CAPSULES
preliminary notes and applications from Bioanalytical Systems, Inc.

Determination of Pivazepam in Tablets and in Urine

Purpose

Pivazepam (I, F1) is a member of the 1,4-benzodiazepine family, which are widely used as antipsychotic drugs. In this study, electrochemical methods for the determination of pivazepam in tablets and in urine were developed.

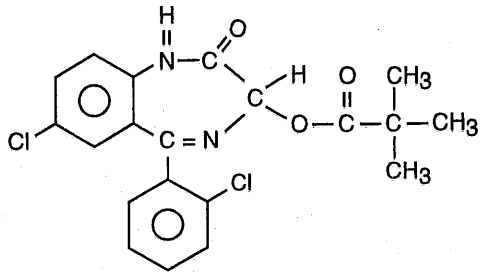

Figure 1. Molecular structure of pivazepam

Method

Differential pulse polarograpy is one of the electrochemical techniques preferred for concentration measurements, due to its relatively low detection limits (which is due to good discrimination against the charging current). The detection limit of the differential pulse technique can be further lowered by allowing analyte accumulation at the electrode before the potential scan. For many organic molecules, this accumulation occurs via adsorption to the surface of a mercury electrode.

One advantage of using electrochemical techniques for the analysis of dosage forms is the simplicity of preparation; in this case, the tablets were ground to a fine powder, dissolved in methanol, decanted, and diluted with an aqueous buffer to give a 10% methanol solution. The preparation of the urine sample involved extraction into ether, solvent evaporation, extraction into methanol and dilution to a 10% methanolic solution using an aqueous buffer.

The concentration of I in tablets and in urine was determined from calibration plots of peak currents vs. concentration.

Results

Many redox processes of organic molecules in aqueous media involve proton transfer. Hence, the pH dependence of such redox processes is an essential part of the investigation of the electrochemical activity of these molecules. One reduction process was found for I using differential pulse polarography, and the peak current and peak potential of this process varied with pH (F2). The highest peak current was found at low pH, but a hydrolysis reaction also occurred at this pH, which caused a slow decrease in the peak current. Hence, a pH of 4 or 5 was used for the analysis.

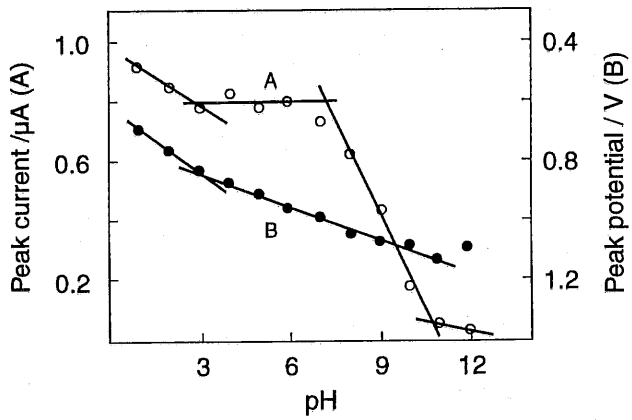

Figure 2. Variation of the peak current (A) and peak potential (B) with pH. Figure adapted from Reference.

The reduction process was shown to be a four-electron irreversible process. The net reaction is shown in F3 (it should be noted that this is a multi-step reaction). The linear relationship between the peak

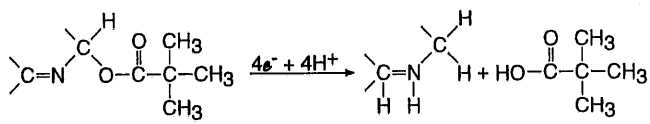

Figure 3. Mechanism for the reduction of pivazepam.

current and concentration required for concentration measurements could not be obtained in all buffers due to the adsorption of I on the electrode.

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The best calibration plot was obtained when using a 0.1 M McIlvaine buffer of pH 4.0, which was linear over the range of 10^{-7} M - 10^{-5}M, with a detection limit of 1.3 x 10^{-8} M and a standard deviation of less than 2.4%. This buffer was used for the analysis of I in tablets.

