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Original Research Article

Colorimetric Determination of Meloxicam in Bulk and Tablet Dosage Forms

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Abstract

Purpose: Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) which belongs to the oxicam class used in the management of pain and inflammation. This research aims to develop a simple, sensitive, accurate, reproducible and affordable method of determination of meloxicam in bulk and tablet dosage forms.

Methods: The method involves oxidation of meloxicam (in sodium hydroxide) with potassium permanganate at room temperature and determination of the wavelength of maximum absorption (λmax) of the oxidized product. The reaction conditions were optimized and the developed method was used to determine the percentage content of the drug in bulk and tablet dosage forms. The validation of the method was carried out using the guideline designated by the International Council for Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH).

Results: The results show that the wavelength of maximum absorption of the oxidized product was 610 nm and all measurements were taken at this wavelength. The equation of regression line for the Beer's plot was: $A = 0.067C + 0.017$ ($R^2 = 0.9965$) and the calibration plot was linear over a concentration range of 1.56 – 9.37 µg/mL with molar absorptivity of 2.3820 × 10 4 L/mol/cm. The limit of detection (LOD) and limit of quantification (LOQ) are 0.3238 and 1.0930, respectively, while the relative standard deviation (RSD) in the intra and inter-day analyses were between 0.16 - 0.18% and 0.21 - 0.29%, respectively.

The method was applied for quantitative analysis of meloxicam in tablet dosage form and the percentage recovery was found to be within the range of 97.11 – 100.89%.

Conclusion: The proposed method was considered accurate, simple and can produce reproducible results. This method can be used for the routine assay of meloxicam in bulk and tablet formulation.

Keywords: Absorbance, meloxicam, oxicam, calibration, quantification, recovery

Introduction

Meloxicam was synthesized by Boehringer - Ingelheim, it was found to be a potent anti-inflammatory drug with a prolonged duration of action and reduced ability to induce gastrointestinal ulceration due to its preferred affinity for COX-2 enzymes over COX-1 enzyme at low dose [1].

Gastrointestinal irritation remains the major side effect of most NSAIDs due to their acidic nature and ability to inhibit the COX enzyme which is gastro-protective [2]; however, this effect is greatly reduced with meloxicam when compared with other NSAIDs of the same class such as piroxicam, tenoxicam and other COX-1 non-selective NSAIDs. This is due to its preferential affinity for COX-2 enzyme over COX-1 at therapeutic dose [3].

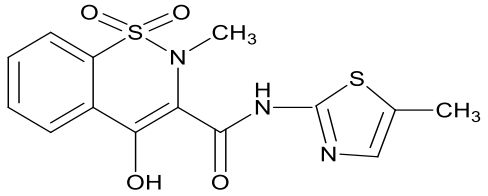

Figure 1: Chemical structure of meloxicam

Meloxicam has the following properties; molecular weight: 351.4 g/mol, boiling point: 581.3℃, melting point: 254℃ and very slightly soluble in methanol. Practically insoluble in water, with higher solubility observed in strong acids and bases. It has two ionisable functional groups, the 4-hydroxyl group of the thiazine and the N1 of the thiazolyl substituent [4].

A literature survey has revealed several methods for the determination of meloxicam and they include the titrimetric method with the most common being the non-aqueous titration. Other methods reported are potentiometric titration [5], UV-spectrophotometric methods [6-11], Visible spectrophotometry [12-17], Near infra-red spectroscopy [18], Voltammetry [19-21], Fluorescence spectrometry [19], Thin layer chromatography (TLC) [22] and High Performance Thin Layer Chromatography (HPTLC) [23,24].

The use of HPLC for the assay of meloxicam in biological fluids and pharmaceutical preparations has also been reported [25-35]. Liquid chromatography-mass spectrometry (LC-MS) [36-38]. Flow Injection (FI) Spectrometry [39], Chemiluminescence [40,41] and microbiological method [42]. Other methods such as capillary zone electrophoresis (CZE) [43] and Polarography [44] have also been reported.

Although several methods have been used for the determination of meloxicam in pharmaceutical formulations, each of these methods either requires the use of expensive reagents that are not readily available or sophisticated equipment (e.g. HPLC) that is expensive and requires an expert to operate coupled with the fact that they are not easy to maintain in developing countries like Nigeria.

This study aims to develop a simple, accurate, sensitive, cost-effective, readily applicable and reproducible colorimetric method of analysis of meloxicam in a bulk and pharmaceutical dosage form as well as compare the developed method with a reported method.

