



Determination of trimetazidine in urine by capillary electrophoresis with amperometric detection

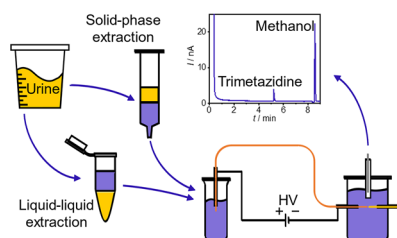
Martin Baroch¹ · Hana Dejmková¹ · Frank-Michael Matysik²

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Abstract

In this contribution, nonaqueous capillary electrophoresis with end-column amperometric detection using a platinum ultra-microelectrode is presented along with several extraction procedures, both liquid–liquid extraction (LLE) and solid-phase extraction (SPE), for extracting trimetazidine from urine. Trimetazidine is an anti-ischemic drug, which changes heart metabolism pathways and is being abused as a doping. Electrochemical detection in a nonaqueous environment provided a stable response with a relative standard deviation of only 3.6% ($n = 10$) in repeatability measurement at concentration of $50 \mu\text{g cm}^{-3}$. LOD and LOQ of the proposed method were determined as $0.054 \mu\text{g cm}^{-3}$ and $0.180 \mu\text{g cm}^{-3}$, respectively. From the point of view of LLE, the most efficient procedure was the double extraction with ethyl acetate as an extraction agent in combination with prior alkalization of the sample by Na_2CO_3 . Nevertheless, the extraction efficiency was only around 68%. The most efficient SPE procedure was based on the combination of HLB cartridge and elution with background electrolyte containing 20% of methanol. Its recovery reached up to 92% and 101% in case of $50 \mu\text{g cm}^{-3}$ and $5.0 \mu\text{g cm}^{-3}$ of trimetazidine in urine, respectively.

Graphical abstract



Keywords Capillary zone electrophoresis · Electrochemistry · Extraction · Trimetazidine

Introduction

Trimetazidine (1-(2,3,4-trimethoxybenzyl)piperazine, Fig. 1), is a drug mainly used in the treatment of myocardial ischemia, yet it does not change heart rate or blood pressure.

✉ Frank-Michael Matysik
frank-michael.matysik@ur.de

¹ Department of Analytical Chemistry, Faculty of Science, UNESCO Laboratory of Environmental Electrochemistry, Charles University, Albertov 6, 128 00 Prague 2, Czech Republic

² Institute of Analytical Chemistry, Chemo- and Biosensors, University of Regensburg, Regensburg, Germany

The mechanism of its action is the change of the energy source for heart activity from fatty acids to glucose, which is less oxygen-demanding [1]. In case trimetazidine is given to a healthy individual, it results in significant improvement of psychomotor performance [2]; it also reduces the occurrence of fatigue and improves heart performance of a person exposed to high altitudes [3]. As a consequence, trimetazidine was added to the list of banned substances by World Anti-Doping Agency [4]. Therefore, finding a suitable method for detection and determination of trimetazidine at the lowest possible concentration is desirable.

In the past two decades, the most frequently used methods for the determination of trimetazidine in body fluids,