These measurements produced a mean value of 2.04 mg of I per tablet, with a standard deviation of less than 1.8%.

The evidence for adsorption of I to the surface of the mercury electrode is shown in F4. The peak current following an accumulation time of 180 s (a) is much higher than the peak current with no previous accumulation time (b). The accumulation depended not only on the accumulation time, but also on the pH, the concentration of the aqueous buffer solution and the accumulation potential. The optimum conditions were found to be 0.2 M acetate buffer at pH 4.0 and an accumulation potential of -0.5 V (vs. the Ag/AgCl reference electrode). The current response was linear over the range 2.5 x 10^{-9} M - 7.8 x 10^{-8} M with a detection limit (as determined by 3 x S/N ratio) of 9.2 x 10^{-10} M.

F5 shows the current response for a concentration of I of 7.0 x 10^{-8} M in the absence (a) and in the presence (b) of urine. The decrease in the current in the presence of urine indicates competitive adsorption of some component(s) of urine; that is, a separate calibration curve is required. The detection limit in urine was found to be 15 ppb, with an upper limit of 400 ppb. The standard deviation (at 200 ppb) was less than 4.6%.

Reference

Electrochemical Behavior of the Psychotropic Drug Pivazepam in Determinations in Pharmaceutical Formulations and in Urine, P. Rivera, E. Bermejo, A. Zapardiel, J. A.P. Lopez and L. Hernandez, Electroanalysis, 3 (1991) 399-404.

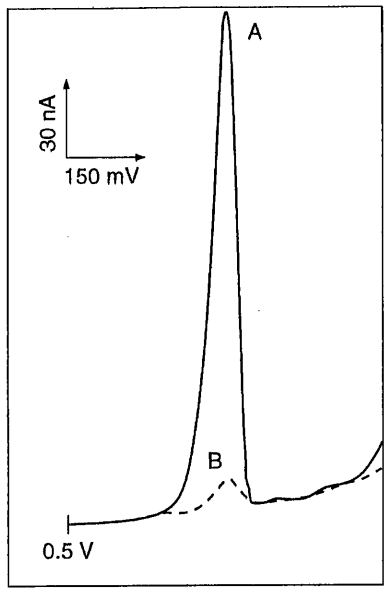

Figure 4. Adsorptive stripping voltammograms for pivazepam (1.7 x 10^{-7} M) in 0.04 M Britton-Robinson buffer (pH 3.0). Accumulation time a) 180s b) 0 s. Accumulation potential = -0.5 V, pulse amplitude = 50 mV, scan rate = 20 mV s^{-1}, stirring rate = 1920 rpm and drop size = 0.60 mm^2. Figure adapted from Reference.

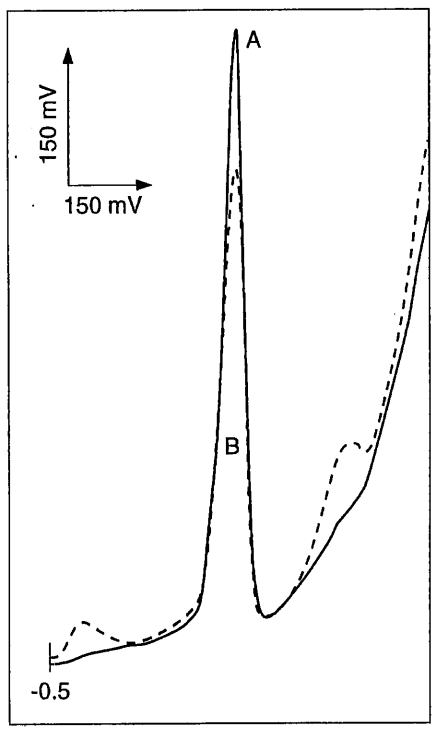

Figure 5. Adsorptive stripping voltammograms of pivazepam (7.0 x 10^{-8} M) in 0.2 M acetate buffer (pH 4.0) in absence of urine (a) and in presence of urine (b). Pulse amplitude = 70 mV, other parameters as in Figure 4. Figure adapted from Reference.