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Novel voltammetric approaches for lipoic acid quantification in pharmaceutical dosage forms

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Kazan Federal University

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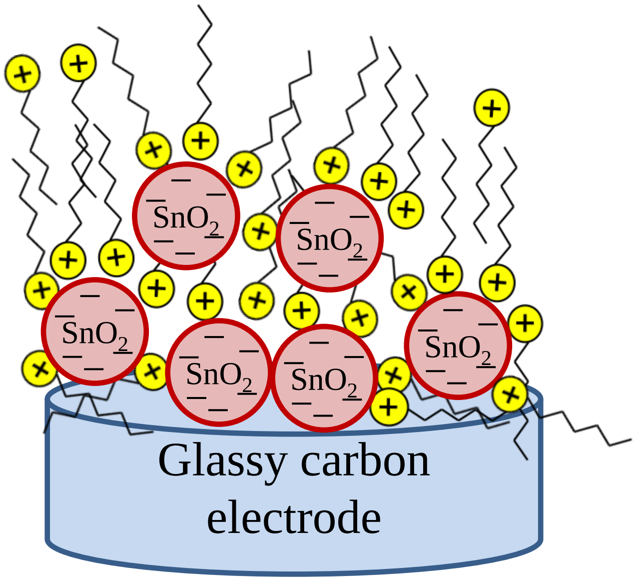

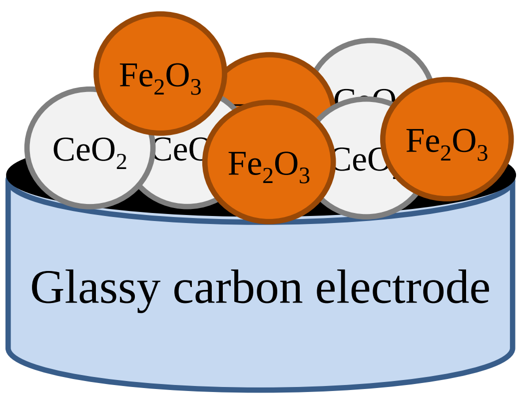

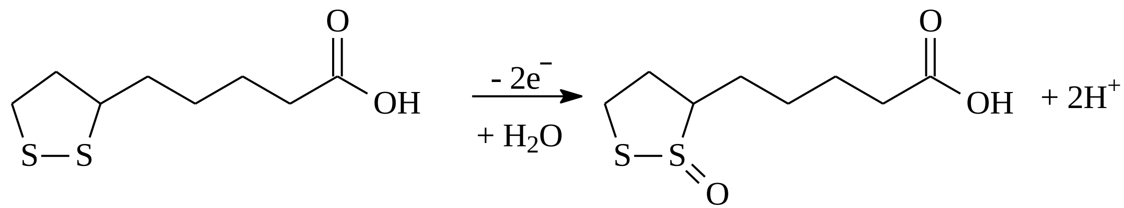

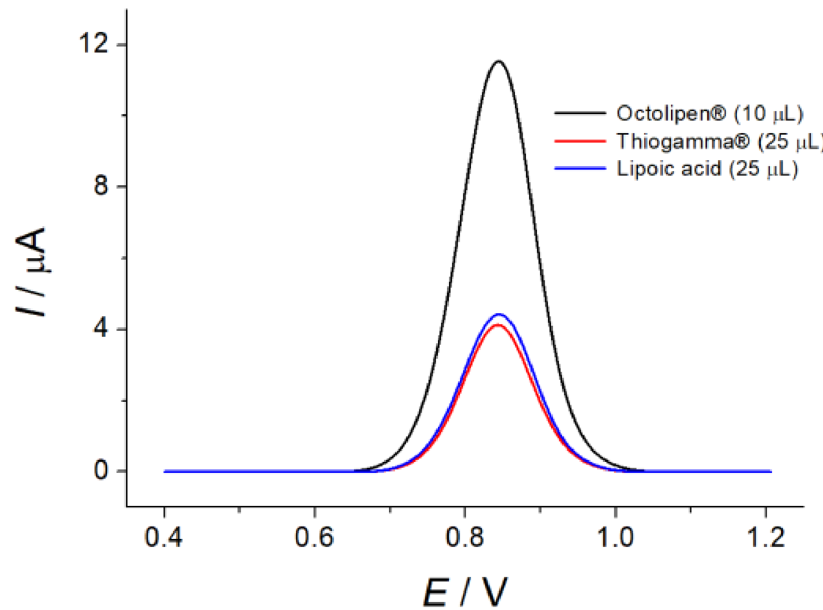

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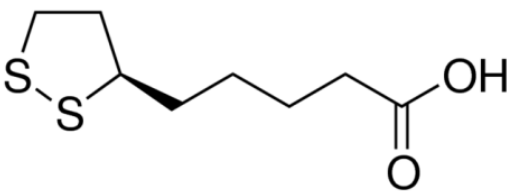
Abstract

