, USA) with a model 303A (EG&G PARC, USA) three-electrode system including a hanging mercury drop electrode (HMDE) as the working electrode (surface area = 0.012 cm^2), a platinum-wire auxiliary electrode and a saturated calomel reference electrode (SCE). The workstation was controlled by CHI660 software and operated under Windows 98 environment. A magnetic stirrer (305-PAR) and a stirring bar were used during the preconcentration step. A Mettler pH meter (320S) was used for pH measurements. A centrifuge (TG16-WS) was used for separation of the precipitated protein from the human serum samples before assay of TOB.

2.2. Materials

TOB was purchased from Eastchinapharm Co. Ltd. (Hangzhou, China) and used as received. Two pharmaceutical dosage forms used were injections (Shangdong Xinhua Pharmaceutical Company Limited, China). The forms were 20 and 40 mg mL^{-1}. Biological samples were kindly provided by Zhejiang Provincial Hospital and kept frozen until analysis.

2.3. Reagents and solutions

A TOB standard stock solution (1.0×10^{-3} mol L^{-1}) was prepared in water and stored in the dark under refrigeration. Two working standard solutions, 1.0×10^{-5} and 1.0×10^{-6} mol L^{-1}, were prepared by appropriate dilution of the standard solution with water. Formaldehyde solution (5%, w/w), acetaldehyde solution (5%, w/w) and *iso*-butyraldehyde solution (5%, w/w) were prepared by diluting formaldehyde solution (37%, w/w), acetaldehyde solution (40%, w/w) and *iso*-butyraldehyde in water, individually. All reagents were of analytical grade, and used without further purification. Twice distilled water was used throughout the experiments.

2.3.1. Injection sample solutions

Five injections were mixed. A 1 mL aliquot of mixed injection was pipetted into a 10 mL volumetric flask, then made up to the volume with water. The suitable concentrations of the drug were obtained by diluting with water. The solution was directly analyzed according to the proposed procedure in Section 2.4.

2.3.2. Spiked biological sample solutions

Drug-free biological samples, obtained from healthy individuals, were stored frozen until analysis. After gentle thawing, serum or urine samples, 1 mL each, were spiked with various amounts of the standard TOB solution, then completed to 10 mL with water. The spiked urine solution was directly analyzed according to the proposed procedure in Section 2.4. The spiked serum solution required the centrifugal separation of protein prior to the assay. A 2.5 mL aliquot of serum solution was diluted to a 5 mL volume with ethanol in a 10 mL volume centrifuge tube. The precipitated proteins were separated by centrifugation for 15 min at 4000 rpm. The protein-free supernatant solution was taken carefully and directly analyzed according to the proposed procedure in Section 2.4.

2.4. Procedures

A certain volume of TOB standard or sample solution, 0.4 mL *iso*-butyraldehyde solution (5%) were successively pipetted into a 10 mL volumetric flask, then made up to the volume with Britton-Robinson buffer (B-R buffer) of pH 9.8. The mixture was stayed for 10 min at room temperature, then transferred into a voltammetric cell and bubbled with nitrogen gas for 10 min. An accumulation potential of −1.10 V (versus SCE) was applied to the HMDE for 120 s while the solution was stirred at 2000 rpm. After a 30 s rest time, the voltammogram was recorded by scanning the potential from −1.10 to −1.65 V at a rate of 90 mV s^{-1} using linear scan technique. The current of the peak was recorded versus the concentration of TOB. The TOB concentrations of injectable formulations were obtained by using the analytical calibration curve, and the standard addition method was applied to determine TOB in spiked biological fluids. All data were obtained at room temperature (25 °C).