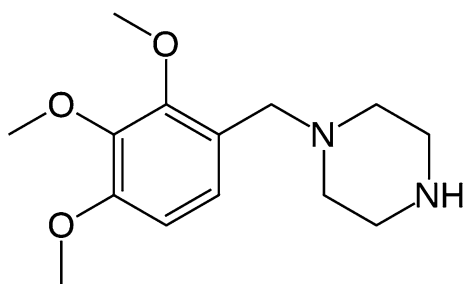


Fig. 1 Chemical structure of trimetazidine

namely urine or plasma, were liquid chromatography with mass spectrometry (LC/MS) [5–8], diode array [9], or UV [10] detection. Utilization of capillary electrophoresis (CE) is, in this particular case, not so common and only a few articles can be found [11, 12]; however, they provide limits of detection in the range of lower tens of $\mu\text{g cm}^{-3}$, which is comparable with LC/MS techniques. At the same time, very low sample consumption (on the order of nanoliters), wide range of separable analytes, user-friendliness, and low financial and material requirements speak in favor of CE [13]. In addition, high selectivity of electrophoresis can be achieved in combination with electrochemical detection, particularly when a nonaqueous background electrolyte is used—in this medium, changes in the physicochemical properties of substances occur, including changes in dissociation constants, hydrodynamic radii of analytes and, as a result, mobility. With the proper choice of the background electrolyte, it is, therefore, possible to tune the separation to the needs of a specific analyte and the matrix [14–16]. Electrochemical detection contributes to the selectivity by the proper choice of the detection potential and working electrode material [17, 18].

Urine, as well as other biological samples, is associated with a very complex matrix. Therefore, a pretreatment of the sample, which can be often a time demanding step, is needed. Mostly used techniques for pretreatment of urine samples containing trimetazidine are liquid–liquid extraction (LLE) [19] and solid-phase extraction (SPE) [7, 20, 21]. Analogous procedures can be also found for plasma samples, where the purification step is even more complicated due to the presence of various compounds, particularly proteins, which needs to be salted out prior extraction [5, 6, 10, 22]. In this work, C18 cartridges based on reversed-phase mode, weak cation exchanger (WCX) cartridges, and HLB type cartridges were tested for extraction. The last mentioned type contains both hydrophilic and lipophilic moieties, and it is thus advantageous for the extraction of charged molecules from aqueous environments [23, 24].

The primary aim of this contribution was to find a suitable method for extraction of trimetazidine from a urine sample, using either LLE or SPE procedures, and subsequent

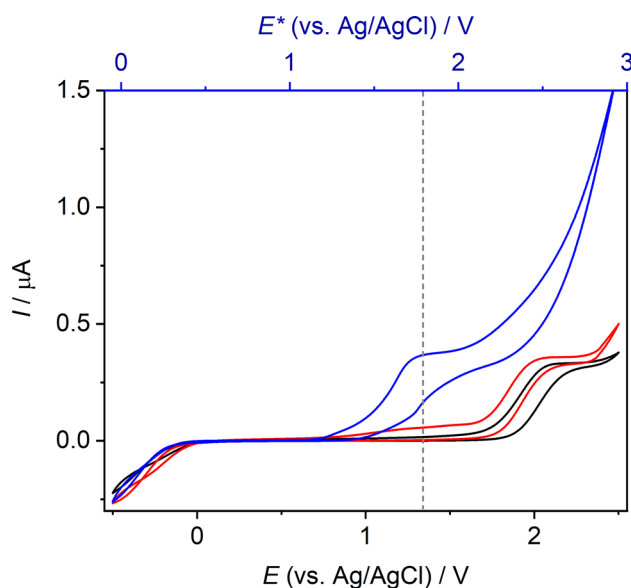


Fig. 2 Cyclic voltammograms ($\nu=250 \text{ mV s}^{-1}$) of background electrolyte composed of 1 mol dm^{-3} acetic acid and 10 mmol dm^{-3} ammonium acetate in acetonitrile (black), electrolyte with addition of 20% of methanol (red) and trimetazidine ($c=500 \mu\text{g cm}^{-3}$) in electrolyte with 20% of methanol (blue) using a platinum disk ultramicroelectrode ($d_{\text{pt}}=50 \mu\text{m}$). Upper blue x-axis shows the equivalent potential when a high voltage of 25 kV is applied to the cell. Dashed line at 1.3 V (equivalent to a potential of 1.75 V with applied high voltage) shows detection potential used in electrophoretic experiments

analysis of the extract by nonaqueous capillary electrophoresis combined with end-column amperometric detection (NACE-AD).