The Lipoic acid is an important biologically active compound functioning as a part of the intracellular antioxidant defense system in living organisms providing their resistance to the development of oxidative stress and its negative effects. Therefore, lipoic acid is widely used in medicine as part of drug therapy for various pathologies. Quantification of lipoic acid is required for its pharmaceutical dosage forms quality control. Electrochemical methods, in particular voltammetry, can be applied for these purposes. To provide high sensitivity and selectivity of quantification, chemically modified electrodes are a promising tool. Among a wide range of electrode surface modifiers, metal oxide nanoparticles are of interest. Electrochemically inert tin dioxide and mixture of cerium dioxide with iron(III) oxide nanoparticles were used as electrode surface modifiers. Tin dioxide nanoparticles were prepared in surfactants providing homogeneous stable dispersion. Electrodes created were characterized by scanning electron microscopy and electrochemical methods. The modified electrodes show a statistically significant increase in the effective surface area and electron transfer rate *vs* bare electrode. Novel highly sensitive and selective differential pulse voltammetric methods were developed for lipoic acid quantification. The analytical characteristics achieved are significantly improved *vs* existing electrochemical methods. The selectivity of lipoic acid response in the presence of typical and structurally related interferences was proved. The approaches have been successfully tested on the pharmaceutical dosage forms and compared to the independent coulometric method. The methods developed are simple, reliable, selective, and sensitive that allows their usage for pharmaceuticals quality control.

Keywords: Antioxidants; lipoic acid; metal oxide nanoparticles; pharmaceutical analysis; voltammetry

Introduction



Lipoic acid

- ✓ antioxidant properties
- ✓ mitochondrial bioenergetics cofactor
- ✓ Stimulation of glucose and lipid metabolism
- ✓ insulin-mimetic agent, regulating the IR/PI3K/Akt pathway
- ✓ stress response regulation
- ✓ anti-inflammatory activity
- ✓ neuronal protection
- ✓ hyperalgesia attenuation

Application in therapy of various pathologies

Quantification of lipoic acid in pharmaceutical dosage forms is required

Introduction

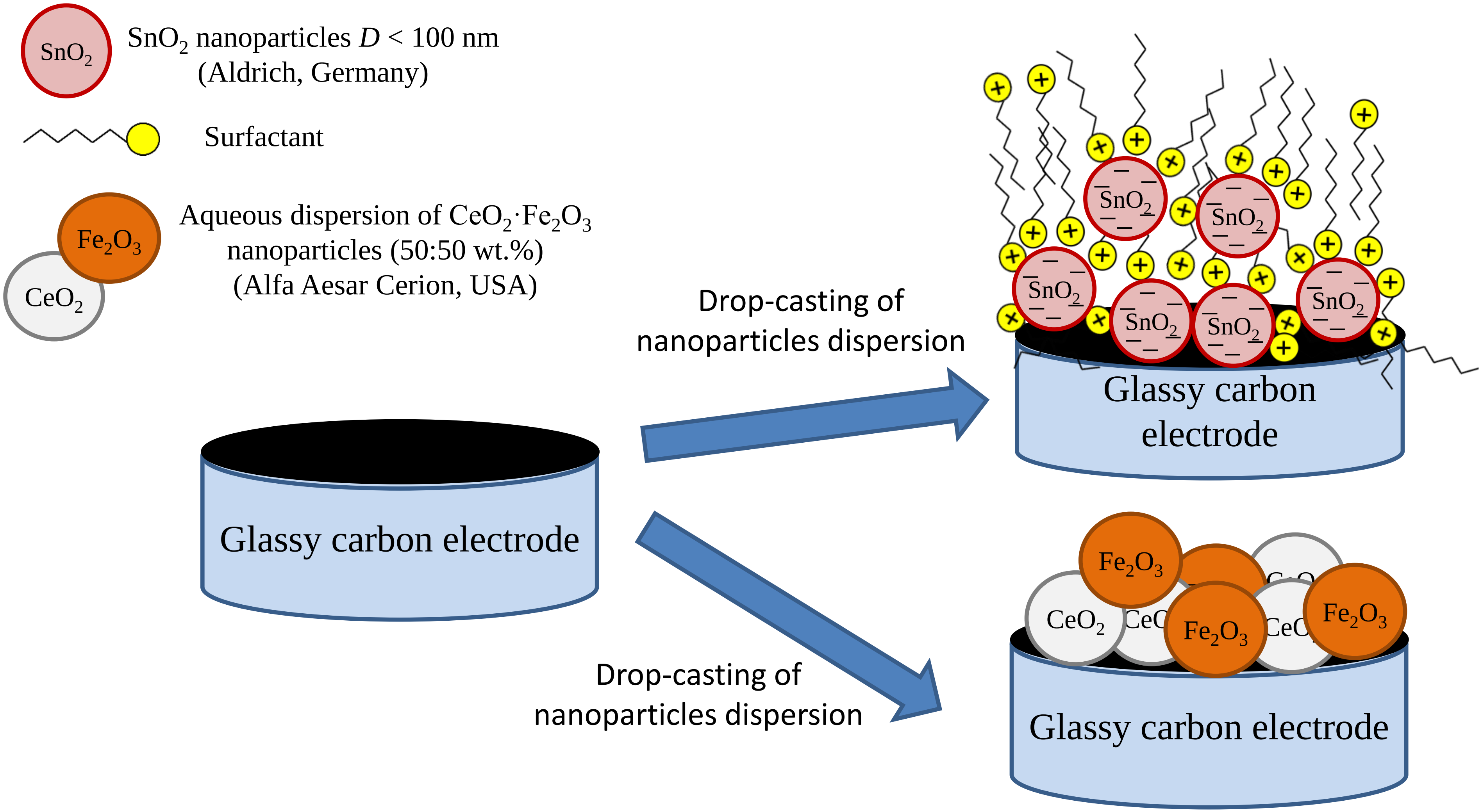
Lipoic acid electrochemical determination