3. Results and discussion

3.1. Selection of aldehyde

In our study, no peak was observed in the linear sweep voltammogram for a 1.0×10^{-7} mol L^{-1} TOB even after a preconcentration step at an accumulation potential in the range of −0.80 to −1.30 V due to voltammetrically inactivity of the antibiotic TOB investigated. In contrast, sensitive peaks were observed after derivatizing with aldehydes, such as formaldehyde, acetaldehyde and *iso*-butyraldehyde, and the peaks after preconcentration step were much larger than those without accumulation. Fig. 1 shows the linear sweep voltammagrams of TOB aldehyde derivatives after the accumulation step. The results revealed that both the peak current and the peak shape were affected by the type of derivatizing agent. The peak of TOB *iso*-butyraldehyde derivative was most sensitive, and its shape was best-defined in the same conditions. Considering sensitivity and shape of the peak, *iso*-butyraldehyde was selected as the derivatizing agent in this work to determine TOB with AdS-LSV.

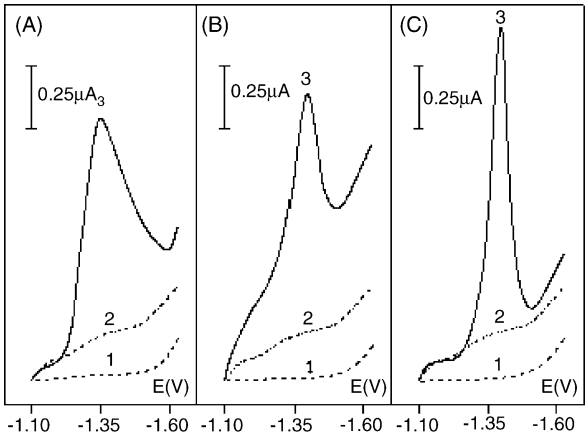


Fig. 1. AdS-LSV voltammograms for the determination of 1.0×10^{-7} mol L^{-1} TOB in B-R buffer (pH 9.8) after reacting with 0.2%: (A) formaldehyde, (B) acetaldehyde, (C) *iso*-butyraldehyde at room temperature for 10 min using a scan rate of 90 mV s^{-1} after a preconcentration step; $t_{acc.}$ 120 s, $E_{acc.}$ −1.10 V and stirring speed 2000 rpm. (1) Blank 1: buffer + aldehyde; (2) blank 2: buffer + TOB; (3) buffer + aldehyde + TOB.

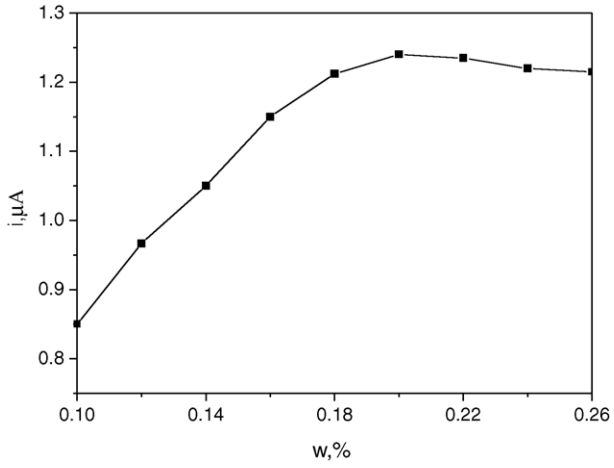


Fig. 2. Effect of the concentration of *iso*-butyraldehyde on the peak current of TOB *iso*-butyraldehyde derivative. Other conditions are as those in Fig. 1.

3.2. Effect of concentration of iso-butyraldehyde

To establish the optimum amount of derivatizing agent for conversion of TOB, different concentrations of *iso*-butyraldehyde in the range of 0.10–0.26% were tested. The results in Fig. 2 show that the largest peak current was obtained as the concentration of *iso*-butyraldehyde was 0.2%, and the peak current decreased slightly as the concentration increased continuously. Moreover, the peak shape turned worse when the concentration of *iso*-butyraldehyde was more than 0.2%. It was due to competitive absorption of *iso*-butyraldehyde on the surface of mercury electrode. Therefore, the *iso*-butyraldehyde concentration of 0.2% was selected in this work.