Results and discussion

Analytical performance

The first part of the experiments was aimed to the selection of a suitable potential for the amperometric detection of trimetazidine. For this purpose, several cyclic voltammograms were recorded: background electrolyte used in electrophoretic experiments (1 mol dm^{-3} acetic acid and 10 mmol dm^{-3} ammonium acetate dissolved in acetonitrile), background electrolyte with addition of 20% of methanol, used for the sample dissolution (addition of methanol is necessary to increase the solubility of the trimetazidine [12, 25]) and trimetazidine solution ($c=500 \mu\text{g cm}^{-3}$) in the background electrolyte containing methanol. As can be seen in Fig. 2, oxidation of trimetazidine begins at approximately 0.8 V and reaches its maximum at 1.3 V; this value had been chosen as a detection potential in all electrophoretic experiments. Comparing the voltammograms of the background

electrolytes, it is worth noting that methanol starts to oxidize at the similar potential as the analyte.

The last part of the detection potential selection was to evaluate so-called potential shift, which is typical for amperometric detection combined with capillary electrophoresis [26, 27]. After the application of the separation voltage, voltammograms showed a typical potential shift of 0.45 V, which depends on the capillary dimensions and the capillary-to-electrode positioning [26, 27]. Therefore, for the present configuration and parameter setting, a working electrode potential of 1.75 V was applied via the potentiostat to ensure an actual (effective) detection potential of 1.3 V (as specified in Fig. 2) during the electrophoretic experiments. The rest of the experimental electrophoretic separation conditions, used in all following experiments, were based on our previous study [12] and chosen as follows: separation voltage 25 kV, injection time 15 s, inlet side of the capillary 10 cm higher than the outlet fixed in the electrochemical detector cell, and the capillary-to-working electrode distance was set to 50 μm .

The concentration dependence (Fig. 3) was studied in the range from 50 $\mu\text{g cm}^{-3}$ down to 0.050 $\mu\text{g cm}^{-3}$ with RSD of the individual calibration points under 5% ($n=3$). The signal dependence on concentration can be described by the following equation: A_p (nC) = 0.207 c ($\mu\text{g cm}^{-3}$) + 0.015, where A_p means peak area and c concentration of the sample. The plot is linear in the concentration range from 50 $\mu\text{g cm}^{-3}$ down to the quantification limit (LOQ), which was determined as 0.180 $\mu\text{g cm}^{-3}$; the limit of detection (LOD) was found to be 0.054 $\mu\text{g cm}^{-3}$. These limits were estimated as a threefold, in case of LOD, or tenfold, for LOQ, of the deviation of the intercept of the calibration plot divided by its slope.

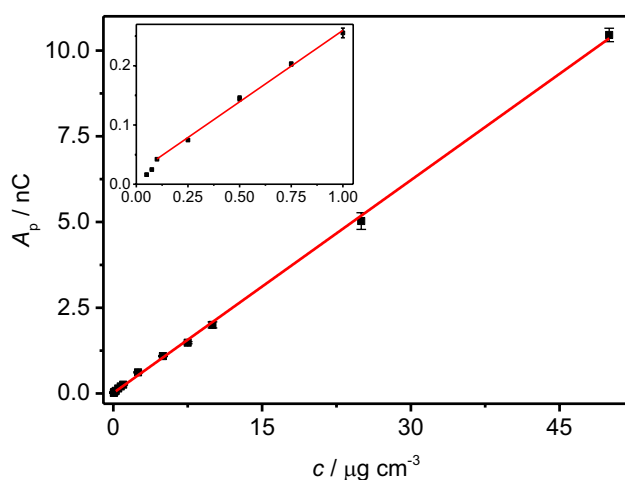


Fig. 3 Concentration dependence of trimetazidine dissolved in background electrolyte with addition of 20% of methanol. Platinum working ultramicroelectrode, effective E_{det} : +1.3 V, l_{sep} : 65 cm, U_{sep} : 25 kV, t_{inj} : 15 s, capillary-to-electrode distance: 50 μm

Repeatability of the measurement was tested by ten consecutive measurements at concentration of 50 $\mu\text{g cm}^{-3}$. Relative standard deviation calculated from peak areas was 3.6%.