- ✓ Coulometric titration with electrogenerated halogens
- ✓ Voltammetry on traditional electrodes (Pt, glassy carbon)
- ✓ **Voltammetry on chemically modified electrodes**

Electrochemically inert metal oxide nanoparticles
(Fe_3O_4, Fe_2O_3, ZnO, CeO_2, SnO_2, TiO_2, In_2O_3) are perspective modifiers

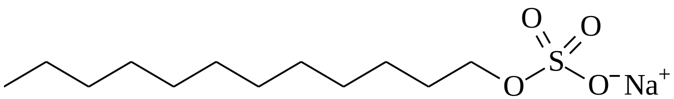
The aim of the work is development of novel sensitive and selective methods for the lipoic acid determination in pharmaceutical dosage forms using electrodes modified with tin dioxide or mixture of cerium dioxide and iron(III) oxide nanoparticles

Results and discussion

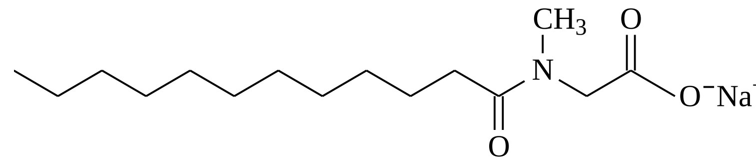


Surfactants

Anionic

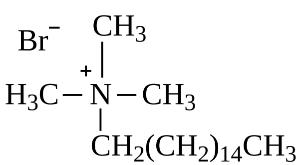


Sodium dodecylsulfate (SDS)

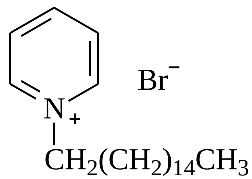


Sodium lauroyl sarcosinate (SLS)

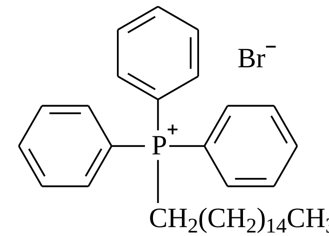
Cationic



Cetyltrimethylammonium bromide (CTAB)

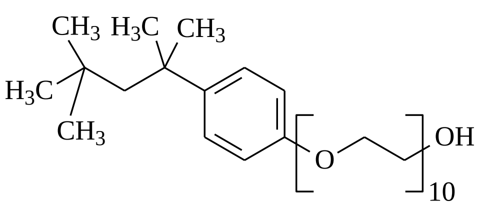


Cetylpyridinium bromide (CPB)

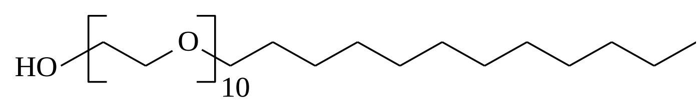


Cetyltriphenylphosphonium bromide (CTPPB)