3.3. Effect of reaction temperature and time

Structurally, TOB has five primary amino groups that can react with *iso*-butyraldehyde. This causes the formation of different adducts under different sets of reaction temperatures and time. The effects of reaction temperature at room temperature and 50 °C and reaction time were studied. The results showed that for derivatization at room temperature, a single well-defined peak was obtained and the formation of the TOB derivative reached equilibrium in 10 min (Fig. 3). However, for derivatization at 50 °C in 3 min, a multi-peak was obtained, and the peak shape turned worse as the time of derivatization prolonged. Considering the different chemical activity of the five primary amino groups in the TOB molecule, at room temperature a schiff bond might be formed

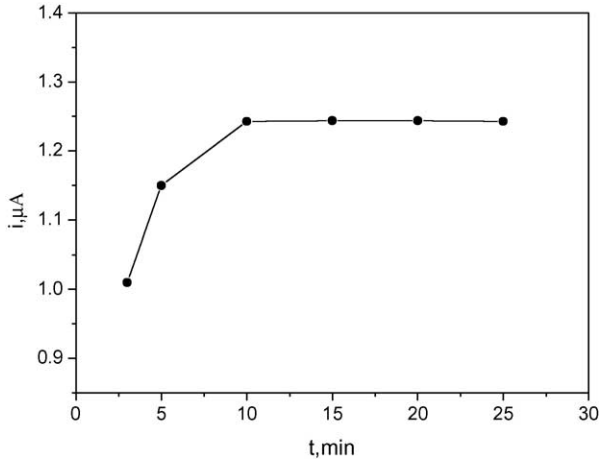


Fig. 3. Effect of reaction time on the peak current of TOB *iso*-butyraldehyde derivative at room temperature. Other conditions are as those in Fig. 1.

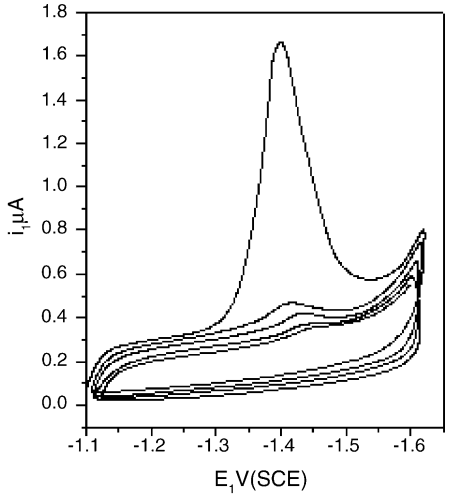


Fig. 4. Cathodic–anodic repetitive cyclic voltammograms of TOB *iso*-butyraldehyde derivative. Other conditions are as those in Fig. 1.

between *iso*-butyraldehyde and the amino group which links to the primary carbon. While at 50 °C, more than one schiff bond might be formed between *iso*-butyraldehyde and other amino groups in the TOB molecule, which resulted in a multi-peak in the AdS-LSV voltammogram. So, the derivatization at room temperature in 10 min was most suitable for the determination of TOB.

3.4. Electrochemical behavior of TOB *iso*-butyraldehyde derivative

As shown in the typical cyclic voltammetric curves of Fig. 4, TOB *iso*-butyraldehyde derivative gave a cathodic peak at about −1.40 V in B-R (pH 9.8) supporting electrolyte, and no peak was observed on the anodic branch. It indicated that the electrode process was totally irreversible. The reduction peak in the second scan was much lower than that in the first one, and the reduction peak current decreased as the scan processed, indicating that the reduction peak was an adsorption peak.