Methods

All the reagents used in this study were of analytical grade; potassium permanganate (Scharlau, Spain), Sodium hydroxide (Lobachemie, India), Chloroform (Lobachemie, India), Ferric chloride (Burgoyne Burbidges & Co., India. Meloxicam used for this study was a donation from Cipla Limited, India. Meloxicam tablets were purchased from different pharmacies in Benin City, Edo state, Nigeria.

Preparation of standard solutions

A 0.1 N solution of sodium hydroxide was prepared by dissolving 1.0 g of pellets in 100 mL of distilled water and further made up to a volume (250 mL) with more distilled water. A 0.02 N of potassium permanganate was also prepared by dissolving 0.0316 g of potassium permanganate in 20 mL of distilled water, transferred into a 50 mL volumetric flask and distilled water was added to make it up to the 50 mL mark.

Meloxicam (0.1 g) was weighed into a 100 mL beaker and dissolved by the addition of 20 mL of 0.1 N sodium hydroxide; the solution was transferred into a 100 mL volumetric flask and 0.1N sodium hydroxide was added to make it up to 100 mL mark. 1.25 mL of the stock solution was transferred using a micropipette into a 100 mL volumetric flask and 0.1 N sodium hydroxide solution was added to make up to the 100 mL mark. This produced the 12.5 µg/mL stock solution.

An amount (2.5 g) of ferric chloride was dissolved in 30 mL of distilled water and transferred into a 50 mL volumetric flask. 1 mL of concentrated hydrochloric acid was added; more distilled water was added to make up to 50 mL.

Determination of wavelength of maximum absorption

A volume (1.0 mL) of the stock solution (12.5 µg/mL) was transferred into a test tube; 1 mL of 0.01 N Potassium permanganate was added. The mixture was allowed to stand for 20 minutes after which 2 mL of 0.1 N NaOH was added to the resulting green-coloured solution which was scanned between a wavelength range of 200 – 800 nm to obtain the wavelength of maximum absorption (λmax) after a baseline correction using the blank solution (1.0 mL of 0.01 N Potassium permanganate and 2.0 mL of 0.1 N NaOH).

Optimization of the concentration, the volume of potassium permanganate (KMnO4) and concentration of sodium hydroxide

Optimization was carried out by varying the concentrations of KMnO4 (0.005 - 0.03N) in the above method and the absorbance taken at 610 nm while the optimization of the volume of KMnO4 was done by using a range of volume (0.5 - 1.0 mL) of 0.02 N KMnO4 in the above procedure. Optimization of NaOH concentration was done by preparing different concentrations of NaOH ranging from 0.05- 0.5 N and the above method was repeated.

Effect of temperature on the absorbance of meloxicam

A volume (1.0 mL) of the stock solution of meloxicam solution, 0.7 mL of 0.02 N KMnO4 and 2.3 mL of 0.1 N NaOH were transferred into a test tube. The resulting solution was heated in a water bath set at 37°C for 5 minutes and allowed to cool for 20 minutes. The absorbance of the solution was taken at 610 nm wavelength against the reagent blank and recorded. This procedure was repeated but the duration of heating was varied (25, 45, 50, 60, and 90°C) and the absorbance was noted at each time.

Effect of reaction time on the absorbance of meloxicam

A similar procedure as above was carried out with the exclusion of heat and varying the reaction time (10, 15, 20, 25, 30, 35 and 40 minutes). The absorbance was noted at each time.

Preparation of calibration plot for meloxicam

Using the optimized conditions, aliquots (0.5, 1.0, 1.5, 2.0 and 2.5 mL) of stock solution meloxicam solution were transferred into a series of test tubes, 0.7 mL of 0.02 N $KMnO_4$ was added and the resultant solution was allowed to stand for about 30 minutes. The volume was made up to the 4.0 mL mark with 0.1 N NaOH and the absorbance of the resulting green-coloured solution was measured at 610 nm against the reagent blank, thereafter, a plot of absorbance against concentration was taken.

Recovery of meloxicam from standard solution

A calibration curve was plotted by using the procedure described above. Aliquots (0.75 mL, 1.25 mL, 1.75 mL, and 2.25 mL) of the drug stock solution were measured and transferred into a series of test tubes and treated as above. The concentrations of the recovery studies were interpolated from the already prepared Beer's plot.

Recovery of meloxicam from standard solution

A calibration curve was plotted by using the procedure described above. Aliquots (0.75 mL, 1.25 mL, 1.75 mL, and 2.25 mL) of the drug stock solution were measured and transferred into a series of test tubes and treated as above. The concentrations of the recovery studies were interpolated from the already prepared Beer's plot.

Method validation

The developed analytical method was validated using the method prescribed by the International Council for Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use [45].