Extraction procedures

Extraction efficiencies of each protocol were determined for a concentration of 50 $\mu\text{g cm}^{-3}$ of trimetazidine in the final extract injected into the CE system. The exact recovery value was obtained by comparing the signal from the extract with the standard solution of trimetazidine measured on the same day.

The first procedures examined to extract trimetazidine from urine were LLEs using acetonitrile or ethyl acetate as extraction solvents. For a single extraction, 0.4 cm^3 of urine sample and 0.8 cm^3 of the particular extraction solvent were used in both protocols. To facilitate the separation of the organic and aqueous phases, the sample was frozen after centrifugation. For details, please see “[Experimental](#)”. Extraction with acetonitrile (LL_ACN in Table 1 and Fig. 4A), based on a previously published report [22], gave only $6 \pm 1\%$ recovery, although in literature the reported efficiency was higher than 60%. In addition, a small signal, at ca. 270 s, of another substance is visible in the electropherogram, as can be seen in Fig. 4A.

Higher extraction efficiencies, ranging between 36 and 68% (see Table 1), were obtained when ethyl acetate was used. The original procedure with a sample pretreatment using 0.24 cm^3 of saturated solution of Na_2CO_3 , based on Ref. [10], provided $59 \pm 10\%$ recovery. In attempt to increase the extraction efficiency, experiments using saturated $(\text{NH}_4)_2\text{CO}_3$ solution (LL_EA_ $(\text{NH}_4)_2\text{CO}_3$) as a less alkaline reagent and 1 mol dm^{-3} NaOH solution (LL_EA_NaOH) as a more alkaline reagent were carried out. These procedures provided extraction efficiencies only $36 \pm 3\%$ and $41 \pm 10\%$, respectively. Therefore, utilization of Na_2CO_3 is a crucial step in these extractions. Improvements in extraction

Table 1 Parameters of trimetazidine peaks and extraction efficiencies of the various extraction protocols

Extraction protocol	h_p /nA	A_p /nC	Recovery ¹ /%
LL_EA_ Na_2CO_3	1.84 ± 0.60	4.55 ± 0.75	59 ± 10
LL_EA_ Na_2CO_3 _Double	2.12 ± 0.24	5.24 ± 0.60	68 ± 8
LL_EA_NaOH	1.43 ± 0.44	3.16 ± 0.75	41 ± 10
LL_EA_ $(\text{NH}_4)_2\text{CO}_3$	1.15 ± 0.14	2.82 ± 0.27	36 ± 3
LL_ACN	0.72 ± 0.09	0.50 ± 0.11	6 ± 1
SP_HLB	2.69 ± 0.45	11.2 ± 0.4	76 ± 3
SP_HLB_BGE	3.14 ± 0.11	9.39 ± 0.39	92 ± 4
SP_HLB_ Na_2CO_3	2.58 ± 0.45	1.26 ± 0.19	9 ± 1

¹Efficiencies calculated from peak areas (A_p) for each procedure separately, by comparison with the standard solution measured on the same day