Nonionic



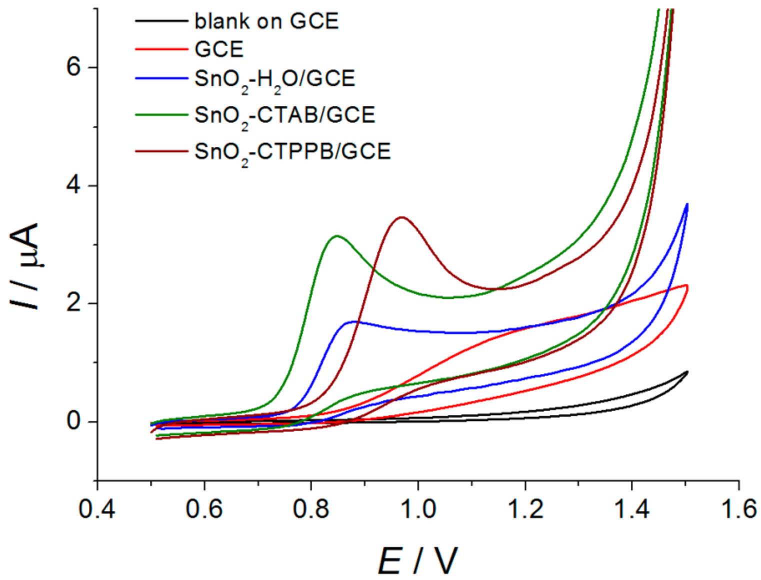
Triton X100



Brij® 35

Cyclic voltammetry of lipoic acid on the glassy carbon and SnO_2-modified electrodes

100 μM of lipoic acid



Blank – Britton-Robinson buffer pH 7.0, υ = 100 mV s^{-1}.

Voltammetric characteristics of α-lipoic acid oxidation

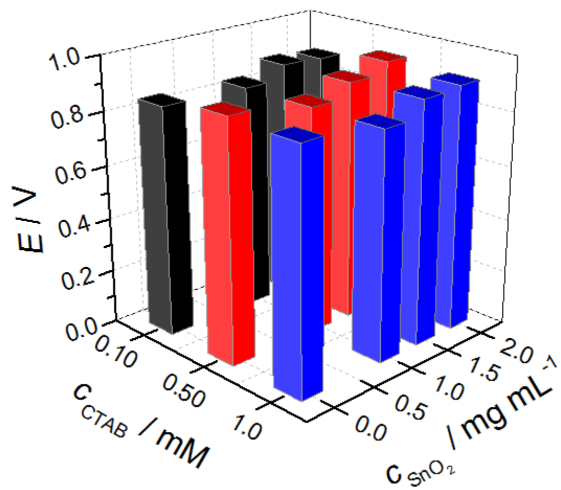
Electrode	c_{surf} / mM	E_p / V	I_p / μA
GCE	0	1.1	0.22 ± 0.01
SnO_2-H_2O/GCE	0	0.86	1.14 ± 0.06
SnO_2-SDS/GCE	0.1	0.83	2.06 ± 0.04
SnO_2-Triton X100/GCE	0.1	0.88	1.71 ± 0.05
SnO_2-Brij® 35/GCE	0.1	0.85	1.65 ± 0.05
SnO_2-CPB/GCE	0.1	0.90	2.04 ± 0.06
SnO_2-CTAB/GCE	0.1	0.84	2.29 ± 0.02
SnO_2-CTPPB/GCE	0.1	0.96	2.26 ± 0.08

