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Electrochemistry and analytical determination of lysergic acid diethylamide (LSD) via adsorptive stripping voltammetry

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ABSTRACT

Lysergic acid diethylamide (LSD) is hardly detectable and quantifiable in biological samples because of its low active dose. Although several analytical tests are available, routine analysis of this drug is rarely performed. In this article, we report a simple and accurate method for the determination of LSD, based on adsorptive stripping voltammetry in DMF/tetrabutylammonium perchlorate, with a linear range of 1–90 ng L^{-1} for deposition times of 50 s. LOD of 1.4 ng L^{-1} and LOQ of 4.3 ng L^{-1} were found. The method can be also applied to biological samples after a simple extraction with 1-chlorobutane.

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1. Introduction

Lysergic acid diethylamide (LSD, Fig. 1) is a semisynthetic product of lysergic acid, a natural substance from the parasitic rye fungus *Claviceps purpurea*. Albert Hofmann, a natural products chemist at the Sandoz AG Pharmaceutical Company (Basel, Switzerland), synthesized LSD in 1938 while searching for pharmacologically active derivatives of lysergic acid. He accidentally discovered its dramatic psychological effects in 1943, and though he synthesized many lysergic acid derivatives, none had LSD's unique spectrum of psychological effects. During the 1950s, LSD (Delysid® Sandoz) was introduced to the medical community as an experimental tool to induce temporary psychotic-like states ("model-psychosis") and later to enhance psychotherapeutic treatments ("psycholytic" or "psychedelic" therapy) [1].

LSD is one of the most potent psychotropic drugs, only few micrograms (50–100) are required for pharmacological effects [1]. LSD is extensively metabolized, but a small fraction is found unchanged in biological fluids, so that the identification of LSD at 200 ng L^{-1} in urine is considered positive for LSD abuse [2]. The detection of very low concentrations of LSD and its metabolites requires the development of specific and sensitive analytical methods. Several gas chromatographic mass spectrometric methods [3] have been developed for LSD analysis providing specificity and high selectivity but they need time-consuming extraction, purification and derivatization procedures. More recently, liquid chromatography–mass spectrometry (LC–MS) methods for its determination have been proposed [4].

In this paper, the electroactivity of the ergot nucleus [5] was exploited to develop a rapid, sensitive and specific adsorptive stripping voltammetric method at glassy carbon electrode in DMF containing 0.1 M tetrabutylammonium perchlorate for the determination of LSD, alternative to LC–MS, less expensive and with comparable sensitivity.

2. Experimental section

2.1. General section

Reagents of the purest grade available were purchased from Sigma-Aldrich and used as received. All electrochemical measurements and characterizations were carried out with a BASI PWR-3 power module and a standard three-electrode EF-1085 C-3 cell with a glassy carbon (0.02 cm^2 geometrical area) electrode as the working electrode, a platinum wire as auxiliary electrode and a Ag/AgCl/NaCl (3 M NaCl saturated with AgCl) reference electrode.

Due to its photoreactivity [6], the synthesis and manipulation of LSD were carried out in a dark environment. Standards (dimethylformamide: DMF) were prepared daily from a 1000 mg L^{-1} stock solution (in DMF), stable for at least 1 week when conserved at –18 °C, and stored in the dark.

Electrochemical potentials are referred to Ag/AgCl/NaCl (3 M NaCl saturated with AgCl). An Orion SA 520 pH meter was used for pH measurements.

In the following, the uncertainty on the last digit has been reported in brackets, when appropriate.

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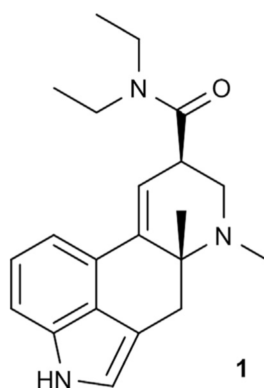

Fig. 1. Chemical structure of LSD (1).

Please notice that LSD tartrate was used for this study, but quantity reported below refer to the free base.

2.2. LSD synthesis

LSD was synthesized from the corresponding lysergic acid hydrate according to the well-known Hoffmann procedure [6]. The compound was purified by column chromatography (neutral alumina; eluent benzene/chloroform 3:1) and crystallized three times from methanol as L-(+)-tartrate [6]. The substance is highly physiologically active and its synthesis and manipulation require special precaution to avoid any contact, also with dilute solutions or samples contaminated with it.