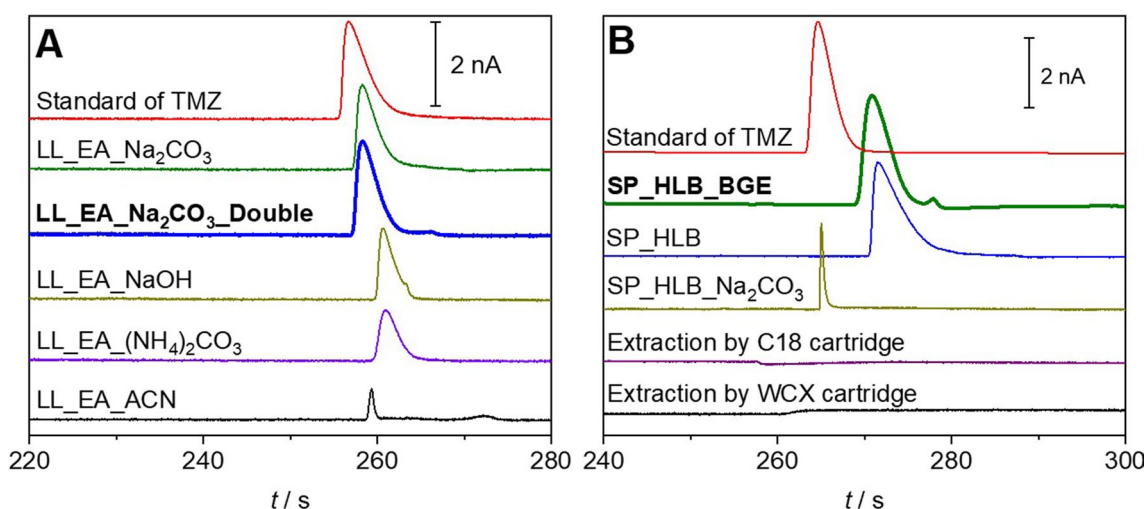


Fig. 4 Cutout of electropherogram of trimetazidine extracts prepared according to various protocols of liquid–liquid extractions **A** and by solid-phase extractions **B**; for the details of labels on curves, see text. Other conditions were as in Fig. 3

have been achieved when we used doubled extraction (LL_EA_Na₂CO₃_Double) in which the spiked urine sample was mixed with Na₂CO₃ and successively extracted twice with ethyl acetate, i.e., a total volume of 1.6 cm³ of the extraction solvent was used. In that case, the recovery reached a value of $68 \pm 8\%$. The shape of the trimetazidine signals obtained by the various LLE protocols can be seen in Fig. 4A.

For the SPE protocols, three types of cartridges were tested. Namely the HLB, WCX, and C18 cartridges, based on mixed hydrophilic–lipophilic balance, cation exchange and reversed-phase mode, respectively, were used. Only the first one provided extracts containing trimetazidine. Measurements performed after extraction with C18 and WCX cartridges did not provide any measurable signal and even the detection of trimetazidine traces is questionable, as can be seen in Fig. 4B. The basic extraction procedure using the HLB cartridge (listed as SP_HLB in Table 1) consisted of the introduction of the spiked urine sample to the cartridge, washing with ultra-pure water and elution with 1.5 cm³ of methanol. The last step was the reconstitution of trimetazidine with background electrolyte containing 20% of methanol, which could be injected into the NACE-AD system. In this procedure, the extraction efficiency reached $76 \pm 3\%$. Alkalinization of the spiked urine sample with a saturated solution of Na₂CO₃ (SP_HLB_Na₂CO₃), similarly to LLE, resulted in a decrease of the efficiency to only $9 \pm 1\%$. Along with the lower extraction, the peak of the trimetazidine was narrower, in comparison with results from other extraction protocols. This was probably caused by stacking effect of the analyte. A similar effect was also noticed for the LL_EA_ACN extraction (Fig. 4A). However, due to the low overall extraction efficiencies, we did not investigate this phenomenon further. Higher extraction efficiency, $92 \pm 4\%$,

was achieved when the elution was done directly by 0.2 cm³ of a mixture of the acetonitrile-based background electrolyte with addition of 20% of methanol (SP_HLB_BGE). The higher efficiency was probably achieved due to the higher elution strength of acetonitrile, contained in the background electrolyte. This procedure also eliminates further treatment of the extract and allows for the direct injection of the extract into the NACE-AD system. The shape of the trimetazidine signals obtained by the SPE protocols can be seen in Fig. 4B.

The most efficient extraction procedure, i.e., SP_HLB_BGE, was repeated with a concentration of trimetazidine of 5.0 μg cm⁻³ to investigate the extraction from samples with lower concentrations. These measurements resulted in an even better extraction efficiency of $101 \pm 7\%$, although the standard deviation increased slightly. The range of the evaluated concentrations covers the concentrations of trimetazidine commonly occurring in patient urine, which are in the units to lower tens of μg cm⁻³ [29].