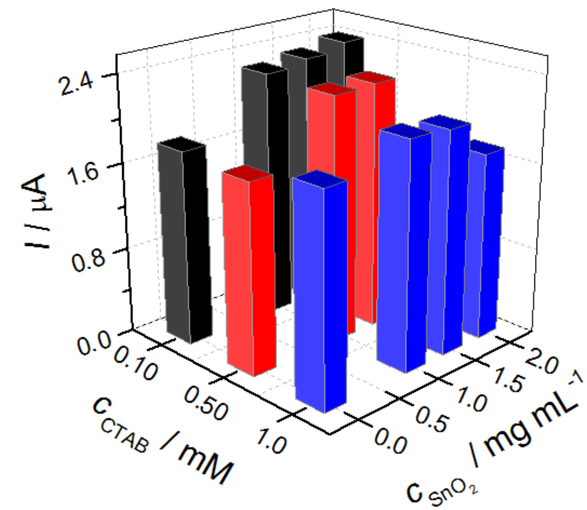
c_{SnO_2} = 1.0 mg mL^{-1}

G. Ziyatdinova, T. Antonova, V. Vorobev, Y. Osin, H. Budnikov, Monatsh. Chem., 2019, 150: 401-410.

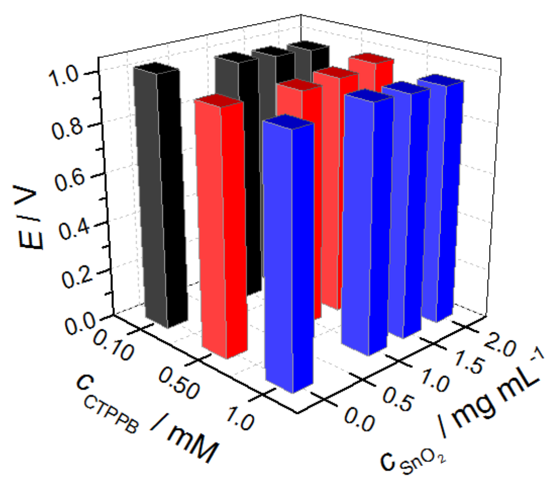
Effect of SnO_2 and surfactant concentration on the voltammetric characteristics of lipoic acid

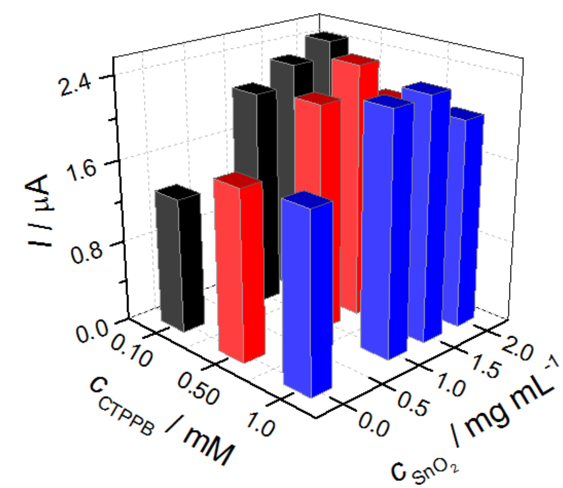
SnO_2-CTAB/GCE





SnO_2-CTPPB/GCE

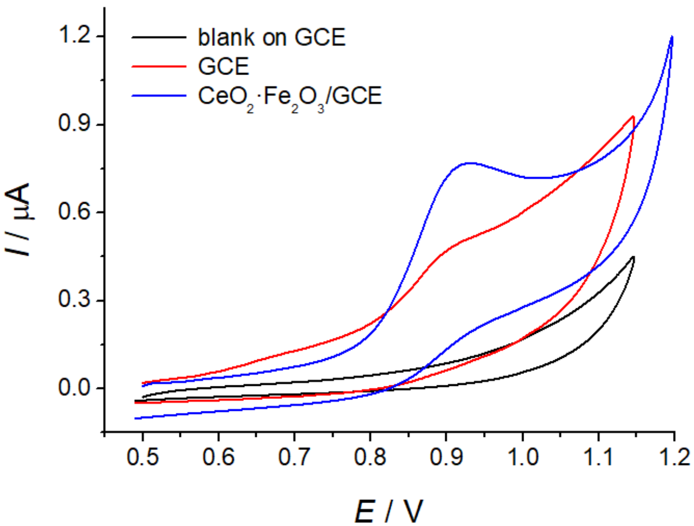




c_{SnO_2} = 1.5 mg mL^{-1}
c_{CTPPB} = 0.50 mM

Cyclic voltammetry of lipoic acid on the glassy carbon and $CeO_2 \cdot Fe_2O_3$-modified electrodes

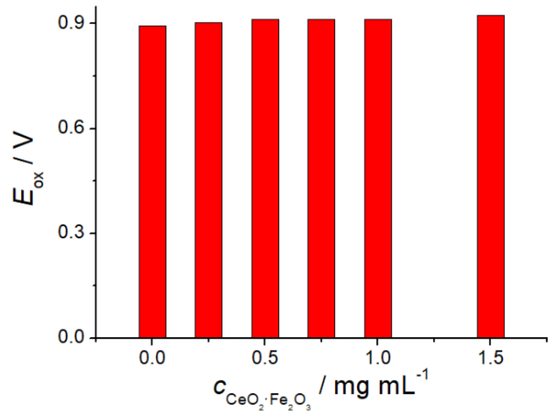
5.0 μM of lipoic acid



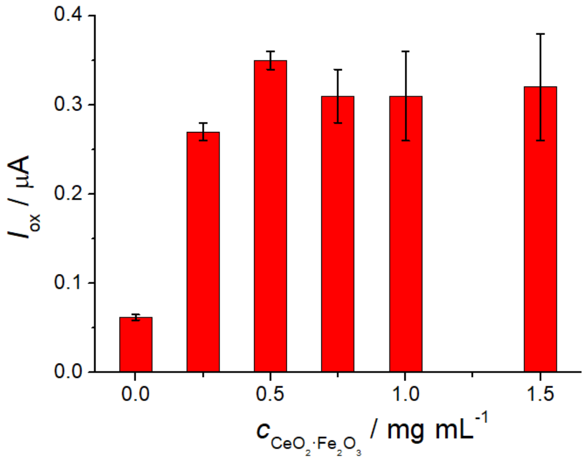
Blank – phosphate buffer pH 7.0, υ = 100 mV s^{-1}.