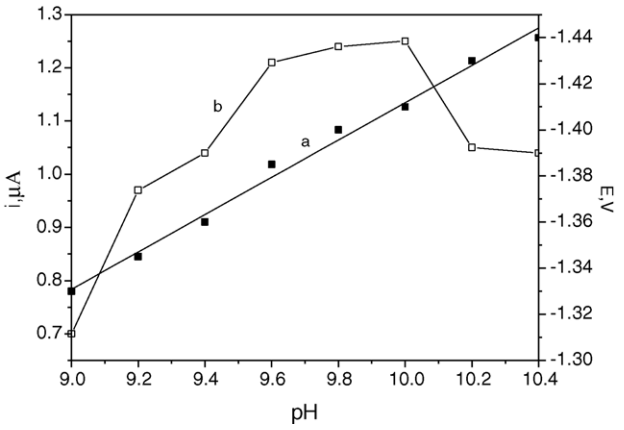
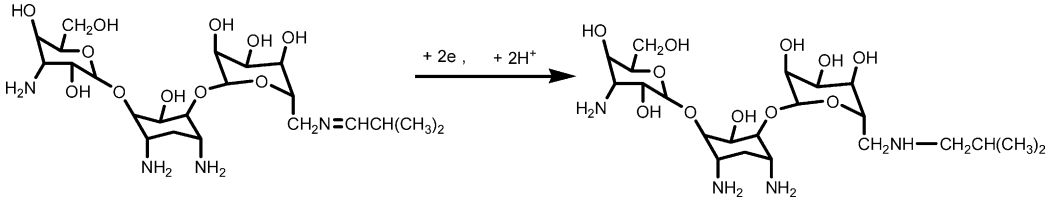


Fig. 5. Effect of pH values on peak potential (curve a) and peak current (curve b) of TOB *iso*-butyraldehyde derivative. Other conditions are as those in Fig. 1.

The number of electrons, *n*, transferred in the electrode process was calculated by the method proposed by Laviron [35]. According to Laviron, the half-peak width in LSV mode, $W_{1/2}$, is given by $W_{1/2} = 62.5/\alpha n$ (mV). Where α is the transfer coefficient. The value of $W_{1/2}$ in Fig. 1(C) was 52 mV suggesting that the number of electrons transferred was 2 ($\alpha = 0.60$). Curve a in Fig. 5 shows the effect of pH value in the range of pH 9.0–10.4 on peak potential (*E*) of the reduction peak of TOB *iso*-butyraldehyde derivative. The peak potential shifted linearly to more negative values with increasing pH with a slope (*S*) of 0.081. According to Zuman [34], this *E*–pH dependent behavior indicated that a transfer of protons was coupled to the electrode process, and the number of protons, *Z*, could be evaluated by the following equation: $S = 0.059Z/\alpha n$. So the number of protons participated in the electrode process was found to be probably 2. Values of *n* and *Z* indicated that the electrode process was coupled with a transfer of two protons and two electrons.

All voltammetric results revealed a good agreement with the electrochemical behavior described for similar imine compounds [36], suggesting that the cathodic peak was due to the irreversible reduction of the schiff bond formed between TOB and *iso*-butyraldehyde. The putative electrode process could be described as follow:



3.5. Effect of supporting electrolyte and pH value

Considering schiff base reaction occurs in the weak basic medium, some basic buffers such as B-R (pH 9.0–10.4), $NH_3{\cdot}H_2O$–NH_4Cl (pH 8.0–11.0), $Na_2B_4O_7$–NaOH (pH 9.3–11.0), Na_2CO_3–$NaHCO_3$ (pH 9.0–11.3) buffers were chosen as supporting electrolytes. TOB *iso*-butyraldehyde derivative yielded a stable and well-defined peak in those buffers. However, best performance was obtained in B-R buffers. Therefore, B-R buffer was selected as the supporting electrolyte in this work.

The effect of pH value in the range of pH 9.0–10.4 on peak current of TOB *iso*-butyraldehyde derivative was examined in B-R buffers. Curve b in Fig. 5 shows that the peak current increased with increasing pH values from 9.0 to 9.6, remained nearly unchanged in the range of 9.6–10.0, and decreased with increasing pH values from 10.0 to 10.4. Therefore, the B-R buffer of pH 9.8 was selected.

3.6. Effect of accumulation potential and time

The dependence of peak current on the accumulation potential was evaluated in the range of −0.80 to −1.30 V. The results in Fig. 6 show that the peak current reached the maximum when the accumulation potential was −1.10 V.

The dependence of peak current on the accumulation time was also studied. The results in Fig. 7 showed that the peak current increased up to an accumulation time of 120 s and then remained unchanged as the accumulation time increased continuously. It indicated that the adsorption of TOB *iso*-butyraldehyde derivative onto the surface of hanging mercury electrode was saturated in 120 s. Considering the sensitivity and time consumed in the analysis process, 120 s of accumulation time was chosen.

