Potentiometric and HPLC Methods for the Determination of Meloxicam in Bulk and Drug Formulations

¹Mohammed A. El-Ries, ²Farida El-Dars, ¹Fekria M. Abou Attia, ²A.B. Farag and ¹Ayat M. Abd El-Hamed

¹National Organization for Drug Control and Research (NODCAR), 35521, Giza, Egypt

²Department of Chemistry, Faculty of Science, Helwan University, Helwan, 11795, Egypt

Abstract: Purpose: The present study describes highly sensitive, precise, economical and quick potentiometric and HPLC methods for the determination of meloxicam in pharmaceutical formulations. **Methods:** The first method is a potentiometric one (I) where the titration of the drug with N-Bromosuccinimide (NBS) and N-Bromophthalimide (NBP) is involved in acid medium and the end point is determined using a platinum indicator electrode. The second one is a sensitive and selective HPLC method (II). The method is applied using a mobile phase consisted of acetonitrile: H₂O:phosphoric acid (70: 30: 0.1, v/v/v) on a 150×4.6 mm C₁₈ column and detection wavelength at 360 nm. The intra-day, inter-day precision and accuracy, recovery, stability, reproducibility and sensitivity of the proposed methods are presented. **Results:** Method (I) is valid over the concentration range 0.176-1.406 mg Mel with mean percentage accuracy 100.26 and 100.08% for NBS and NBP, respectively. The content of the mobile phase in method (II) is simple in preparation, does not depend on adjusting pH and is found to be fast (single sharp and symmetric peak is obtained after retention time ~2.1 min) at room temperature. In addition, this system provides a linear response over the concentration range 5-200 µg mL⁻¹ Mel, with mean percentage accuracy of 99.41%. The intra-and inter-day relative standard deviation over the entire concentration range is less than 1.5%. **Conclusion:** The proposed methods are successfully applied to pharmaceutical dosage forms and the results are in agreement with those given by the official method.

Key words: Meloxicam, Potentiometry, N-Bromosuccinimide, N- Bromophthalimide, HPLC, Commercial formulations

INTRODUCTION

Meloxicam (Mel) (4-hydroxy-2-methyl-N-{{5-methyl-2-thiazolyl}}-2-H-1, 2-benzothiazine 3-carboxamide 1,1-dioxide) (Fig. 1) is a Non-steroidal Anti-inflammatory Drug (NSAID) of the oxycam class. The drug is effective in the treatment of rheumatoid, arthritis, osteoarthritis and related conditions (Martindale, 2002).

A review of analytical techniques for determination of oxycams, nimesulide and nabumetone covers the time period from 1990 to 2008, in which analytical methods

including all types of chromatographic, spectrophotometric and voltammetric techniques are reported (Jan and Starek, 2009). The literature survey reveals that HPLC methods (Yuan, Chen and Zhong, 2007; Desai and Amin, 2008; Sinha *et al.*, 2009; Bandarkar and Vavia, 2009; Lee *et al.*, 2009; Eroglu *et al.*, 2010; Mahmood *et al.*, 2010; Radia and Moulay-Hassan, 2010), are the most commonly used methods for the estimation of Mel in human plasma and pharmaceutical forms. Other analytical techniques have been reported for the analysis of Meloxicam in formulations and biological samples, such as spectrophotometry (Liu *et al.*, 2005; Al-Nimer and Ali, 2009; Huazhen *et al.*, 2009; Al-Kindy *et al.*, 2010); Thanh *et al.*, 2010); Dhandapani *et al.*, 2010), voltammetry (Cheng *et al.*, 2006; Farhadi and Karimpour, 2007) and polarography (Acuna *et al.*, 2004).

While HPLC methods continue to play a major role in the development of analytical procedures applying in laboratory for the determination of pharmaceutical

Fig. 1: Structure of meloxicam

compounds, NBS has been widely used as an oxidizing agent in acidic media (Kumar and Inrasenan, 1988), Titrimetric methods for the determination of some sulpha drugs using N-bromophthalimide and N-bromosaccharin and more extensively, it has been used in the determination of a vast number of compounds, especially those of pharmaceutical interest.

Up till now, there has been no publication on determination of Meloxicam using potentiometric titration with N-halo compounds. In this study, in addition to HPLC method, we have developed a selective potentiometric titration method based on using NBS and NBP as oxidizing agents. This reaction is studied in order to intercept the mechanism and to understand the redox chemistry of NBS and NBP with Mel in such media. The proposed methods are simple, accurate and reproducible indicating their suitability for routine determination of Mel in bulk and dosage forms.

