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Electrochemical reduction of meloxicam at mercury electrode and its determination in tablets

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Abstract

The electrochemical reduction of meloxicam has been studied at a mercury electrode using various electrochemical methods in aqueous solutions over a wide pH range. The reduction of the drug produced a single reduction step in acidic media, whereas in slightly acidic and neutral media two reduction steps were observed. In alkaline media meloxicam shows a single pH-independent reduction step. The irreversibility of the electrode process was verified by different criteria. At all pH values, reactant adsorption at mercury electrode was observed. The mechanism of reduction was discussed. Using differential-pulse voltammetry, the drug yielded a well-defined voltammetric response in Britton–Robinson buffer solution, pH 4.0 at -1.286 V (vs. Ag/AgCl). This process could be used to determine meloxicam concentration in the range 1.0×10^{-8}–5.0×10^{-6} M. The method was successfully applied for the analysis of meloxicam in the tablet dosage form.

Keywords: Meloxicam; Pharmaceutical analysis; Polarography

1. Introduction

Meloxicam, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide, is a highly potent non-steroidal anti-inflammatory drug (NSAID) of enolic acid class of oxicam derivatives. The anti-inflammatory properties of these drugs has been attributed to their ability to inhibit the enzyme cyclooxygenase [1], which catalyzes the transformation of arachidonic acid to prostaglandin H_2 (PGH_2), the key step in the biosynthesis of prostaglandins (PGH). It is indicated for the treatment of rheumatoid arthritis, osteoarthritis, and other joint diseases. Its therapeutic benefits combined with a good gastrointestinal tolerability are well documented [2–4].

There have been few reports for the determination of the drug in formulations or in biological media including ultraviolet spectrophotomety,

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densitometry [5], high-performance liquid chromatography (HPLC) with UV detector [6,7].

Up to date, no electroanalytical data concerning meloxicam are available in the literature. However, the polarographic behavior of the two oxicams, piroxicam and tenoxicam at mercury electrodes were reported [8,9]. It was reported that the drugs exhibit a reduction mechanism highly dependent on the pH. At pH <2, the drugs showed a four-electron transfer process corresponds to the opening of the thiazine ring, immediately followed by reduction of the double bonds. The same mechanism was observed at pH >9.5.

In the present study, the electrochemical behavior of meloxicam has been studied at mercury electrodes using various voltammetric techniques. The mechanism of the electrochemical process has been elucidated. A differential-pulse voltammetric method was developed for the determination of meloxicam in tablets.

2. Experimental

2.1. Reagents

A stock solution of 1.0×10^{-3} M meloxicam (Boehringer Ingeheim, International, GmbH Ingeheim am Rhein, Germany) was prepared in 0.01 M sodium hydroxide solution and more dilute solutions were prepared daily with deionized water just before use. Britton–Robinson buffer (0.04 M, pH 2.0–12.0) was used as supporting electrolyte. All chemicals used were of analytical-reagent grade. Ultra-pure water was used throughout.

2.2. Apparatus

All voltammograms were recorded with a voltammetric analyzer PAR 273A (EG&G) equipped with a static mercury drop electrode assembly (PAR 303A). A large hanging mercury drop electrode with a surface area of 0.026 cm^2 was used as the working electrode. The reference electrode was the Ag/AgCl (sat. KCl), and a platinum wire was the counter electrode. Controlled potential coulometery (CPC) was performed using a potentiostat/Galvanostat Model 173 PAR (EG&G) with a digital coulometer Model 179 PAR (EG&G). The stirring mercury pool was used as the working electrode, with a SCE reference electrode and a platinum gauze counter electrode. An Orion SA 720 pH meter was used to carry out the pH measurements.

2.3. Procedure

A 10 ml of the supporting electrolyte solutions were pipetted into the voltammetric cell, de-aerated with nitrogen for 8 min and the background voltammograms were obtained. A stock solution of meloxicam was added to the buffer solution and the mixture was purged for a further 30 s. After an equilibrium time of 2 s, the voltammetric curves were recorded in the negative-going direction. A calibration graph was prepared by first recording the differential-pulse voltammogram of the blank and then by successive addition of ten aliquots of 40 μl of meloxicam standard solution (5.0×10^{-5} M) into the polarographic cell. Each voltammogram was recorded twice using a new mercury drop. The calibration graph was constructed by plotting the peak current against the corresponding concentration. All data were obtained at room temperature.

