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Voltammetric analysis of disulfiram in pharmaceuticals with a cyclic renewable silver amalgam film electrode

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Abstract: Electrochemical properties of disulfiram, representative of highly significant bioactive compounds, were studied with a cyclic renewable silver amalgam film electrode (Hg(Ag)FE) using square wave cathodic stripping voltammetry (SWCSV). The influence of various factors such as pH, buffer concentration, buffer composition, and SWCSV parameters on current response was investigated. The optimum results in terms of signal shape and intensity were recorded in Britton–Robinson buffer (pH 7.5) at –0.5 V versus Ag/AgCl/3 mol L^{-1} KCl. An elaborated electroanalytical procedure was used to determine disulfiram at the Hg(Ag)FE in the concentration range from 0.05 to 5.00 μM. Precision, repeatability, and accuracy of the method as well as the influence of possible interferences were ascertained. The detection and quantification limits were 11 nM and 37 nM, respectively. The applicability of the developed method was tested in the determination of disulfiram in the commercial formulation Anticol. Thin-layer chromatography with image processing software was used to validate the accuracy of the method.

Key words: Disulfiram, silver amalgam electrode, square wave voltammetry, drug analysis, Anticol

1. Introduction

The analysis of pharmaceuticals is an important field of analytical chemistry undergoing rapid development and playing meaningful role in cases of drug intoxication, drug therapy, or antidrug control. [1–5] The thiocarbamate drug disulfiram (DSF) (Figure 1) has been used for decades in aversion therapy for alcoholism. DSF disrupts the metabolism of alcohol by inhibiting the activity of the enzyme aldehyde dehydrogenase, resulting in blocking of the oxidation of acetaldehyde to less harmful acetic acid. This leads to high blood levels of acetaldehyde, which causes symptoms of intoxication: hypotension, flushing, systemic vasodilation, nausea, and respiratory difficulties.[6,7] Recent studies showed that disulfiram may also play an important role in the chemotherapy of human cancers: acting as a protective agent against cyclophosphamide-induced urotoxicity,[8] it decreases the toxicity and increases the therapeutic index of *cis*-platin[9] and prevents drug-resistant fungal infections.[10] Several electrochemical[11–17] and other instrumental analytical methods[18–31] were developed for determination of disulfiram in commercial formulations and biological samples such as blood serum or urine. As it is well known in the field of voltammetric determinations of thiocarbamates, the best results were obtained on mercury electrodes. However, because of concerns about mercury toxicity, there is a tendency to limit the use of mercury

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electrodes in analytical practice. The increased risk associated with the use, manipulation, and disposal of metallic mercury has led to a search for appropriate alternative. Such an alternative sensor would utilize mercury either in the safe form of an amalgam or in very small amounts, making the use of such electrodes less hazardous. A viable example is the cyclic renewable silver amalgam film electrode (Hg(Ag)FE).[32–34] The construction of the Hg(Ag)FE enables reproducible formation of silver amalgam film of the desired surface area. The electrode can be used for several months in a stable manner[35] and preserves the properties of the mercury electrode with very small amounts of mercury being consumed (about 1 μL per 1000 measurement cycles).[35] The renewable silver amalgam film electrode Hg(Ag)FE has been successfully applied for the determination of several elements[36–41] and organic compounds.[42–44] To the best of our knowledge, there is no voltammetric method dedicated to the determination of DSF based on the use of a silver amalgam electrode. Moreover, a literature survey revealed that there is no other analytical method of DSF determination to date showing lower LOD and wider linear range than the method developed herein. In the present communication, the quantitative determination of DSF at a Hg(Ag)FE was also studied under SWCSV conditions for the first time. For comparison of results, thin-layer chromatography with image analysis [45,46] was chosen as a reference method.

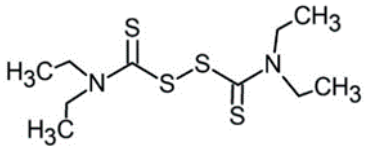

Figure 1. Chemical structure of disulfiram.