Conclusion

In this work, suitable extraction techniques for extracting trimetazidine from synthetic urine, combined with nonaqueous capillary electrophoresis with end-column amperometric detection (NACE-AD), were studied. Of the several procedures tested, including both LLE and SPE techniques, SPE extraction using HLB cartridges in combination with elution of trimetazidine by an acetonitrile-based background electrolyte with 20% of methanol proved to be the most advantageous. The extraction efficiency in this particular case was as high as $101 \pm 7\%$. Recoveries of other tested procedures ranged between 6 and 76%. The high extraction

efficiency of the mentioned method, combined with very small sample volumes used in capillary electrophoresis, has the potential for a significant sample preconcentration in the order of hundred or thousand times, which overcomes the limitation of the relatively high limit of quantification (LOQ) of trimetazidine, determined as $0.180 \mu\text{g cm}^{-3}$. This value is in good agreement with our previously published work concerning a dual-detection concept [12]. On the other hand, both LOQ and LOD of this method are comparable not only with optical detections [9–11], but also with most MS detections, in which LOQ for trimetazidine were found in a range from tenths to hundreds of ng cm^{-3} [5–7]. Moreover, electrochemical detection can be beneficial, compared to the above-mentioned procedures, due to its lower financial and instrumental requirements and certain selectivity.

Experimental

Stock solutions and background electrolyte

All chemicals used were of analytical grade. For electrophoretic measurements, the nonaqueous background electrolyte consisted of 1 mol dm^{-3} acetic acid (Carl Roth, Germany) and 10 mmol dm^{-3} ammonium acetate dissolved in acetonitrile (both Merck, Germany). A stock solution of trimetazidine (Sigma-Aldrich, USA) with a concentration 0.5 mg cm^{-3} was prepared by dissolving the appropriate amount in background electrolyte with addition of 20% of methanol. This solution was used for calibration measurements and for determination of extraction efficiencies. Based on our previous experience [12] and on literature [25], addition of methanol is necessary to increase the solubility of trimetazidine. A simulated urine sample was prepared by addition of trimetazidine spike stock solution (1.0 mg cm^{-3}), prepared in ultra-pure water, to a synthetic urine sample (CleanU, Germany) to achieve a concentration of $25 \mu\text{g cm}^{-3}$ in the extracting sample and, therefore, $50 \mu\text{g cm}^{-3}$ in the final extract, unless stated otherwise.

Electrophoretic system

The electrophoretic apparatus consisted of a laboratory-made CE system, enclosed in a safety housing made of plexiglass, connected to a high voltage source. The laboratory-made amperometric end-column detection cell is described in detail elsewhere [28]. As a working electrode, a platinum wire with a diameter of $50 \mu\text{m}$, sealed in glass tube, was used. The capillary-to-electrode distance was set to $50 \mu\text{m}$. Proper placement of the working electrode against the separation capillary was controlled by an UltraZoom Pro digital microscope (dnt Innovation GmbH, Dietzenbach, Germany). The reference electrode comprised a chlorinated

silver wire submerged in background electrolyte enclosed in a glass tube with a frit. The counter electrode was made of a stainless-steel tube which served also as a grounding electrode for CE system and as a guiding rail for the separation capillary. All the electrodes were placed in a Faraday cage and connected to a $\mu\text{Autolab III}$ potentiostat (Metrohm, Switzerland). For signal/noise ratio improvement the Femto DDPCA-300 current amplifier (FEMTO Messtechnik Berlin, Germany) was connected to the working electrode.