Electrode	E_p / V	I_p / μA
GCE	0.893	0.061±0.002
$CeO_2 \cdot Fe_2O_3$/GCE	0.913	0.35±0.01

Effect of nanoparticles quantity on the lipoic acid response

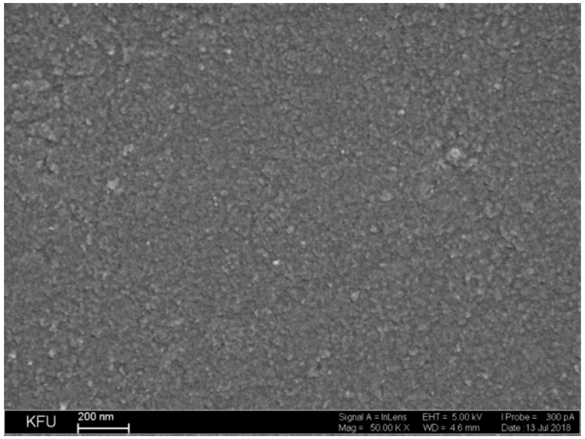


$c_{CeO_2 \cdot Fe_2O_3}$ = 0.5 mg mL^{-1}

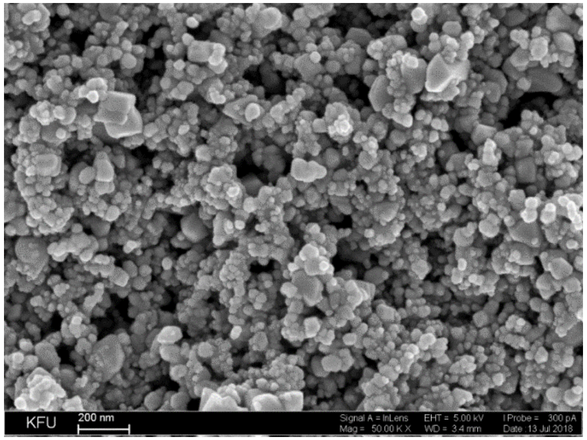


Characterization of the electrodes surface by SEM and voltammetry

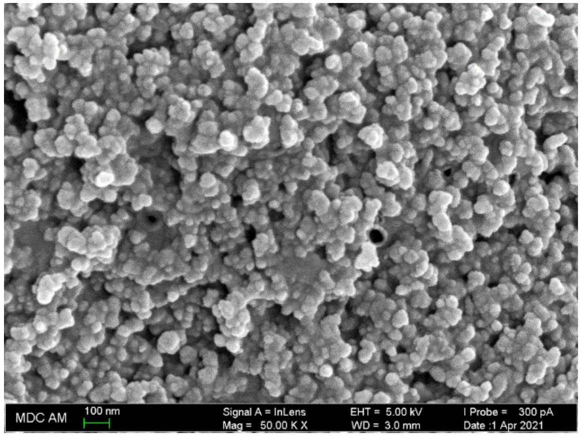
GCE



SnO_2-CTPPB/GCE



$CeO_2 \cdot Fe_2O_3$/СУЭ

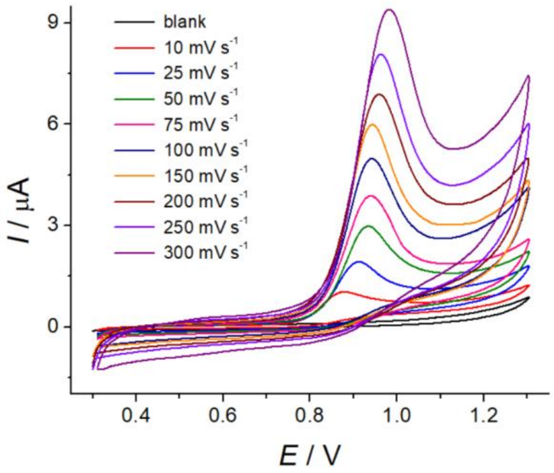


Electroactive surface area of the electrodes

Electrode	A / mm^2
GCE, 7.07 mm^2 geometric area (CHI)	8.2 ± 0.3
SnO_2-CTPPB/GCE	13.7 ± 0.2
$CeO_2 \cdot Fe_2O_3$/GCE	38.9±0.6