2. Results and discussion

2.1. Preliminary studies

The selection of supporting electrolyte is an important stage in electrochemical studies. The effect of pH on the voltammetric response for 5×10^{-7} mol L^{-1} disulfiram solution was investigated in the pH range 2.0–8.7 using 0.04 mol L^{-1} Britton–Robinson (BR) buffer solutions (Figure 2A). The highest signals for DSF were obtained in pH 6.0–8.0. Thus, the voltammetric response of DSF in this pH range was investigated using two other supporting electrolytes: phosphate and citrate-phosphate buffer. The results showed that the voltammograms provided similar current responses in all types of buffers; however, the best-defined peak was observed in BR buffer at pH 7.5. Hence, BR buffer pH 7.5 was chosen as the most suitable supporting electrolyte for analytical application in all further voltammetric experiments. As a popular electrochemical method with good discrimination against capacitive current, SWCSV has been applied to numerous electrochemically active compounds in trace analysis. The SWCSV parameters' optimization was performed based on change in SW frequency, height of SW pulses (amplitude), step potential of the staircase waveform, accumulation potential, and accumulation time, with regard to the greatest selectivity and the highest sensitivity for DSF analysis. Each parameter was varied while the others were kept constant for measurement of 5×10^{-7} mol L^{-1} DSF chosen as the test solution. First the height of SW pulses was set between 5 and 150 mV. As expected from SWV theory,[47] a linear response of the peak current was attained up to $E_{SW} = 60$ mV; hence, this value was selected for further studies. The variations in the SW frequency, considering values from 8 to 300 Hz, showed that a well-shaped signal of DSF can be obtained only at small values of frequency. For analytical purposes, a low frequency value of 25 Hz was used subsequently. Then the step potential of the staircase waveform

was adjusted between 1 and 25 mV. The DSF signal increased linearly up to 20 mV, but ΔE higher than 7 mV caused deterioration of the signal; therefore, 7 mV was chosen for further studies. The influence of the accumulation potential was ascertained in the potential range from 0.2 V to –0.4 V in steps of 0.05 V using t_{acc} = 30 s at each potential. The highest DSF signals were recorded with 0 V. Accumulation time was investigated in the range 5–150 s and the maximum reduction signal of DSF was observed with 30 s. Overall, amplitude of 60 mV, frequency of 25 Hz, step potential of 7 mV, accumulation potential 0 V, and accumulation time 30 s represent the optimum parameters for SWCSV providing satisfactory current response and well-defined shape of reduction peak. Subsequently, these parameters were used for construction of the calibration curve and analysis of samples spiked with known amounts of DSF. In the next step, cyclic voltammetry was used to investigate the electrochemical behavior of DSF. The cyclic voltammogram of DSF, recorded in supporting electrolyte, is presented in Figure 2B. As can be seen, DSF exhibits a single irreversible reduction peak around potential –0.5 V. Influence of scan rate (ν) on DSF peak height and potential was studied in range 10–400 mV s^{-1}. Linear dependence of peak potential vs. scan rate (signal shifts to more negative values when scan rate increases) clearly indicates that the observed reduction peak is connected with an irreversible electrode reaction.[48] Moreover, slope of the $\log I_p = f(\log \nu)$ dependence ($R^2 = 0.996$) is equal to 0.76, and so it can be concluded that the electrode reaction is influenced by both diffusion and adsorption processes.[49]