2.3. Glassy carbon (GC) electrode pretreatment/characterization

Before use, following standard procedures, the GC electrode was abraded with successively finer grades alumina (from 1 µm to 0.05 µm), rinsed with 5% nitric acid and water and cleaned in an ultrasonic bath to remove any trace of alumina. Then the smooth surface was electrochemically cleaned by Cyclic Voltammetry (CV) in a 0.5 M H_2SO_4 solution (15 cycles, initial potential E_i=0.0 mV, final potential E_f=+1400 mV, scan speed ν=200 mV s^{-1}) in order to obtain low background currents and reproducible results [7]. Effective glassy carbon electrode area was determined by applying the Randles–Sevcik equation by CV in a 1.0 mM ferrocene/0.1 M tetrabutylammonium perchlorate solution in acetonitrile (E_i=+200 mV, E_f=+800 mV, scan speed ν=100 mV s^{-1}) [8,9].

2.4. Electrochemical investigations of LSD

Measurements in CV to evaluate the redox activity of the drug were performed in 0.1 M tetrabutylammonium perchlorate ($(Bu_4N)ClO_4$) in DMF, in the potential range from –600 mV to +1500 mV (accessible to the GC electrode in these conditions) with a title compound concentration of 1 mg L^{-1} at variable scan speeds, from 50 mV s^{-1} up to 1000 mV s^{-1}.

To evaluate whether the electrochemical processes were diffusion-controlled, plots of current intensity (i) vs. square root of the scan speed ($\nu^{1/2}$) or vs. scan speed (ν) were performed (CV, 0.05 M $(Bu_4N)ClO_4$ in DMF as described, E_i=+700 mV, E_f=+1500 mV, title compound concentration 50 mg L^{-1}, scan speeds from 10 to 200 mV s^{-1}). The scan window was limited only to $E > 700$ mV as no peaks were found at more negative potentials (see below). The relationships between log i and log ν in the same conditions, the behavior of $i/\nu^{1/2}$ vs. log ν and the peak's potential dependence with respect to the logarithm of scan speed were investigated as well, to better assess the nature of the electrochemical processes.

The number of electrons involved in the electrochemical rate-determining step was obtained by CV at different scan speeds (from 10 to 200 mV s^{-1}; potential range from +700 mV to +1300 mV) in 0.05 M $(Bu_4N)ClO_4$ in DMF as described, drug concentration of 50 mg L^{-1}; the equation for reversible processes was applied, being:

$$|E_p - E_{p/2}| = (2.218RT)/(nF) = [57.7/(n)]\,\text{mV} \quad (1)$$

where symbols have the usual meaning [10].

For further details, see Supplementary information.

2.5. Electrochemical determination of LSD

For the quantification of LSD, a method based on adsorptive stripping voltammetry (AdSV) was developed. The quantitative determination was done on the oxidation wave, by the standard addition method. Different supporting electrolytes, viz. $(Bu_4N)ClO_4$, $LiClO_4$, tetrabutylammonium tetrafluoroborate in different solvents (methanol, acetonitrile, *N*,*N*-dimethylformamide) were tested, as well as the effect of the presence of water in the media. The influence of the main parameters (namely, deposition potential, deposition time, scan speed) was verified.

2.6. Extraction of LSD from biological matrices and toons

Biological matrices were spiked with realistic amounts of LSD, taking into account the dose usually taken and metabolism [2,11] and half-life of the dose ingested [1].

For the extraction of LSD from biological matrices and toons, known procedures were followed, in particular:

- *Toons*: LSD was extracted from toons (2×3 cm^2, usual LSD content ranging from 50 µg to 100 µg) with 15 mL DMF (ambient temperature) in ultrasonic bath for 10 min.
- *Hairs*: Approximately 50 mg of hair, accurately weighted, were cut into small pieces of about 3 mm in length, and then washed with water, methanol and cyclohexane (5 mL each, to remove any residual detergent, dye or traces of grease). The sample was extracted with 5 mL DMF in ultrasonic bath at 50 °C for 10 min. A second extraction was performed to asses that recovery was quantitative.
- *Plasma and urine*: Following a known procedure [12] slightly modified and adopted, 1 mL of sample (adjusted to pH=9 with phosphate buffer in the case of plasma) was extracted with 1 mL 1-chlorobutane with strong agitation (Autovortex®) for 2 min; the solution was centrifuged at 4500 rpm for 10 min. The organic phase was diluted 1:100 with a 0.1 M $(Bu_4N)ClO_4$ solution and analyzed by the standard additions method by AdSV.

A known amount of each extract was added to 10 mL DMF 0.05 M $(Bu_4N)ClO_4$ in order to have a final concentration in the range 10–50 ng L^{-1}, and analyzed.

3. Results and discussion

3.1. Electrode characterization

Glassy carbon electrode area was estimated to be 0.083(1) cm^2, in good accordance with geometrically calculated area. This indicated that the surface was well polished and with low roughness.

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