MATERIALS AND METHODS

Meloxicam is obtained from (Delta Pharma Company) 99.95% purity (USP, 2009) and is used as received. Preparations containing Meloxicam (Melocam tablets labeled to contain 15 and 7.5 mg/tablet, Amoun Pharma, Cairo, Egypt) and (Mexicam tablets labeled to contain 15 and 7.5 mg tablet, Delta Pharma, Cairo, Egypt) are purchased from local sources. NBS and NBP are obtained as reagent grade chemicals form (Alfa Aesar).

All chemicals used are HPLC analytical reagent grade; methanol, acetonitrile (Lab Scan Analytical Sciences), ortho-phosphoric acid (Fisher, USA), sulfuric, hydrochloric, acetic, perchloric acids BDH (UK) and sodium hydroxide (Loba Chemie). Double distilled water is used for preparing solutions and cleaning all glass equipment. HPLC method is applied using a mobile phase consisting of acetonitrile: H₂O: phosphoric acid in ratio of (70:30:0.1v/v/v), this mixture is filtered and degassed before application.

HPLC analysis is conducted using Agilent 1200 which is equipped with quaternary pump, variable wavelength detector (UV/VIS Detector), Agilent 1200 series vacuum degasser and a manual injector 20 μ L loop. The compounds are measured on a 150 $\times$ 4.6 mm C₁₈ column (Agilent-Eclipse XDB 5 μ m particle size) that is conditioned at 25 $\pm$ 5°C with an injection volume of 20 μ L. Potentiometric titrations are carried out using a JENWAY pH/mV-meter (Model 4510) with a combined platinum-saturated calomel electrode.

Preparation of standard solutions: Standard solutions of Meloxicam 1×10^{-3} mol. L⁻¹ for potentiometric method (I)

and 1 mg mL⁻¹ for HPLC method (II) are prepared by dissolving the required amount of drug in 50:50 (%v/v) methanol: 0.5N NaOH solution, sonicated for a minimum of 20 min and the solutions are filtered. For HPLC method (II), working standard solution of Mel (0.1 mg mL⁻¹) is prepared by diluting 5mL from 1 mg mL⁻¹ standard solution into 50mL volumetric flask with methanol. NBS solution (2×10^{-3} M) is prepared by dissolving 17.79 mg of NBS in 50 mL water while (2×10^{-3} M) NBP solution was prepared by dissolving 23.09 mg of NBP in 25 mL acetic acid and, after mixing, 25 mL of water are added to the 50 mL mark and were standardized according to (Barakat and El-Wahab, 1954). These solutions are stored in amber colored bottles and refrigerated at 4°C.

Preparation of marketed formulations: To eliminate the inconsistency of weight, five tablets of Melocam or Mexicam are crushed and ground to powdered in an agate mortar. 1×10^{-3} mol L⁻¹ and 1 mg mL⁻¹ are prepared as under (Preparation of Standard Solutions). For HPLC method, 5 mL exactly measured of the filtrate into 50 mL volumetric flask are transferred and diluted to volume with methanol to get final concentration of 0.1 mg mL⁻¹.

Analytical method validation

Potentiometric Method (I): 0.5-4.0 mL of the standard Meloxicam solution (1×10^{-3} M) are accurately measured and transferred into 50 mL volumetric flask. Each solution is made acidic by adding 1 mL of (20% HCl or 20% CH₃COOH) for NBS and NBP, respectively, after mixing, it is completed to the 50 mL mark with H₂O. The content of these solutions is titrated with 2×10^{-3} M NBS or NBP, respectively and the amount of NBS or NBP solution equivalent to the reacted drug amount is calculated.

HPLC method(II): Aliquots of standard Meloxicam solution (1 mg mL⁻¹) are taken in calibrated flasks and are made up to the volume with methanol to obtain the concentration range of 5-200 μ g mL⁻¹. The linearity experiment is carried out in triplicates to ascertain accuracy and precision of the method. Samples are injected at intervals of 3 min apart of each concentration and the average peak areas are calculated then plotted versus drug concentrations. Statistical and regression analysis of the calibration data are recorded and fitted to the equation $y = a+bx$. In order to evaluate the applicability of the method to pharmaceutical preparations, the flow rate is set at 2 mL min⁻¹ and the detection wavelength at 360 nm. The drug is measured on a 150 $\times$ 4.6 mm C₁₈ column (Agilent-Eclipse XDB 5 μ m particle size) that is conditioned at 25 $\pm$ 5°C. the injection volume is 20 μ L.