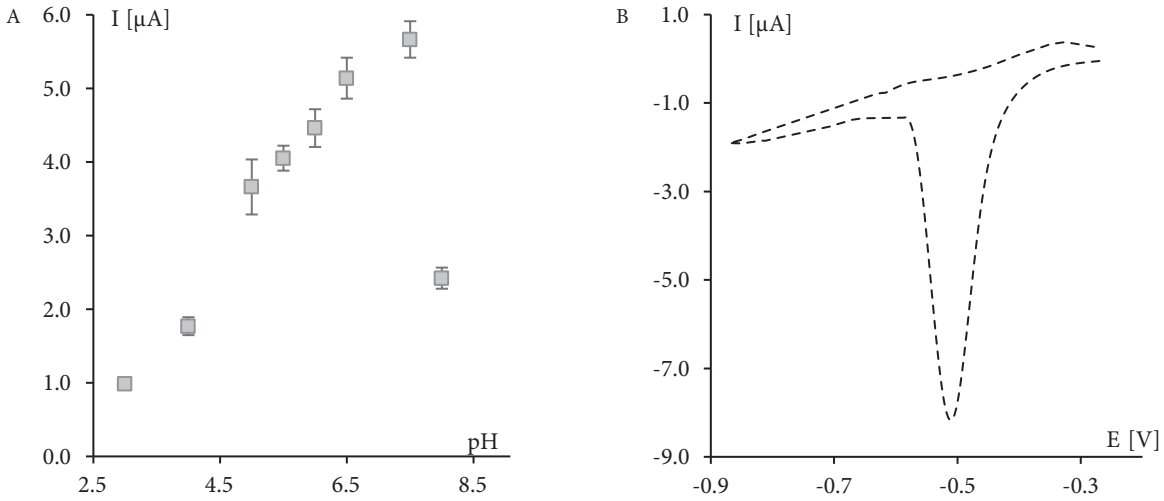

Figure 2. (A) SWCSV dependence of BR buffer pH on DSF peak current, $C_{DSF} = 5.0 \times 10^{-7}$ mol L^{-1}; (B) Cyclic voltammogram recorded in BR buffer pH = 7.5, $C_{DSF} = 5.0 \times 10^{-4}$ mol L^{-1}, scan rate 50 mV s^{-1}.

2.2. Analytical application

As mentioned before, in order to develop an analytical method for determination of disulfiram, square wave cathodic stripping voltammetry at a Hg(Ag)FE was selected as the technique to guarantee effective and rapid determination with low background current and detection limit. Quantitative measurements were performed in BR buffer pH 7.5 and determined the optimum conditions for analytical application. The obtained peak current increased linearly with increasing concentration of DSF in the concentration range from 5×10^{-8} to 5×10^{-6} mol L^{-1} (Figure 3A). A calibration curve for the SWCSV technique was constructed by plotting the peak currents against the concentration of disulfiram (Figure 3B). The characteristics of the calibration plot are provided in Table 1. The limits of detection (LOD) and quantification (LOQ) were calculated from the

calibration curve as k × SD/b (k = 3 for LOD, k = 10 for LOQ, SD - standard deviation of the intercept, b - slope of the calibration curve).[50] Reproducibility of the peak current and potential was calculated on the basis of five measurements on different days.[51] Repeatability of the procedure was estimated with 3 measurements at the same DSF concentration. In order to check the accuracy of the method, the precision and recovery of the method were also calculated for different concentrations in the linear range (Table 2).

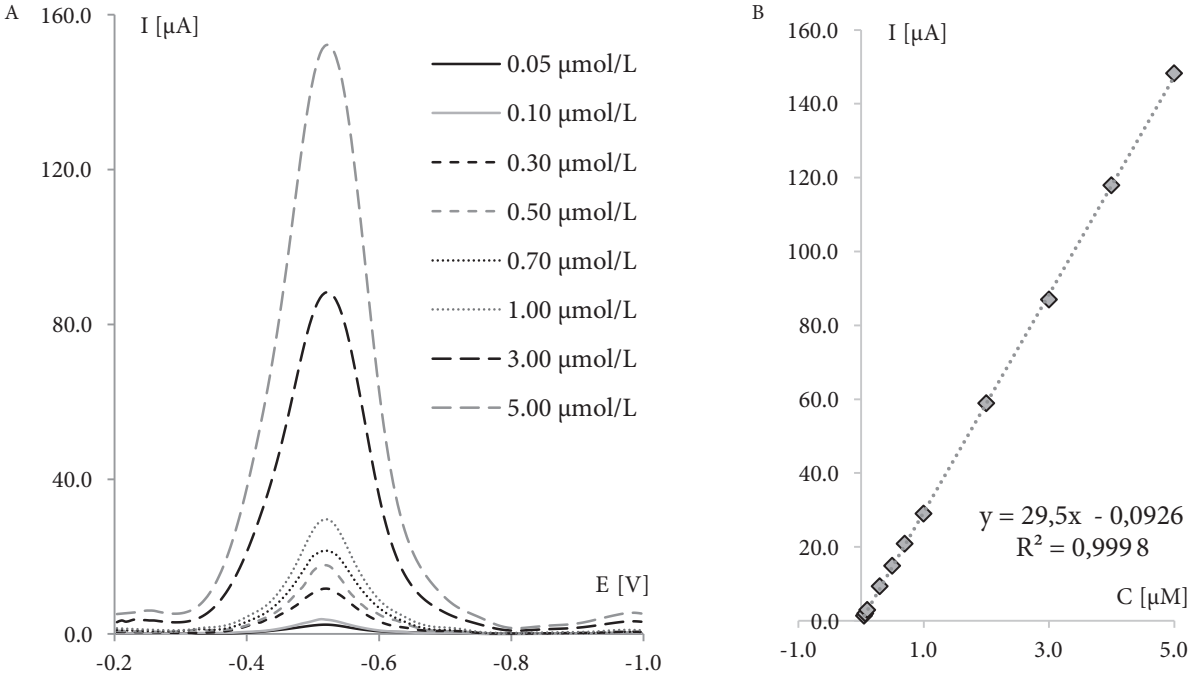

Figure 3. (A) SWCS voltammogram of disulfiram in BR buffer pH 7.5, concentration of analyte indicated in each line. The other experimental conditions were amplitude E_{sw} = 60 mV, step potential ΔE = 7 mV, frequency f = 25 Hz. (B) Calibration curve.