The effect of rest time was also studied. The results showed that the rest time affected little on the peak current. So a normal rest time of 30 s was finally chosen.

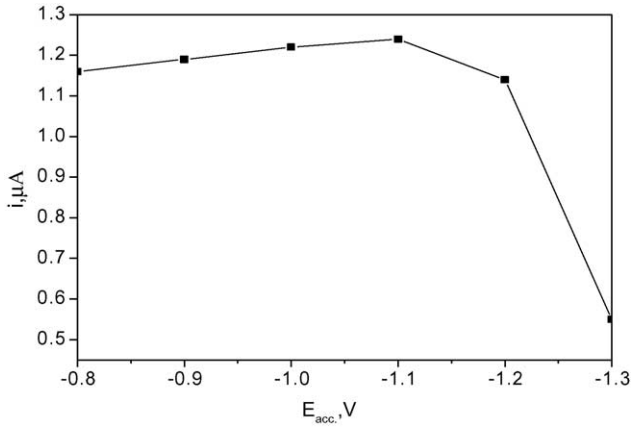


Fig. 6. Effect of accumulation potential ($E_{acc.}$) on peak current of TOB *iso*-butyraldehyde derivative. Other conditions are as those in Fig. 1.

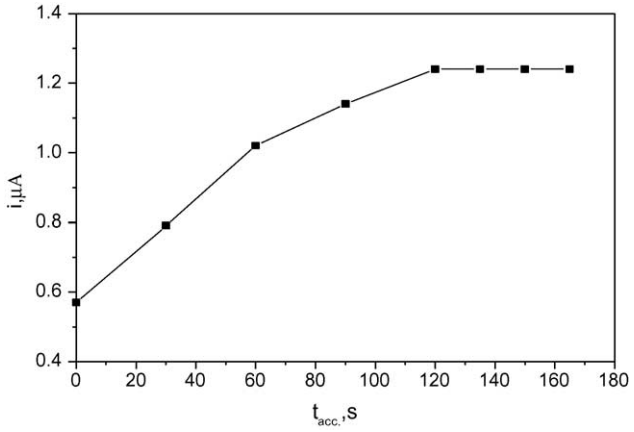


Fig. 7. Effect of accumulation time ($t_{acc.}$) on peak current of TOB *iso*-butyraldehyde derivative. Other conditions are as those in Fig. 1.

3.7. Calibration curve, detection limit and precision

Under the optimal conditions selected in this work, a stable and well-defined peak was obtained at −1.40 V. The peak current was linearly proportional to the TOB concentration in the range of 6.87×10^{-9}–3.44×10^{-7} mol L^{-1}. The linear regression equation was i (μA) = 5.6971×10^6 C (mol L^{-1}) + 0.6703 with a regression coefficient $r = 0.9965$ ($n = 8$). The detection limit of 3.44×10^{-9} mol L^{-1} was calculated based on an S/N = 3. The precision was evaluated by repeating nine independent determination of 1.0×10^{-7} mol L^{-1} TOB and the relative standard deviation was calculated to be 4.4%. The peak current remained unchanged over 6 h.

3.8. Interferences

Possible interferences from various inorganic ions and organic substances that are commonly found in urine and serum were investigated by adding these interfering substances to the B-R buffer (pH 9.8) containing 1.0×10^{-7} mol L^{-1} TOB before derivatizing with *iso*-butyraldehyde. The results showed that a 500-fold of Na^+, K^+, Cl^-, Cu^{2+}, uric acid, glucose, 250-fold of Mg^{2+}, NO_3^-, Ca^{2+}, tyrosine, 100-fold of Al^{3+}, Zn^{2+}, Fe^{3+}, cystine, amylum, lysine, 50-fold of Se^{2+}, Fe^{2+}, Ni^{2+}, Cd^{2+}, serine did not interfere with the determination of TOB.