The above methods are applied to the analysis of Mel containing tablets.

RESULTS AND DISCUSSION

Potentiometric methods (I): Taking advantage of the rapid oxidation and bromination reaction of NBS and NBP with different aromatic compounds (Mathur and Narang, 1975), a quantitative and accurate potentiometric method is developed for the determination of the studied drug. A study of the optimum conditions is carried out and the stoichiometry of the reaction of the Mel with NBS or NBP is ascertained in acidic medium. The conditions optimized are the choice of medium for a quantitative reaction to proceed towards completion and the amount of reagent added.

Effect of acids: Figure 2 shows the effect of using different acid media (hydrochloric, sulphuric, acetic, perchloric, acetic and phosphoric acid) upon the reaction between the drug and NBP (as an example), using a suitable ratio [drug]:[reagent] of 1:2. The data indicates that reproducible and stoichiometric results are obtained using HCl and CH_3COOH as medium for the Mel reaction with NBS and NBP reagent, respectively. As shown in the figure, a sharp inflection lying in the immediate vicinity of the expected end point using hydrochloric and acetic acid more than the other acids is found in the case of NBS and NBP, respectively. So, hydrochloric and acetic acid are preferred for carrying out the potentiometric titration of Mel using NBS and NBP, respectively.

Also, the results obtained reveals that the end point is unaffected by the addition of (1-3 mL) of any acid used as shown in Fig. 3. However, it is observed that the use of 1 mL from 20%v/v HCl or CH_3COOH causes a sharp inflection at the expected end point for NBS and NBP, respectively. Thus, 1 mL HCl or CH_3COOH is maintained during the current investigations.

Effect of NBS and NBP reagents: For the quantitative determination of Mel, the effect of NBS and NBP concentration is tried and 2×10^{-2} M, is chosen as an optimum concentration to achieve a constant and highly stable potential reading during the mixing time. Concentration less than this leads to unstable readings and more time is needed to obtain constant values.

Also arising temperature does not accelerate the oxidation process but tends to cause inaccurate results and creates difficulty in detecting the end point, because NBS or NBP decomposes at high temperature, thus room temperature is the most suitable.

Fig. 2: The effect of acids on the titration of 2 Meloxicam with NBP reagent [Meloxicam] = 1×10^{-3} M, [NBP] = 2×10^{-3} M and [Acid] = 20% v/v

Fig. 3: The effect of HCL concentration on the titration of Meloxicam with NBS reagent [Meloxicam] = 1×10^{-3} M, [NBS] = 2×10^{-3} M and [Acid] = 20% v/v

Based on the obtained experimental results and the chemical property of Mel, NBS and NBP, the reaction between Mel with each of NBS and NBP may take place via the attack on the respective NH and OH groups of the drug (Mathur and Narang, 1975). The first molecule of NBS or NBP may be consumed in the bromination of Mel NH group while the second one in the bromination of OH group or vice versa, to give the dibromo derivative of the drug as previously reported (El-Ries *et al.*, 2003).

Potentiometric titration of meloxicam: The reaction is found to be quantitative with a stoichiometry of 1:2 (Mel: NBS or Mel: NBP) for the investigated concentration range of 0.176-1.406 mg Mel for NBS and NBP, in hydrochloric and acetic acid, respectively. The titration curves of drug show one well-defined S-shaped

Fig. 4: Typical titration curves for potentiometric determination of the end point of different concentrations of Meloxicam, against NBS reagent. [Meloxicam] = 1×10^{-3} M and [NBS] = 2×10^{-3} M

Fig. 5: Differential curves for the potentiometric titration of different concentrations of Meloxicam against NBP reagent. [Meloxicam] = 1×10^{-3} M and [NBP] = 2×10^{-3} M

stoichiometric end point using a Pt-electrode as an indicator electrode. The titration data is given in Fig. 4 and 5 for NBS and NBP, respectively. Figure 4 represents the plot of E vs. volume (mL) of NBS titrant for the determination of Meloxicam. The first differential curves which represent the plot of $\Delta E/\Delta V$ vs., mean volume of NBP titrant are characterized by sharp inflections lying in the immediate vicinity of the expected end points (Fig. 5). These sharp inflections permit the accuracy of the end point which indicate that NBS and NBP can be used as reagents for a sensitive determination of Meloxicam.

