Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(7):3601-3605

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Voltammetric methods for the determination and electrode process of nitazoxanide bulk drug industry

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ABSTRACT

The voltammetric methods were used for investigating the electrochemical properties and the quantitative analysis of nitazoxanide at the Hanging mercury dropping electrode (HMDE). The experimental conditions were optimised to obtain the best characterized peak in terms of peak height with analytical validation of the methods for each nitazoxanide.. All nitazoxanide were found to adsorb and undergo irreversible reduction reaction at the working Hanging mercury dropping electrode.

Keywords: Nitazoxanide, Determination, Reduction process, Voltammetry,

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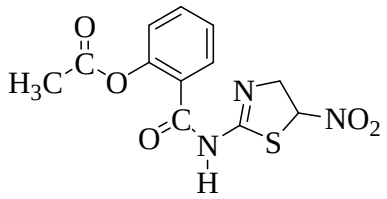
INTRODUCTION

Nitazoxanide is used to treat diarrhea in children and adults caused by the protozoa Cryptosporidium or Giardia. Protozoa are suspected as the cause when diarrhea lasts more than seven days. Nitazoxanide is in a class of medication called antiprotozoal agent. It works by stopping the growth of protozoa that causes diarrhea. It is chemically [2-[(5-nitro-1,3-thiazol-2-yl)carbamoyl]phenyl]ethanoate. The antiviral mechanism of action of nitazoxanide is different from the mechanism of action in protozoa and anaerobic bacteria *via* direct inhibition against the pyruvate-ferrodoxin oxidorectase reaction, and appears in recent studies to involve activation of the protein kinase activated by double-stranded RNA (PKR), an interferon-induced mediator of the cellular antiviral response.

Nitazoxanide is a thiazolide with a broad spectrum of activity against several nematodes, cestodes and trematodes as well as protozoan parasites such as Giardia, Cryptosporidium and Entamoeba. The thiazolides are believed to act by interference with pyruvate ferredoxin oxidoreductase, an enzyme important in anaerobic metabolism. Nitazoxanide may also have antiviral activity in vitro against hepatitis B and C, the basis of which is not known. Nitazoxanide was approved for use in the United States in 2004 and current indications are for diarrhea due to infection with Giardia lamblia or Cryptosporidium parvum. Nitazoxanide is available in tablets 500 mg and as an oral suspension (100 mg/5 mL) under the brand name Alinia. The typical dose for treating giardiasis and cryptosporidiosis in adults is 500 mg orally every 12 hours for 3 days. Nitazoxanide is generally well tolerated; side effects are usually mild and can include diarrhea, gastrointestinal upset, headaches and hair loss.



Structure of Nitazoxanide

EXPERIMENTAL SECTION

Voltammetric Techniques

Voltammetry is an electrochemical method in which current is measured as a function of the applied potential. It is a branch of electrochemistry in which the electrode potential, or the faradaic current or both are changed with time. The principle of this technique is a measurement of the diffusion controlled current flowing in an electrolysis cell in which one electrode is polarisable . In this technique a time dependent potential is applied to an electrochemical cell, and the current flowing through the cell is measured as a function of that potential. A plot of current which is directly proportional to the concentration of an electroactive species as a function of applied potential is called a voltammogram. The voltammogram provides quantitative and qualitative information about the species involved in the oxidation or reduction reaction or both at the working electrode. Polarography is the earliest voltammetric technique which was developed by Jaroslav Heyrovsky in the early 1920s, for which he was awarded the Nobel Prize in Chemistry in 1959. It was the first major electro analytical technique. Since then many different forms of voltammetry have been developed such as direct current polarography (DCP), normal polarography (NP), differential pulse polarography (DPP), square-wave polarography (SWP), alternate current polarography (ACP), cyclic voltammetry (CV), stripping voltammetry (SV), adsorptive stripping voltammetry (AdSV) and adsorptive catalytic stripping voltammetry (AdCSV) techniques.