In this work, fused silica capillary (65 cm length, $50 \mu\text{m}$ I.D., $360 \mu\text{m}$ O.D., Polymicro Technologies, USA) was used. Prior to the very first electrophoretic measurement approximately 0.5 cm of the polyimide coating on both sides was removed by a razor blade and the tips were polished to be smooth. The capillary was conditioned by flushing with 0.1 mol dm^{-3} sodium hydroxide solution for 10 min , then ultra-pure water for 10 min and finally with background electrolyte for 30 min . This procedure was also repeated once a week to ensure a higher stability of the measurement. An electrochemical pretreatment of the platinum working microelectrode was necessary before each run to increase the repeatability of the measurement. This was done by applying $+2.5 \text{ V}$ for 10 s and consequently -0.5 V for 10 s to the working electrode in the nonaqueous background electrolyte. Then, the measuring potential was applied. The detection potential of the working electrode was corrected for a potential shift due to the influence of the electrophoretic high voltage. The correction value was determined at the beginning of each day by comparison of cyclic voltammograms obtained with and without applied separation voltage [26]; an offset potential between $+0.4$ and $+0.5 \text{ V}$ had to be applied to ensure an actual working potential corresponding to the current–potential characteristics without high voltage. At the same time, this value served as a verification of the correct functioning of the electrochemical cell and proper alignment of the electrode and capillary. Other electrophoretic conditions were chosen as follows: separation voltage 25 kV , injection time 15 s , an inlet side of the capillary 10 cm higher than the outlet in the electrochemical cell.

Extraction procedures

The main parameters of the extractions were based on previously published reports ([10] and [22] in case of liquid–liquid (LLE) and on Ref. [20] in case of solid-phase extraction (SPE)), respectively. These procedures were then adapted to our needs as follows. For LLE with ethyl acetate, 0.4 cm^3 of spiked urine sample was mixed with 0.24 cm^3 of 1 mol dm^{-3} NaOH or saturated aqueous solutions of Na_2CO_3 or $(\text{NH}_4)_2\text{CO}_3$ (all Merck, Germany) in an Eppendorf tube. This mixture was then stirred on Vortex for 5 min . Consequently, 0.80 cm^3 of ethyl acetate (Acros Organics, Belgium) was added to the mixture and again mixed for 5 min .

After that, the sample was placed in a centrifuge (VWR 1207, VWR, USA) for 10 min at 5 000 g. Immediately after removal from the centrifuge, the sample was placed in a freezer to promote separation of aqueous and organic phase. After the aqueous phase froze, the organic phase was taken out, evaporated and the remaining residue was reconstituted with 0.2 cm³ of background electrolyte with 20% of methanol. In the case of repeated extractions, the aqueous phase was again mixed with the appropriate amount of ethyl acetate and the whole procedure was repeated. The second LLE protocol consisted of mixing 0.4 cm³ of spiked urine with 0.8 cm³ of acetonitrile and 0.2 cm³ of 5 mol dm⁻³ ammonium acetate solution on vortex for two minutes. Then, the mixture was centrifuged for 10 min at 5 000 g. Finally, the organic layer was taken out, evaporated, and redissolved with background electrolyte with 20% of methanol.

In the case of SPE, the sample with or without the addition of saturated Na₂CO₃ solution was allowed to flow slowly, approximately 2 cm³ min⁻¹, through the Oasis HLB 1 cc cartridge (Waters, USA). After the application of the sample, the cartridge was washed with 1.5 cm³ of ultra-pure water. Then, the trimetazidine was eluted either by 1.5 cm³ of methanol, with consequent evaporation and reconstitution of the residue with 0.2 cm³ of background electrolyte with 20% of methanol, or the sample was eluted from the cartridge directly by 0.2 cm³ of background electrolyte with 20% of methanol without any following treatment. Similar SPE protocols were also tried with C18 (Phenomenex, USA) and weak cation exchanger (WCX) cartridges (Waters, USA). Prior to the extraction, the cartridges were conditioned by 3 cm³ of methanol and 3 cm³ of ultra-pure water.

Calculation of limit of detection and quantification

The limit of detection (LOD) was estimated as three times the standard deviation of the intercept of the calibration plot divided by its slope. The limit of quantification (LOQ) was determined in a similar manner, but instead of a threefold the standard deviation, a tenfold of it was used.

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