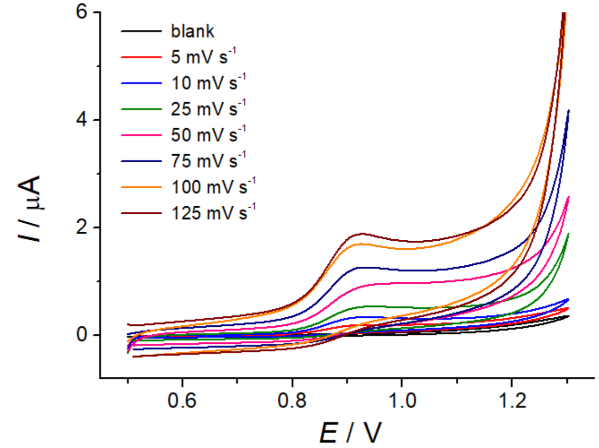
Electrooxidation of lipoic acid at the modified electrodes

100 μM of lipoic acid



Blank – Britton-Robinson buffer pH 4.5.

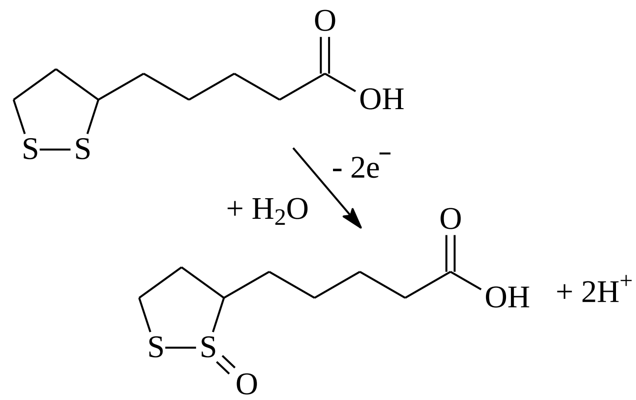
10 μM of lipoic acid



Blank – phosphate buffer pH 7.0.

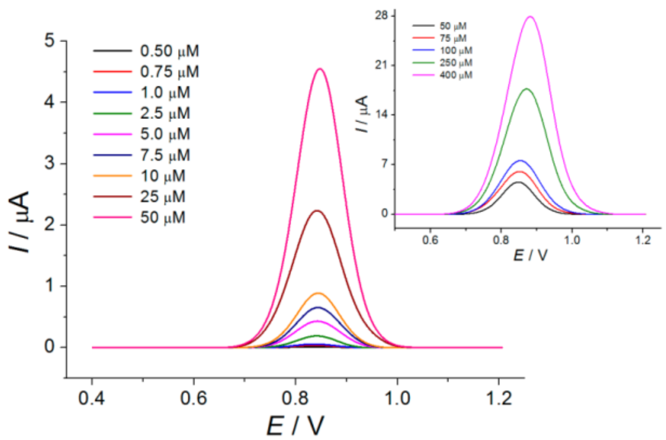
Electrooxidation parameters

Electrode	Protons	Process nature	α_a	n
SnO_2-CTPPB/GCE	Without protons participation	Diffusion control	0.50	2.0
$CeO_2 \cdot Fe_2O_3$/GCE			0.46	2.0



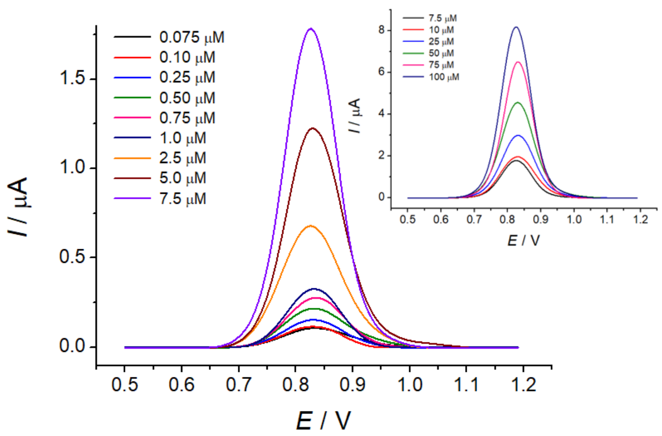
Differential pulse voltammetric determination of lipoic acid at the modified electrodes

SnO_2-CTPPB/GCE



Blank – Britton-Robinson buffer pH 4.5, ΔE_{pulse} = 100 mV, t_{pulse} = 50 ms, υ = 10 mV s^{-1}.