2.3.1. Determination of meloxicam in tablets

Ten tablets (Mobic 7.5 mg) were selected at random, thoroughly ground and mixed. An amount equivalent to a single tablet was dissolved in 5 ml of 0.01 M sodium hydroxide solution. A series of serial dilution with de-ionized water was then performed to give a final nominal concentration of 5.0×10^{-4} M meloxicam. After the non-dissolved excipients have settled down, then an aliquot of the clear supernatant liquor was transferred into a voltammetric cell containing 10 ml of BR buffer (pH 4.0) to yield a final concentration of 1.0×10^{-7} M meloxicam. The differential pulse voltammogram was subsequently recorded employing a scan rate of 5 mV s^{-1}. The content of the drug in tablet was determined referring to the regression equation.

3. Results and discussion

3.1. Differential-pulse voltammetry

The effect of pH on the voltammetric behavior of 5×10^{-6} M meloxicam was studied in 0.04 M Britton–Robinson buffer solution as supporting electrolytes using differential-pulse voltammetry. Fig. 1 shows some of the differential-pulse voltammograms obtained at a hanging mercury drop electrode (HMDE). A single reduction peak

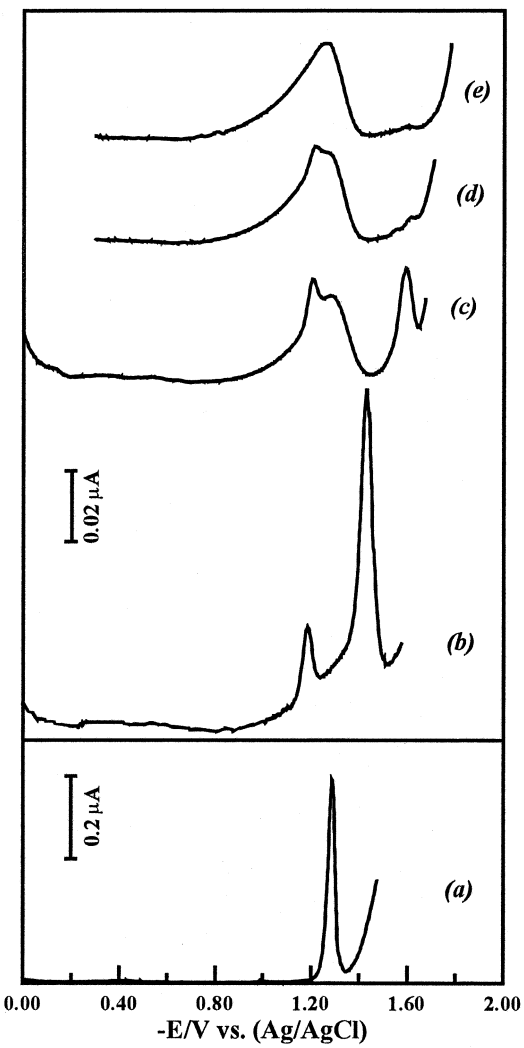


Fig. 1. Differential-pulse voltammograms of 5×10^{-6} M meloxicam in Britton–Robinson buffer solution of pH: (a) 4.0; (b) 6.0; (c) 7.0; (d) 8.0; and (e) 10.0.

(I_1) was observed within the pH range 2.0-4.0. Simultaneously, a new peak (I_2), at a less negative potential than that of (I_1) appears at pH >4.0. However, peak (I_1) decreases sharply with increasing pH and disappears completely at pH 8.0. The second peak (I_2) appears as unresolved pair of peaks at pH 7.0 and 8.0.

The peak potential of the first reduction step E_{p1} was shifted with increasing pH to more negative potentials by about 0.61 V per pH unit, up to pH 6.0. In the pH range 6.0–7.0, the slope of the plot E_{p1}–pH is 0.164 V per pH unit; above pH 7.0 it is 0.015 per pH unit (Fig. 2A). The i_1–pH plot (Fig. 2B) has the shape of dissociation curve of a monobasic acid with an inflection point at pH of ca. 5.5. The decrease of peak current i_1 with increasing pH was accompanied by an appearance of second reduction step at less negative potentials. The peak potential of the second reduction step shifted with increasing pH by 0.018 V per pH unit; in more alkaline solution, it became practically pH-independent.