Analytical parameters

Potentiometric method: To ascertain the accuracy and precision of the proposed methods, three replicate

Table 1: Summary of validation data for the proposed methods for the analysis of Meloxicam in bulk solution

Parameters	Methods		
	NBS reagent	NBP reagent	HPLC method
Range of Concentration	0.176-1.406 mg	0.176-1.406 mg	5-200 μ g
Correlation Coefficient	1.000 ^a	0.998 ^a	0.999
Slope	1.006 ^a	1.007 ^a	66.021
Intercept	0.002 ^a	0.001 ^a	67.13
N	3	3	3
Mean $\pm$ RSD%	100.26 $\pm$ 0.73	100.08 $\pm$ 0.68	99.41 $\pm$ 0.49%
SD	0.73	0.68	0.49
SE	0.42	0.39	0.28

^aObserved vs. theoretical values

determinations using four different concentration of the drug are performed. The mean recovery values and the Relative Standard Deviation (RSD) are 100.26 $\pm$ 0.73 and 100.08 $\pm$ 0.68% for NBS and NBP, respectively and the standard error are presented in Table 1. These data indicate high accuracy and precision of the methods. In order to establish whether the proposed potentiometric methods exhibited any fixed or proportional bias, a simple linear regression (Miller and Miller, 1993) of the observed drug concentration against the theoretical values is obtained. The slope and intercept of the regression line was 1.006 and 0.002 for NBS and 1.007 and 0.001 for NBP while the correlation coefficient is 1.000 and 0.999 for NBS and NBP, respectively.

HPLC method: The experiment is applied to various parameters such as efficiency resolution and peak symmetry. In order to avoid ion suppression induced by endogenous substances, the mobile phase for the reaction is selected after several trials with acetonitrile, water and phosphoric acid in various ratios and at various pHs. However, the optimal mobile phase is found to be consisting of a mixture of 70: 30: 0.1 (v/v/v) acetonitrile: H₂O: phosphoric acid.

Meanwhile, under the present chromatographic conditions, the mobile phase provides good linearity for the studied concentration, the run time between each sample is 3 min and the retention time is 2.1 min for the drug.

For quantitative analysis using HPLC method, the linearity experiment is carried out in triplicates to ascertain its accuracy and precision. The method exhibits a good linear response for the range of concentrations from 5-200 μ g mL⁻¹ with coefficient of determination 0.999. Typical standard curve is [y = 66.0 x + 67.13, r² = 0.999] where y is the area and x is the concentration of the drug. While LOD/LOQ parameters are not a requirement for drug assay; it is always useful to demonstrate that the analysis is being conducted in a region which is above the LOQ value. The limits of detection (LOD = 3SD/b) and

quantification ($LOQ = 10SD/b$) are calculated according to ICH (Aeri *et al.*, 2010). The values are derived from the Standard Deviation of the response (SD) and the slope of calibration curves (b) and are found to be 0.04 and 0.14, respectively.

The intra-day accuracy and precision of the assay is evaluated by analyzing nine samples of the drug at concentrations (80, 100 and 150 $\mu\text{g mL}^{-1}$) and was found to ranged from 99.87-102.02 and 0.76-1.12%, respectively. The inter-day accuracy and precision is determined over three days. The inter-day accuracy range from 98.21-100.08% while relative standard deviation obtained are ranged from 0.84-1.3%.

Stability of the standard solution: For short-term stability determination, standard solution is monitored by analyzing standard solution aged at ambient temperature and ambient light against freshly prepared standards. Samples are pretreated and analyzed as abovementioned. The mean recoveries ranges from 99.89-100.01%. These results indicate reliable stability behavior under the experimental conditions.

The ruggedness of the method is also proved by using two chromatographic columns from two different suppliers. The mean percentage found ($n = 9$) were 99.57 and 99.47% while the precision is 1.45 and 0.53% for Agilent-Eclipse XDB C_{18} 150 $\times$ 4.6 mm, 5 μm and Luna-Phenomenex C_{18} 150 $\times$ 4.6 mm, 5 μm column, respectively.

Application to pharmaceutical formulations: Specificity is the ability to assess clearly the analyte in the presence of components which may be expected to be present. The proposed methods (potentiometric and HPLC) are applied to the analysis of pharmaceutical formulations of the drug (Meloxicam and Mexicam tablets). The fact that the shapes of the potentiometric titration curves of bulk drug and its formulations are nearly the same, proves that the excipients which may be present in the pharmaceutical formulations has no effect on the determination of the drug applying the proposed method.