Instrumentation

Voltammetry technique makes use of a three-electrode system such as working electrode (WE), reference electrode (RE) and auxiliary electrode (AE). The whole system consists of a voltammetric cell with a various volume capacity, magnetic stirrer and gas line for purging and blanketing the electrolyte solution.

Working electrodes and LOD for modern and voltametric techniques

Technique	**Working electrode**	**LOD** M
TAST	DME	10^{-6}
Normal pulse voltammetry (NPV)	HMDE	10^{-7}
Differential pulse voltammetry (DPV)	HMDE	10^{-8}
Cathodic stripping voltammetry (CSV)	MFE	10^{-9}
Anodic stripping voltammetry (ASV)	HMDE	10^{-10}

Polarography is used extensively in the analysis of metal ion, inorganic anions and organic compounds containing easily reducible or oxidisable functional groups. A list of electro reducible and electro oxidisable organic functional groups is shown in below Table

Electroreducible and electrooxidisable organic functional groups

Electroreducible organic functional groups	Aromatic carboxylic acid, azomethines, azoxy compounds conjugated alkene, conjugated aromatic, conjugated carboxylic acid conjugated halide, conjugated ketone, diazo compounds, dienes, conjugated double bond, nitroso compounds, organometallics, disulfide, heterocycles, hydroquinones, acetylene, acyl sulfide aldehyde, hydroxylamines, imines, ketones, nitrates, nitriles nitro compounds, oximes, peroxides, quinones, sulfones, sulfonium salts and thiocyanates.
Electrooxidisable organic functional groups	Alcohols, aliphatic halides, amines, aromatic amines, carboxylic acids, ethers, heterocyclic amines, heterocyclic aromatics, olefins, organometallic and phenols.

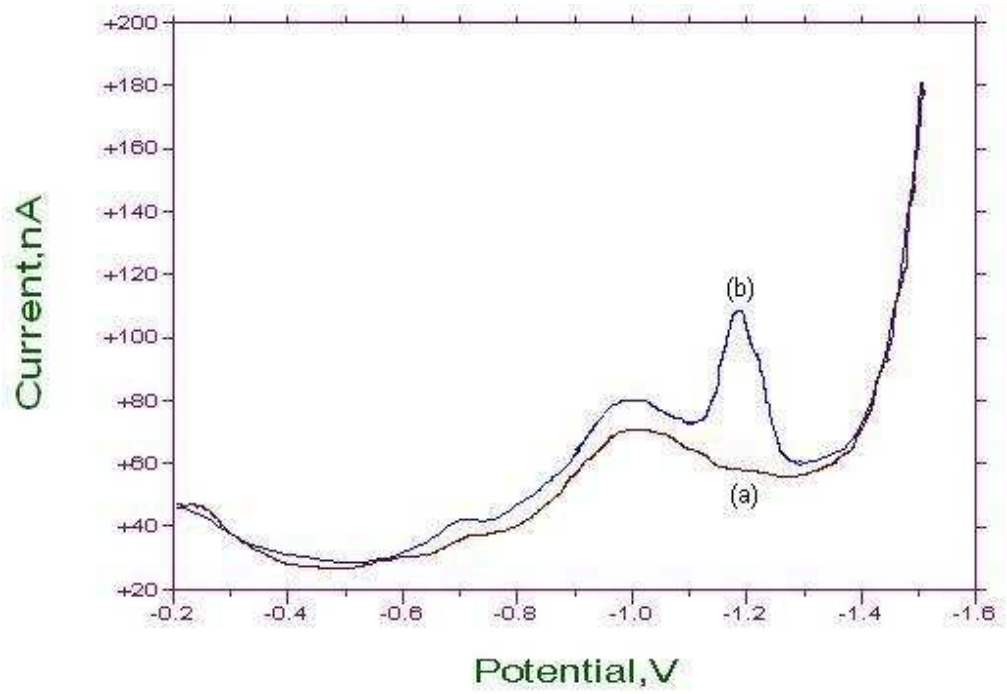
Stripping Voltammetry:
Stripping technique is one of the most important and sensitive electrochemical technique for measuring trace metals and organic samples. The term stripping is applied to a group of procedures involving preconcentration of the determinant onto the working electrode, prior to its direct or indirect determination by means of a potential sweep. The preconcentration (or accumulation) step can be adsorptive, cathodic or anodic deposition step: In this step, analyte will be preconcentrated on the WE within a certain time while solution is stirred. The deposition potential imposed on the WE is chosen according to the species to be determined and is maintained for a deposition period depending on their concentration. The choice of deposition potential can provide some selectivity in the measurement.