Since meloxicam exhibits an acid–base dissociation or, keto–enol tautomerism [10] (Scheme 1 Step I → II), it was concluded that such process is responsible for the observed voltammetric behavior of meloxicam. Meloxicam is a zwitterion with enol function at pH <4.0, and anionic with keto form at pH >4.0. The keto form possesses a β-dicarbonyl function moiety. The peak process (I_1) may arise from the reduction of the enol form of meloxicam and the second peak (I_2) from the reduction of its keto form. When both enol and keto forms are present, two voltammetric signals are observed. Electrochemical reduction of the enol form of meloxicam takes place at a more negative potential than β-dicarbonyl function moiety present in the keto form and this may result from the increased stability of enol form due to the formation of a hydrogen bond, which makes the reduction process more difficult to occur.

3.2. Normal pulse voltammetry

Fig. 3 shows the normal pulse (NP) voltammogram for solution of 5.0×10^{-6} M meloxicam

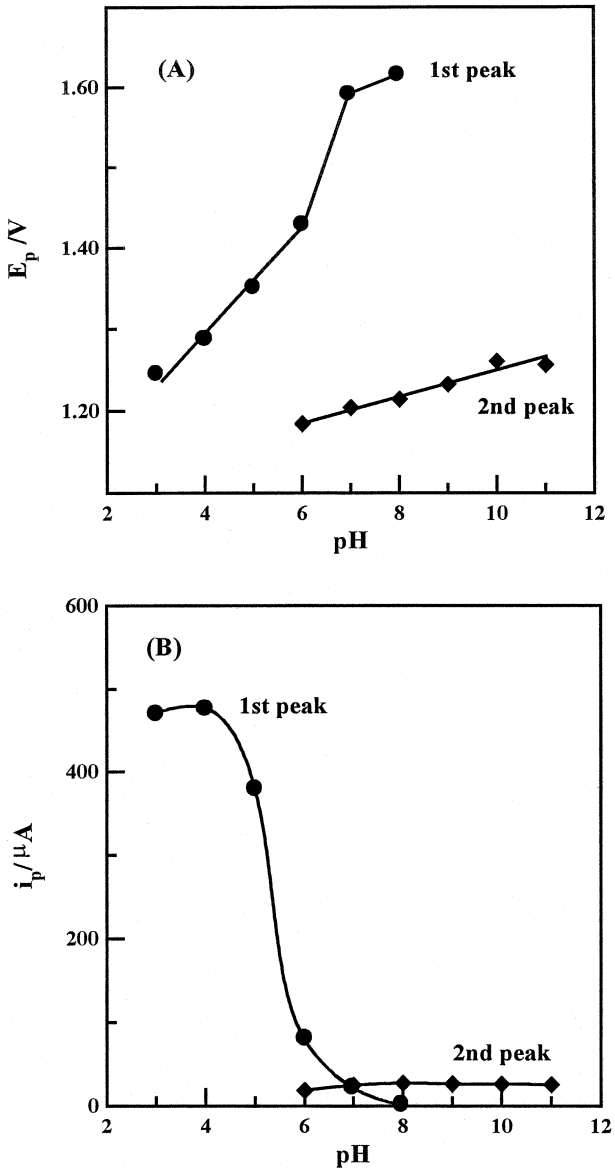


Fig. 2. The dependence of differential-pulse peak potentials (A); and peak currents (B) of 5.0×10^{-6} M meloxicam on pH.

in buffer solution of pH 4.0. The reduction process has characteristics of reactant adsorption since a peak rather than a sigmoidal curve is observed [11].

The plot of $-E$ against log $(i_d - i/i)$ for d.c. polarography (where i_d is the limiting current and E is the potential) of a 5.0×10^{-6} M meloxicam solution was linear with a slope of 0.032 V. For an irreversible system, the slope involves the transfer coefficient, α, and is equal to $-0.059/\alpha \times n_a$, where n_a is the number of electrons involved in the rate determining step. So, the number of electrons transferred in the reaction showed to be equal to two, a free radical one-electron transfer is not likely to occur.

The fact that the slope of the E_p versus pH plot corresponds to the $dE_p/dpH = -0.059/\alpha n_a \times m$ (where m is the number of hydrogen ion involved in the reaction) indicates that two protons are involved in the rate-determining step. The reaction seems to involve two electrons and two protons for the reduction process of the double bond in meloxicam molecule yielding a dihydrogen derivative (Scheme 1).