Table 1. Quantitative determination of DSF in BR buffer (pH 7.5) by SWCSV. Basic statistic data of the linear regression.

Linear concentration range [mol L^{-1}]	5.0×10^{-8}–5.0×10^{-6}
Slope of calibration graph [μA L μmol^{-1}]	29.5
Intercept [μA]	0.926
Correlation coefficient	0.9998
Number of measurements	3
LOD [mol L^{-1}]	1.1×10^{-8}
LOQ [mol L^{-1}]	3.7×10^{-8}
Reproducibility of peak current [RSD%]	1.5
Reproducibility of peak potential [RSD%]	0.8

2.3. Analysis of commercial formulation

The standard addition method was used to determine the content of disulfiram in tablets. One tablet of Anticol contains 500 mg of DSF. In each experiment, three equal additions of standard were realized, as described in the Materials and methods section. Other ingredients of Anticol tablets did not interfere in the determination and

did not produce additional peaks in the examined potential window. The recovery results for DSF in Anticol tablets are given in Table 3.

Table 2. Recovery and precision of the peak currents at various DSF concentrations.

Concentration given [μmol L^{-1}]	Concentration found [μmol L^{-1}]	Precision CV [%]	Recovery [%]
0.0500	0.0495	3.71	99.0
0.0700	0.0697	2.64	99.6
0.1000	0.1012	1.58	101.2
0.3000	0.3022	2.31	100.7
0.5000	0.5072	5.47	101.4
0.7000	0.7106	0.81	101.5
1.000	0.9840	1.79	98.4
3.000	2.951	3.34	98.4
5.000	5.029	0.78	100.6

Table 3. Results of the DSF determination in Anticol by SWCSV technique and comparison with reference method.

Technique	Declared [mg]	Found [mg]	Precision CV [%]	Recovery [%]
SWCSV	500.0	498.76 $\pm$ 1.24[a]	0.25	99.75
TLC	500.0	504.10 $\pm$ 0.90	0.45	100.82

[a] $t(S/n^{1/2})$, $p = 95\%$, $n = 3$.

2.4. Interferences

The selectivity of the proposed method was evaluated by the addition of substances commonly found in pharmaceuticals and/or biological fluids (glucose, fructose, sucrose, L-lysin e, L-proline, glycine, L-threonine, tryptophan, valine, phenylalanine, Ca^{2+}, Mg^{2+}, Fe^{2+}, Al^{3+}, SO_4^{2-}, F^-) and possible drug interferents (acyclovir, ambazone, captopril, ibuprofen, ascorbic acid, mercaptopurine, mesna, metformin, moroxydine, paracetamol, penicillamine, proguanil, propylthiouracil, tioguanine, trimetazidine). Interferents were added to 5×10^{-7} mol L^{-1} disulfiram solution at the concentration ratios 1:0.2, 1:1, 1:2, 1:10, 1:20, 1:100, and 1:200. The current responses were compared with that obtained for disulfiram standard solution. It was stated that captopril and tioguanine interfere in the whole range of studied concentrations, while ambazone and mercaptopurine interfere above ratio 1:2. Ascorbic acid and trimetazidine interfere above ratio 1:100 and 1:20, respectively. Other studied substances did not interfere in the quantitative determination of DSF.