3.9. Sample analysis

3.9.1. Determination of TOB in injectable formulation

The proposed procedure was successfully applied to the analysis of TOB injections without the need for any pretreatment step prior to the analysis. Two types of injection, 20 and 40 mg mL^{-1}, were tested. The contents were calculated by using the analytical calibration curve, and the results were summarized in Table 1.

To study the accuracy of the proposed method and to check the interference from excipients used in the injectable formu-

Table 1
Analytical results of injectable formulations

Samples	Label value (mg mL^{-1})	Determined value (mg mL^{-1})	Mean value (mg mL^{-1})	R.S.D. (%)
A	20	19.5, 19.7, 19.8, 20.3, 19.8, 20.4, 20.1	19.9	1.7
B	40	39.6, 39.7, 42.2, 40.3, 39.2, 39.8, 40.1	39.8	1.0

lation, three aliquots of 20, 60, 100 μL of 1.0×10^{-5} mol L^{-1} TOB were added to the different preanalyzed TOB injection solutions and the mixtures were stayed at room temperature for 10 min, then reanalyzed by the proposed method. Each recovery was calculated by comparing the results obtained before and after the addition with the analytical calibration curve. The results were summarized in Table 2.

3.9.2. Determination of TOB in spiked biological samples

The proposed method was successfully applied to the determination of TOB in spiked human urine and serum samples using the standard addition method.

Normal concentrations of TOB in urine and serum of treated patients are in the range of 75–100 and 4–8 mg L^{-1}, respectively [2]. So the human urine and serum samples were spiked at different level: 2.0×10^{-4}, 1.2×10^{-4} and 4.0×10^{-5} mol L^{-1} for urine samples and 2.0×10^{-5}, 1.2×10^{-5} and 4.0×10^{-6} mol L^{-1} for serum samples. The volume of the urine sample used was 0.5 μL and the volume of the serum sample was 5 μL. The spiked urine and serum samples were determined by the following procedure: a sample was spiked and analyzed according to the procedure described in Section 2, then the preanalyzed sample solution was added with a 100 μL aliquot of 1.0×10^{-5} mol L^{-1} TOB, after that the mixture was stayed at room temperature for 10 min and reanalyzed. The amount of TOB present in the sample was calculated based on the peak currents obtained before and after addition. The results were summarized in Table 2. The detection limits of 7.45×10^{-6} and 1.04×10^{-6} mol L^{-1} TOB in human urine and serum samples were achieved based on an S/N = 3, respectively.

As shown in Tables 1 and 2, the proposed method had a good accuracy and precision.

Table 2
Mean recoveries of the samples ($n = 7$)

Samples	Added (mol)	Found (mol)	Recovery (%)	R.S.D. (%)
Injection	1.00×10^{-9}	9.84×10^{-10}	98.4	2.8
	6.00×10^{-10}	6.02×10^{-10}	100.3	2.1
	2.00×10^{-10}	2.02×10^{-10}	101.0	2.5
Urine	1.00×10^{-9}	9.94×10^{-10}	99.4	4.2
	6.00×10^{-10}	6.09×10^{-10}	101.5	3.3
	2.00×10^{-10}	2.04×10^{-10}	102.0	3.9
Serum	1.00×10^{-9}	9.46×10^{-10}	94.6	4.3
	6.00×10^{-10}	5.75×10^{-10}	95.8	3.8
	2.00×10^{-10}	1.97×10^{-10}	98.5	4.6

4. Conclusion

A new AdS-LSV method is proposed to determine TOB. In a medium of B-R buffer (pH 9.8), at room temperature for 10 min TOB is converted to its *iso*-butyraldehyde derivative, which can be reduced on the HMDE. The reduction is an irreversible and adsorption-controlled process coupled with a transfer of two protons and two electrons. The present results show that AdS-LSV on HMDE is a useful technique for the determination of TOB in injectable formulations and biological matrices with adequate precision and accuracy. Compared with other techniques, the method is rapid, cheap and time-saving. Moreover, this method is environmentally benign because of avoiding the use of organic solvents, which are volatile and toxic.

Acknowledgements

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