3.3. Cyclic voltammetry

To elucidate further the electrode reaction of meloxicam, a cyclic voltammogram at (HMDE) was recorded. As shown in Fig. 4, the cyclic

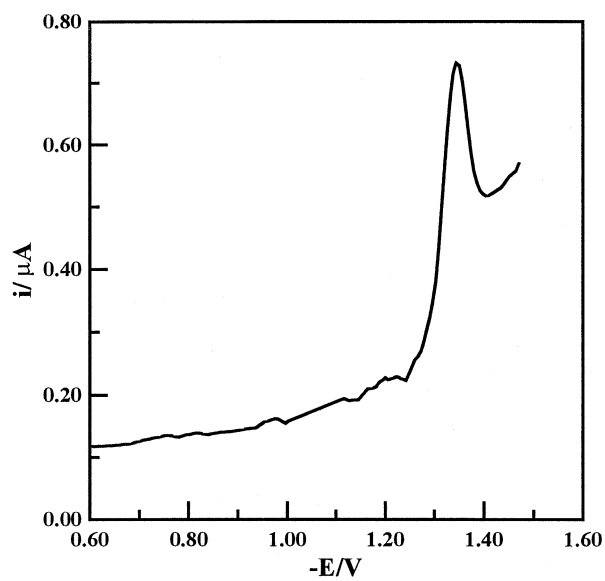


Fig. 3. Normal pulse voltammogram of 5.0×10^{-6} M meloxicam in Britton–Robinson buffer solution (pH 4.0), scan rate: 5 mV s^{-1}.

voltammogram of meloxicam in Britton–Robinson buffer solution of pH 5.0 exhibits a single cathodic peak, with no peak on the reverse scan, indicating the irreversible nature of the electrode reaction. The peak current changes linearly with scan rate (v) according to the equation $i_p = Av^x$. The x values 1.0 and 0.5 are expected for adsorption-controlled and diffusion-controlled reactions, respectively, [12,13]. For 5.0×10^{-6} M meloxicam solution, the regression of log i_p versus log v gave a slope value of 0.76 indicating that the reduction current had contributions from both diffusion and adsorption currents. The dependence of peak current of meloxicam on the potential scan rate is affected by the concentration of the drug. The x value decreases with increasing the concentration of meloxicam, indicating that the electrode process changes from being adsorption controlled to diffusion controlled. As scan rate was increased from 10 to 200 mV s^{-1}, the peak potential shifted towards more negative potential as expected for an irreversible reduction process. Furthermore, E_p shifted towards more cathodic values with the increase in the drug concentration indicating possible role of adsorption. The peak half-width of the cyclic voltammogram of the drug was determined and found to be 0.035 V. The αn_a value was calculated and found to be 1.77, which agreed well with the value obtained from d.c. polarography.

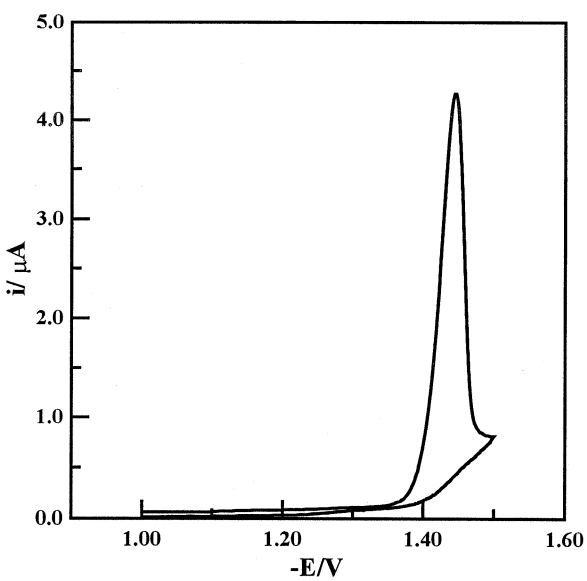


Fig. 4. Cyclic voltammogram of 5.0×10^{-5} M meloxicam in Britton–Robinson buffer solution (pH 4.0), scan rate: 100 mV s^{-1}.