2.4.1. Conclusion

The present study showed that SWCSV along with a Hg(Ag)FE electrode can be successfully used to determinate the disulfiram content in its commercial pharmaceutical formulations. Optimization of the experimental parameters yielded a detection limit of 1.1×10^{-8} mol L^{-1} and linear range of 5.0×10^{-8}–5.0×10^{-6} mol L^{-1}. The use of a cyclic renewable silver amalgam electrode enables us to combine the sensitivity at the level of mercury electrodes (with very low mercury, almost negligible, use) with mechanical stability comparable to that of solid electrodes. Therefore we can say that this type of electrode has the advantages of other types of electrodes while avoiding their drawbacks. This kind of cyclic renewable silver amalgam electrode is used with operating comfort, large measurement rate, and easiness in automation of the electrode surface refreshing

step (therefore possible use in automatic or flow through processes). The sensitivity of the elaborated method significantly surpasses those from previously reported electrochemical methods (Table 4). The linearity range covers two orders of magnitude of disulfiram concentration, which is not the case in any previous electroanalytical methods. Comparison with other nonelectrochemical methods places the method reported here among other most sensitive disulfiram determination methods, while its prevalence occurs as shorter determination time, and low cost in analysis and instrumentation as well as no need for any pretreatment or time consuming extraction steps. Thus, combination of SWCSV and a Hg(Ag)FE electrode is a promising alternative for the analytical determination of disulfiram in various samples.

Table 4. Comparison of analytical methods established for quantification of disulfiram.

Nonelectrochemical techniques			
Method	Detection	Analytical parameters (LOD, LOQ, linear range)	Literature reference
HPLC	DAD, 250 nm	1.5 ng/mL, 5.0 ng/mL, 5–500 ng/mL	18
HPLC	UV 254 nm	NA	19
HPLC	amperometric	0.7 mg/L, 2.3 mg/L, 6–100 mg/L	20
MLC	DAD 248 nm	15 ng/mL, 70 ng/mL, 15–2500 ng/mL	21
HPLC	UV 435 nm	3 ng, NA, 1–200 ppm	22
HPLC	UV 280 nm	25 ng/mL, NA, 50–500 ng/mL	23
HPLC	UV 254 nm	10 pmol/L, NA, 25–1500 nmol/L	24
HPLC	UV 254 nm	5 ng/mL, NA, 0.5–2.0 μg/mL	25
HPLC	MS	NA, NA, 0.25–2.5 mg/kg	26
UPLC	ESI-MS/MS	NA, 0.6 ng/ml, 0.6–1200 ng/mL	27
LC	UV	NA, NA, 0.1–0.8 μmol/L	28
GC	-	NA, NA, 0.2–9 μg/mL	29
spectrophotometric		NA, NA, 36–110 mg	30
optical density		NA, NA, 5–50 μg/mL	31

Electrochemical techniques					
Electrode type	Technique	Linear range (mol L^{-1})	LOD, LOQ (mol L^{-1})	Samples	Literature reference
AuMe	DPAdSV	5×10^{-7}–1×10^{-6}	6.3×10^{-8} 2.0×10^{-7}	pea seeds	11
IDA	Amperometry	2.5×10^{-6}–7.5×10^{-6}	1×10^{-6} NA	pharmaceuticals	12
Modified CPE	DPAdSV	NA	2.2×10^{-8} NA	strawberries	13
Graphite-PTFE	LSAdSV	2×10^{-7}–1×10^{-6} 1×10^{-6}–8×10^{-6}	6.5×10^{-8} 2.0×10^{-8}	strawberries	14
Ag	CSV	4×10^{-5}–5×10^{-4}	5.6×10^{-5} NA	pharmaceuticals	15
DME	DPP	0.5–30 ppm	NA NA	pharmaceuticals	16 17
DME	DPP	5×10^{-5}–5×10^{-3}	5.0×10^{-7} NA	-	
Hg(Ag)FE	SWCSV	5×10^{-8}–5×10^{-6}	1.1×10^{-8} 3.7×10^{-8}	pharmaceuticals, urine	This work

IDA - interdigitated microelectrode array
NA - not available

3. Experimental

3.1. Materials and methods

Disulfiram standard (99%) was purchased from Sigma-Aldrich (Hamburg, Germany), copper(II) sulfate anhydrous from Merck (Darmstadt, Germany), Anticol 500 mg from Polfa S.A. (Warsaw, Poland), and methanol (HPLC grade) from POCH (Gliwice, Poland). The supporting electrolytes were 0.2 mol L^{-1} citrate-phosphate buffers (pH 6.5–8.0), 0.04 mol L^{-1} Britton–Robinson buffers (BR, pH 2.0–8.7), and 0.02 mol L^{-1} phosphate buffers (pH 6.5–8.0). All chemicals used for preparation of buffer solutions were from Sigma Aldrich. In voltammetric analysis, solutions were purged with pure argon (Linde Gas) prior to each voltammetric scan for at least 10 min and argon was passed over the solutions during the measurements. Fresh stock solution of 1.00×10^{-3} mol L^{-1} DSF was prepared weekly by dissolving 7.4 mg of the compound in 25 mL of methanol/water (2:3 v/v) solution. All electrochemical measurements were carried out at the ambient temperature of the laboratory (20–22 °C). Water was demineralized in PURELAB UHQ (Elga LabWater, UK).