$CeO_2 \cdot Fe_2O_3$/GCE



Blank – phosphate buffer pH 7.0, ΔE_{pulse} = 100 mV, t_{pulse} = 25 ms, υ = 20 mV s^{-1}.

Analytical characteristics of determination

Electrode	LOD / μM	Linear dynamic range / μM
SnO_2-CTPPB/GCE	0.13	0.50 – 50 and 50 – 400
$CeO_2 \cdot Fe_2O_3$/GCE	0.053	0.075 – 7.5 and 7.5 – 100

Comparison of the analytical characteristics of nanoparticle-based electrochemical electrodes for lipoic acid determination

Electrode	Method	LOD / µM	Analytical range / µM	Ref.
Co_3O_4-SWNT-CPE	SWV	0.37	2 − 100	Electroanalysis 2021
MnO_2/Screen-printed graphene electrode	SWASV	0.43	1.45 − 121	Anal. Chim. Acta 2018
Carboxylated MWNT-polyindole-Ti_2O_3/GCE	AdDPV	0.012	0.39 − 115.8	Sens. Actuators B 2018
Fluorine-doped SnO_2 electrode	SWV	3.68	5 − 500	J. Electroanal. Chem. 2012
SnO_2-CTPPB/GCE	DPV	0.13	0.50 − 50 and 50 − 400	Monatsh. Chem. 2019
$CeO_2{\cdot}Fe_2O_3$/GCE	DPV	0.053	0.075 – 7.5 and 7.5 – 100	Current

Electrode's response selectivity

$c_{\text{lipoic acid}} = 1.0\ \mu M$

Typical interferences

1000-Fold excess of K^+, Mg^{2+}, Ca^{2+}, NO_3^-, Cl^- and SO_4^{2-}

100-Fold excess of glucose, rhamnose and sucrose

1000-Fold excess pf ascorbic acid

Specific interferences

100-Fold excess of dopamine, uric acid, cysteine, methionine, cystine and glutathione

Do not show interference effect

Quantification of lipoic acid in pharmaceutical dosage forms (n=5; P=0.95)

Sample	Electrode	Labelled content / mg, *mg cm^{-3}	Found by voltammetry / mg, *mg cm^{-3}	RSD / %	Found by coulometry / mg, *mg cm^{-3}	RSD / %	t-test[a]	F-test[b]
Thiogamma®, tablets	SnO_2-CTPPB/GCE	600	598±3	0.45	598±3	0.40	0.372	1.28
	$CeO_2 \cdot Fe_2O_3$/GCE		611±19	2.5	612±12	1.6	0.173	2.65
Octolipen®, concentrate for the infusion preparation	SnO_2-CTPPB/GCE	30*	31±2*	6.2	30±1*	2.9	0.274	4.55
	$CeO_2 \cdot Fe_2O_3$/GCE		29.5±0.6*	1.5	29.6±0.3*	0.70	0.183	4.58
Lipoic acid, tablets	SnO_2-CTPPB/GCE	25	25.0±0.7	2.4	25.0±0.6	1.8	0.119	1.77
	$CeO_2 \cdot Fe_2O_3$/GCE		25.0±0.5	1.5	25.0±0.4	1.4	0.089	1.07
	SnO_2-CTPPB/GCE	12	11.9±0.2	1.6	12.0±0.1	0.78	2.00	4.17
Lipoic acid, bioactive additive	SnO_2-CTPPB/GCE	30	30±2	5.9	29±1	3.6	0.883	2.76

[a] t_{crit} = 2.31 at P = 0.95 and f = 8   [b] F_{crit} = 6.39 at P = 0.95 and f_1 = 4, f_2 =4

Conclusions

Electrodes modified with tin dioxide nanoparticles in combination with surfactants and $CeO_2 \cdot Fe_2O_3$ nanoparticles for the voltammetric determination of lipoic acid have been fabricated. Metal oxide nanoparticles provide statistically significant increase of the electrode effective surface area. Application of metal oxide nanoparticles as electrode surface modifier leads to the improvement of voltammetric characteristics of lipoic acid.

Novel sensitive and selective methods for the quantification of lipoic acid using differential pulse voltammetry have been developed. The analytical characteristics achieved are the best ones among reported for other modified electrodes. Another advantage of the methods is the high selectivity of the electrodes response towards lipoic acid in the presence of inorganic ions, ascorbic acid, saccharides as well as other S-containing compounds (cysteine, cystine, glutathione and methionine).

The approaches developed have been used in the pharmaceutical dosage forms analysis and compared to the independent coulometric method. The results obtained show similar accuracy of the methods and the absence of systematic errors allowing recommendation of the methods developed as a good alternative to spectroscopy and chromatography for the fast quality control of the samples.