3.4. Controlled potential electrolysis (CPE)

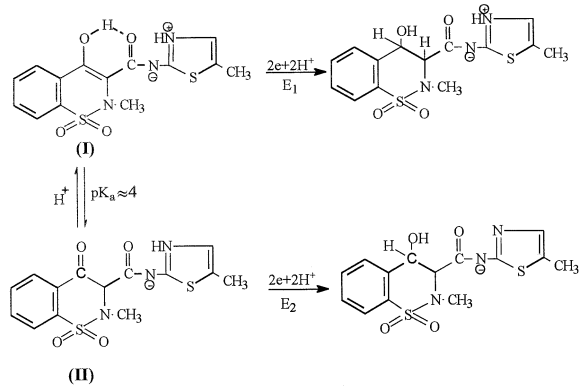
The CPE of meloxicam at stirred mercury pool electrode was carried out on 20 ml of 5.0×10^{-5} M meloxicam solution in a Britton–Robinson buffer of pH 4.0. The potential was controlled at -1.4 V (vs. SCE). During electrolysis the color of solution changed gradually from yellow to colorless, and there was no precipitate observed in solution or on the surface of the electrode. After completion of CPE, a net charge of 0.185 C was obtained, according to Faraday law, $n = 1.84 \approx 2$ can be obtained. At various time intervals both cyclic voltammogram and UV spectra were recorded. As the time of electrolysis increases, the reduction peak decreases, and no oxidative response was observed, indicating that the electroreduction of meloxicam is totally irreversible (Fig. 5). The fact that adsorption at 360 nm which is due to the enolic double bond in meloxicam disappears during the course of electrolysis suggests that the reduction occurs at this group in acidic media.

3.5. Reaction mechanism

Taking into account the results of pH effect, logarithmic analysis, cyclic voltammetry and coulometery studies, a reduction pathway for meloxicam at mercury electrode can be suggested (Scheme 1). The first reduction step (I_1) may be assigned to the reduction of the double bond in the enol form (I); while the second reduction step may correspond to the reduction of the carbonyl group of the keto form (II), to yield a saturated dihydrogen derivatives. Kauffmann et al. [9] proposed a two electrons–two protons process for the reduction of the double bond of the enol function in a structurally and pharmacologically similar drug, piroxicam (Scheme 1).

3.6. Analytical application

The influence of meloxicam concentration on the peak current in Britton–Robinson buffer solution of pH 4.0 using differential pulse voltammetry (pulse heights: 25 mV and scan rate 5 mV s^{-1}) is shown in Fig. 6. A linear range was observed for concentrations between 1.0×10^{-8} and 5.0×10^{-6} M; then the plot leveled off at higher concentration, as expected for a process that is limited by adsorption of analyte. The detection limit [14] (estimated as 3 s m^{-1}; s = standard deviation of blanks; m = slope of calibration straight line) was 2.9×10^{-9} M. The



Scheme 1. Electrode reaction pathway.