3.2. General voltammetric procedure, instrumentation, and software

All voltammetric experiments were performed on μAutolab Type III/GPES (General Purpose Electrochemical System, version 4.9, Eco Chemie, the Netherlands) and an M164 electrode stand (mtm-anko, Cracow, Poland). Experiments were performed in a three-electrode system consisting of Ag/AgCl/3 mol L^{-1} KCl as a reference electrode, Pt wire as a counter electrode, and a renewable silver amalgam film electrode (mtm-anko, Cracow, Poland) as a working electrode. The construction and parameters of the Hg(Ag)FE were described earlier.[40] Basically, Hg(Ag)FE consists of micrometer screw, piston pin with Ag cylindrical electrode, 1% liquid silver amalgam (10 μL), Ag foil, O-ring, and electric contact pin, with electrode surface area of 12 mm^2.[33,36] This simple construction allows the amalgam film to be renewed in less than 1 s before recording each voltammogram. The refreshing procedure involves two stages: i) pulling up the silver electrode inside the electrode holder through a Hg reservoir and then ii) pushing it back outside. The preparation of the liquid silver amalgam (1% w/w) is based on dipping several silver wires (0.5 mm diameter) in 0.5 mL of mercury for 7 days to obtain the saturated concentration of silver. The liquid amalgam, whose volume does not exceed 10 μL, enables the electrode to function stably for several months. Measurements of pH were made using a CP-315M pH-meter (Elmetron, Poland) with a combined glass electrode. The general procedure used to obtain voltammograms was as follows: 10 mL of supporting electrolyte was transferred to the electrochemical cell, degassed by passing through an argon stream for 10 min, and then a voltammogram was registered under the inert atmosphere. After the initial blank was recorded, the required volumes of disulfiram were added to the supporting electrolyte by means of a micropipette. In the present study, the optimal results for square wave voltammetry experiments were obtained in BR buffer at pH 7.5, using amplitude $E_{sw} = 60$ mV, frequency $f = 25$ Hz, step potential $\Delta E = 7$ mV, accumulation potential $E_{acc} = 0$ V, and accumulation time $t_{acc} = 30$ s.

3.3. Anticol analysis

Anticol tablets, each containing 500 mg of disulfiram, were powdered and amounts corresponding to 1.0×10^{-2} mol L^{-1} of DSF were weighed and dissolved in methanol/water (2:3 v/v) solution. After sonication, working solutions were prepared by serial dilution. In all experiments, voltammograms were recorded under the same conditions as for pure DSF. Disulfiram concentration was analyzed using the standard addition method. DSF concentration in the electrochemical cell, for the sample, was equal to 1.0×10^{-6} mol L^{-1}. Each

addition contained 10 nmol of disulfiram. Corresponding voltammograms were recorded after each addition. Recoveries were calculated after three replicate experiments. To check the accuracy of the experiments, thinlayer chromatography (TLC) was used as a reference method.

3.4. Reference method

Reference method conditions were previously described in detail.[52] Briefly, TLC analysis was performed on RP-18 TLC F_{254} aluminum plates (Merck, Germany). Under a nitrogen blanket, 10 mm from the edge of the plate, analytes were applied as dots (0.5 μL) by means of a semi-automatic applicator, Linomat 5 (Camag, Switzerland, application rate of 250 nL s^{-1}) and a 100-μL microsyringe (Camag, Switzerland). Each plate was developed to a distance of 4.0 cm in a horizontal DS chamber (Chromdes, Poland) previously saturated with water/methanol (1:9 v/v) for 600 s. Developed plates were dried in hot air, sprayed with 0.5 mol L^{-1} $CuSO_4$, and dried at 50 °C for 120 s. Subsequently, visualized plates were scanned immediately with an HP ScanJet G4010 office scanner (Hewlett-Packard, Hungary) at 300 dpi resolution. The program TLSee (AlfaTech, Italy) was used as image processing software to evaluate the plates.

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