As shown in Fig. 6 and 7, the HPLC chromatogram of bulk Meloxicam is nearly the same as for Melocam tablet without any considerable changes in retention time, so it recommends that the proposed HPLC method is suitable for determination of the drug.

The results of the assay of meloxicam in pharmaceutical formulations are compared with those obtained by the official method (USP, 2009). Statistical comparison of the results is performed with regard to accuracy and precision using the Student's t-test and F-tests (Table 2). At 95% confidence level, the calculated

Fig. 6: Chromatogram of meloxicam

Fig. 7: Chromatogram of melocam tablets

t- and F-values does not exceed the theoretical values, indicating that there is no significant difference between the proposed methods and the official method with regard to accuracy and precision. The data obtained also shows good recoveries and low standard deviations.

The recovery studies of standard additions to commercial pharmaceuticals are also carried out to provide further support for the validity of the method. The related data are given in Table 3. These results also confirm the precision and the validity of the proposed method.

In pharmaceutical formulations analysis, it is necessary to test the selectivity towards excipients and fillers added to pharmaceutical preparations. The proposed methods are applied to the analysis of Meloxicam in tablets and the results are compared with those obtained by the official method. Commonly encountered excipients such as starch, talc, glucose, alginate and stearate are not interfere with the proposed methods. Statistically, Table 2 indicates that the

Table 2: Determination of Meloxicam in some pharmaceutical preparations applying the proposed methods

Method	Recovery%±SD			
	Melocam tablets		Mexicam tablets	
	(7.5 mg)	(15 mg)	(7.5 mg)	(15 mg)
NBS Mean Recovery	100.74±0.60	99.91±0.46	98.99±0.21	100.04±0.38
N	3	3	3	3
SD	0.60	0.46	0.21	0.38
SE	0.34	0.26	0.12	0.22
t-value	1.94	1.94	1.94	1.94
F-value	4.29	2.52	1.91	1.72
NBP Mean Recovery	99.96±0.18	100.06±0.32	100.13±0.77	99.96±0.98
SD	0.18	0.32	0.77	0.98
SE	0.10	0.18	0.44	0.56
t-value	0.86	0.86	0.86	0.86
F-value	2.59	1.22	7.06	11.43
HPLC	100.10±1.09	100.01±0.91	99.89± 0.59	99.12±0.49
SD	1.09	1.09	1.09	1.09
SE	0.63	0.53	0.34	0.28
t-value	0.18	0.04	0.26	2.66
F-value	14.14	9.86	4.14	2.86
Official ⁽²⁾ HPLC method	99.99±0.29			

The tabulated values of t- and F-tests at 95% confidence limit = (2.77) and (19), respectively

Table 3: Accuracy of the proposed potentiometric methods by recovery studies of standard addition to some pharmaceutical preparations

Pharmaceutical preparation	Reagent	Taken (mg)	Added (mg)	Found (mg)	Recovery
Melocam tablets (15mg)	NBS	0.3	0.2	0.498	99.6
		0.3	0.4	0.710	101.4
		0.3	0.6	0.903	100.3
		0.3	0.8	1.079	98.1
					99.85
Average					1.221
RSD%					
Mexicam tablets (15mg)	NBP	0.4	0.2	0.611	101.833
		0.4	0.4	0.802	100.250
		0.4	0.6	1.01	101.000
		0.4	0.8	1.197	99.750
					100.708
Average					0.67
RSD%					

calculated values of t and F test do not exceed the theoretical values. Therefore, there is no significant difference in the mean recoveries and precision between the proposed and official method.

CONCLUSION

In conclusion, the described methods are suitable for the determination of Meloxicam in pure form and in formulated products. The proposed potentiometric method have some specific advantages, that its oxidants are the most effective and stable brominating agent colorless, easily available, less expensive, provided higher sensitivity and they have the ability of being dissolved in the aqueous and non-aqueous solvents.

The proposed HPLC method is precise and accurate, selective, in addition, the mobile phase of acetonitrile, H₂O and acetic acid in the ratio of 70: 30: 0.1 (v/v/v) without the need to adjust the pH, is found to be ideal for the analysis of Mel.

The experimental data are considered satisfactory and indicate specificity, linearity, accuracy, repeatability

and sensitivity of the developed methods. These results indicate that these methods are suitable for routine quality control analysis.

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