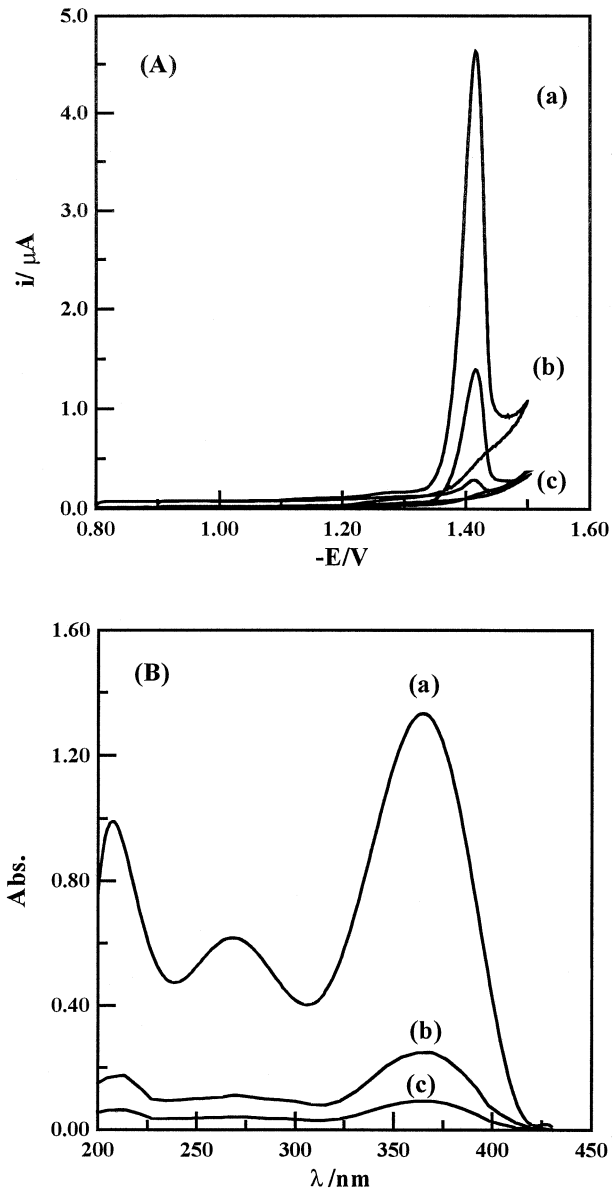


Fig. 5. (A) Cyclic voltammograms; and (B) UV absorption spectra obtained during controlled potential reductive electrolysis of meloxicam in Britton–Robinson buffer solution (pH 4.0) at times: (a) 0, (b) 15 and (c) 30 min after commencement of electrolysis.

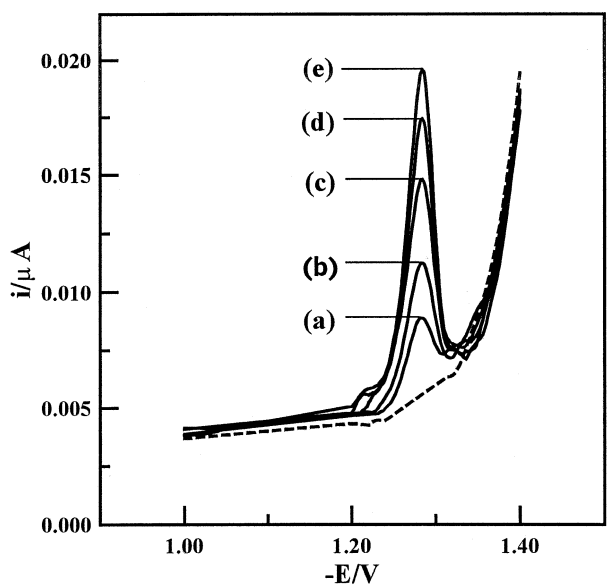


Fig. 6. Differential-pulse voltammograms for different meloxicam concentrations in Britton–Robinson buffer solution (pH 4.0), (a) 2.0×10^{-8} M; (b) 4.0×10^{-8} M; (c) 6.0×10^{-8} M; (d) 8.0×10^{-8} M; and (e) 1.0×10^{-7} M.

Table 1
Results of meloxicam analysis in tablets using DPV and UV methods

Sample number	Average amount found ± S.D. (mg per tablet)[a]	
	DPV	UV
1	7.45 ± 0.089	7.30 ± 0.131
2	7.30 ± 0.120	7.25 ± 0.159
3	7.54 ± 0.078	7.40 ± 0.089
4	7.40 ± 0.103	7.50 ± 0.081
5	7.43 ± 0.099	7.29 ± 0.111
Mean ± S.D.	7.42 ± 0.087	7.35 ± 0.101
$t_C = 1.17$	$t_T = 2.31$ ($P > 0.05$)	

[a] Each value is an average of three determinations.

precision of the determination of meloxicam is excellent; at a concentration of 2.0×10^{-8} M the relative standard deviation (R.S.D.) was 4.2% ($n = 10$).

The developed differential-pulse voltammetric method was applied for the determinations of meloxicam in its tablet form Mobic® 7.5 mg per tablet (supplied by boehringer Ingeheim, International GmbH, Ingeheim am Rhein, Germany). There is no need for any extraction procedure before voltammetric analysis. A spectrophotometric method [6] was employed for comparison to evaluate the validity of the developed method. Table 1 gives the results obtained using the two methods for five separate determinations starting from different groups of tablets of meloxicam. The results were compared by a student's t-test. The calculated t-values did not exceed the tabulated values, indicating that there was no significant difference between the methods. The sensitivity of spectroscopic method was much lower than that of the developed DPV method. The detection limit obtained by DPV method was 0.702 ng ml^{-1} compared with 0.9 μg ml^{-1} for spectroscopic method.

4. Conclusion

It can be concluded that the reduction of meloxicam is an irreversible process with adsorption characteristics. The differential-pulse voltammetric method described here, is sensitive, rapid, reliable and simple to perform, and thus suitable for analysis of pharmaceutical preparations of meloxicam drug.

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