Rest step:
In this step, it allows formation of a uniform concentration of the ions of interest on the mercury. As the forced convection is stopped at the end of the deposition period, the deposition current drops almost to zero and a uniform concentration is established very rapidly. It also insures that the subsequent stripping step is performed in a quiescent solution.

Stripping step:
This step consists of scanning the potential anodically for anodic stripping and cathodically for cathodic stripping. When the potential reaches the standard potential of a certain ion of interest–metal ion complex, the particular ion of interest is reoxidised or reduced back into solution and a current is flowing. The resultant voltammogram recorded during this step provide the analytical information of the ions of interest.

RESULTS AND DISCUSSION

The cyclic voltammograms of nitazoxanide in BRB pH 9.0, a reduction peak was observed at -1245 mV (against Ag / AgCl) and no anodic peak at oxidation wave. The results of these CVs showed that nitazoxanide underwent irreversible reduction reaction at the mercury electrode (20). Due to these electroanalytical properties, differential pulse cathodic stripping voltammetric technique was applied in this study using the same supporting electrolyte. By using initial parameters as mentioned before, the peak potential (Ep) of 0.15 uM nitazoxanide was obtained at -1175 mV with peak current (Ip) of 34.73 nA. Several parameters have been optimised so as to obtain a more symmetrical and higher reduction peak.



Voltammograms of 0.15 uM Nitazoxanide (b) in BRb pH 9.0 (a). Condition; scan rate; 40 mV/s, accumulation potential (Eacc); -800 mV, accumulation time (tacc); 40 s, pulse amplitude; 50 mV, pulse width; 50-ms and pulse period; 200- ms.

Effect of pH of BRB

The effect of different pH medium of BRB has been studied. The results showed that a reduction peak was first observed at pH 5.0 which increases in peak height as the pH increases. It reaches its optimum height at pH 9.0. At pH more than 9.0, the peak height decreases rapidly and no peak was observed at pH more than 12.0.

Effect of instrumental parameters

As the scan rate was varied from 20 to 100 mV s^{-1}, the Ip increases and reached it maximum value at scan rate of 50 mV s^{-1} , after which the peaks became broader with undesired tail at their end. A similar pattern for Ip was obtained with increasing pulse amplitude (from 30 to 120 mV). A pulse amplitude of 80 mV with scan rate of 50 mV s^{-1} were chosen for further studies.

Calibration graph, detection limit, precision and recovery

The Ip of Nitazoxanide increased linearly with increasing concentration up to 0.26 uM. A linear calibration graph was obtained in the concentration range 0.02 to 0.26 uM Nitazoxanide (n = 10, r = 0.9980). At higher concentrations Ip tend to level off which may be due to electrode surface saturation (20). The detection limit (three times signalto-noise) was found to be 0.015 uM Nitazoxanide.

Recovery of spiked Nitazoxanide standard in BRB pH 9.0

Nitazoxanide injected	Ip (nA)	Ep (-mV)	Nitazoxanide obtained	% recovered
0.10 uM	55.35 55.84 55.62	1250 1250 1250	0.0940 uM 0.0948 uM 0.0942 uM	95.00 95.80 95.20 x = 94.50 +/- 0.41 (RSD = 0.43%)
0.15 uM	75.21 75.19 75.20	1040 1040 1040	0.1330 uM 0.1313 uM 0.1313 uM	86.68 87.51 87.51 x = 87.91 +/- 0.58 (RSD = 0.77%)
0.20 uM	97.42 97.23 97.14	1240 1240 1240	0.1691 uM 0.1705 uM 0.1686 uM	85.57 85.75 85.30 x = 84.87 +/- 0.77 (RSD = 0.91

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