

STRUCTURE OF CHEMICAL COMPOUNDS, METHODS OF ANALYSIS AND PROCESS CONTROL

QUANTITATIVE DETERMINATION OF ENDURACIN IN BLOOD SERUM

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Enduracin is a new medication form of nicotinic acid, which will probably return this agent to the group of drugs most frequently administered both for the purpose of dyslipidemia correction and for the therapy and prophylaxis of atherosclerosis as a systemic disorder of arterial vessels. The new drug form makes use of a special tropical wax to form a tablet matrix providing uniform absorption of nicotinic acid from the intestine into blood.

In recent years, an important place between physicochemical methods used for the drug analysis belongs to the electrochemical techniques, including inversion voltammetry (IVA). The IVA procedure consists in the electrically driven accumulation of an organic substance on an electrode in the form of a low-soluble compound, followed by measurement of the deposit dissolution current. For example, the ability of nucleic acid bases to form poorly soluble compounds with mercury was employed [1] for the determination of adenine, cytosine, and thymine on the level of 10^{-9} gM in alkaline borate buffer solutions. There are data on the application of IVA to determination of some other drugs [2].

The purpose of this work was to develop an IVA based technique for the quantitative determination of nicotinic acid in the blood serum.

Because enduracin, selected as the object for analysis, represents a prolonged form of nicotinic acid, the procedure is aimed at the quantitative determination of the nicotinic acid ions. The method is based on the accumulation of a low-soluble mercury salt of nicotinic acid on an electrode in the working electrolyte solution.

In this work, the quantitative determination of enduracin was performed using an aqueous solution of sodium acid

phosphate Na_2HPO_4 as an electrolyte and a mercury-film-pin system as the working electrode.

The optimum range of potentials for the preliminary electrolysis was 0.05–0.1 V (versus silver-chloride electrode). The electrolysis duration was 5–6 min, and the optimum potential sweep rate was 20 mV/sec. At a higher sweep rate, the current increases but at the expense of reduced reproducibility of the data; the lower sweep rates lead to a loss of sensitivity.

The deposit dissolution current registered on the voltamperogram is proportional to the concentration of nicotinic acid in solution; the concentration range of proportionality extends from 10^{-9} to 10^{-3} g/ml. The minimum detectable drug concentration is 4.6×10^{-7} g/ml ($S_r = 0.1$). This concentration range is retained in the presence of plasma, but the magnitude of the current somewhat increases. This is probably related to the fact that a certain amount of nicotinic acid (up to 0.2 mg%) is initially present in the human organism.

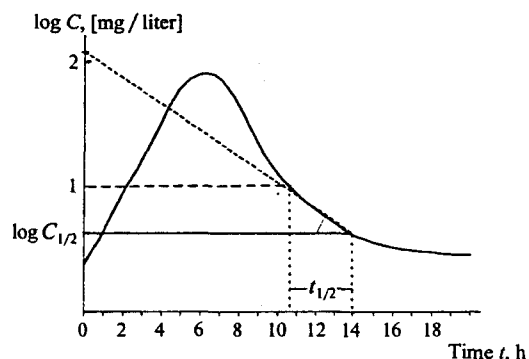


Fig. 1. Variation of the nicotinic acid concentration in the human blood upon a single peroral administration of enduracin.

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This fact does not hinder quantitative determination of the administered drug.

An analysis of the measurement conditions allowed us to develop a method for the rapid voltammetric analysis of enduracin in the blood serum *in vitro*. According to this procedure, 10 ml of 0.2 M Na₂HPO₄ in a 20-ml quartz cylinder is deoxygenated by purging for 5 min with nitrogen (or argon) containing less than 0.003% oxygen. Not interrupting the solution stirring by the inert gas bubbles, the solution is electrolyzed at $E_u = 0.05$ V for $\tau = 300$ sec. The gas supply is switched off and the cathode voltamperogram is measured. Then 0.02 ml of a blood serum (separated from proteins by treating it with sulfuric acid [3]) is added, the solution is stirred by inert gas bubbling, and the electrolysis is repeated under the same conditions as above. The measurements of nicotinic acid are conducted in the range of potentials from -0.45 to -0.50 V at an instrument sensitivity of 1×10^{-7} A/mm.

The quantitative determination of nicotinic acid is provided by adding standard solutions. A single analysis takes about 20 min.

The method was verified by measuring the known introduced amounts of the drug.

It was found that the determination of enduracin was not hindered by the presence of impurities such as oxalic acid, phenol derivatives, and some other oxy compounds.

The method described above was used to study the pharmacokinetics of enduracin in the blood serum of patients. The level of nicotinic acid was measured prior to the enduracin introduction and 30 min or 2, 6, 8, 11, and 24 h after peroral administration of the drug. The pattern of variation of the

nicotinic acid concentration in the blood serum of patients receiving enduracin is shown in Figure 1.

The observed dynamics of the drug concentration in the blood plasma was described in terms of a well-known mathematical model frequently used to study the drug pharmacokinetics upon peroral administration:

$$C_t = C_0 \frac{k_{01}}{k_{01} - k_{el}} \left(\exp(-k_{el}t) - \exp^{-k_{01}t} \right)$$

where t is the time passed after the drug administration, C_0 is the apparent initial drug concentration, (determined by extrapolation to $t = 0$), C_t is the drug concentration at the current time instant, and k_{01} is the absorption constant.

According to this model, the organism is considered a whole unit and a decrease in the drug concentration is described by the elimination constant (k_{el}) independent of the drug dose (within the range of therapeutic doses). In the model adopted, the drug concentration C_t is proportional to the dose administered.

As is seen from Fig. 1, the maximum concentration of nicotinic acid in the blood upon a single peroral administration of enduracin (0.5 g) is attained 6 h after taking the tablet. The drug elimination half-time is 10.5–14 h.

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