Determination of percentage content of meloxicam in tablet dosage forms

A total number of twenty tablets of meloxicam were accurately weighed and reduced to powder; an amount equivalent to 0.10 g of meloxicam was weighed and transferred into a 100 mL volumetric flask, 20 mL of chloroform was added and the content of the flask was thoroughly mixed, additional 20 mL of chloroform was added to the mixture which was then shaken and filtered using a Whatman No. 41 filter paper. The filtrate was allowed to dry and 30 mL of 0.1 N NaOH was added to the precipitate and stirred using a glass rod until a clear solution was obtained.

The solution was then transferred into a 100 mL volumetric flask and more 0.1 N NaOH was added to make up to the volume to give a stock solution of 1.0 mg/mL concentration. The stock solution (1.0 mg/mL) was further diluted to obtain concentration of 12.5µg/mL (working solution). This solution was assayed using the procedure described for the recovery of meloxicam from standard solution. Same procedure was used for all the different brands of meloxicam.

Assay of meloxicam using the reported method

A previously reported method by [8] was used to assay the various brands of meloxicam and the results statistically compared with the results from the developed method.

Statistical analysis

All the data obtained from the two methods were compared by been subjected to Student t-test statistical analysis to test for significance of difference. $P < 0.05$ was considered to be significant.

Results

Results obtained from the investigation of the wavelength of maximum absorption (λ_{max}) before and after oxidation of pure meloxicam solution show that there was a bathochromic shift from 364 nm to 610 nm and the results are shown in Figures 2 and 3, respectively.

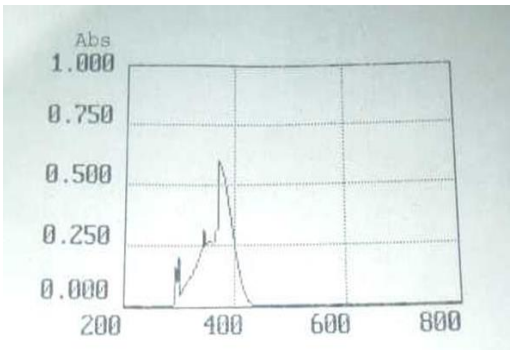

Figure 2: Spectrum of meloxicam solution before oxidation

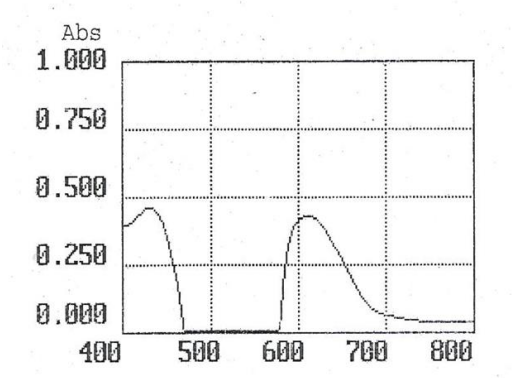

Figure 3: Visible spectrum of oxidized meloxicam

The results obtained for the optimization of the concentration of potassium permanganate and sodium hydroxide used in this research are as shown in Figure 4 and the optimum conditions are 0.02 N and 0.1 N for potassium permanganate and sodium hydroxide, respectively.

The effect of temperature on the absorbance of meloxicam is as shown in Figure 5. The result obtained for the effect of reaction time on the absorbance of meloxicam in this research is as shown in Figure 6.

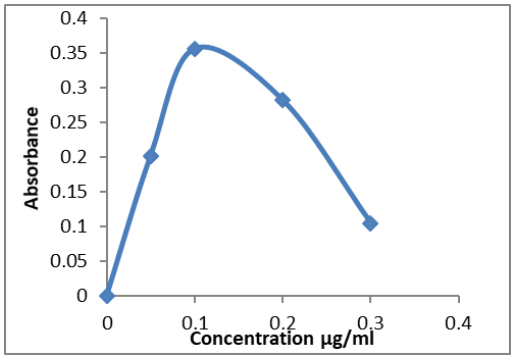

Figure 4: Optimization of potassium permanganate concentration

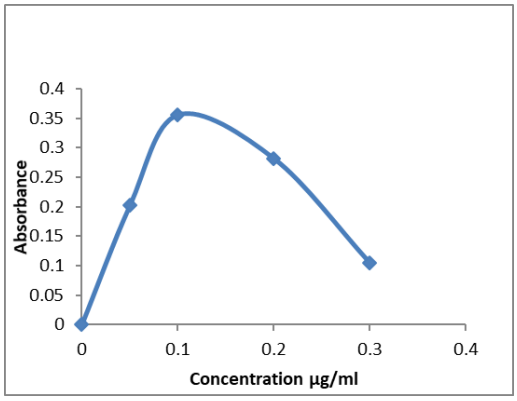

Figure 5: Effect of temperature on the absorbance of meloxicam

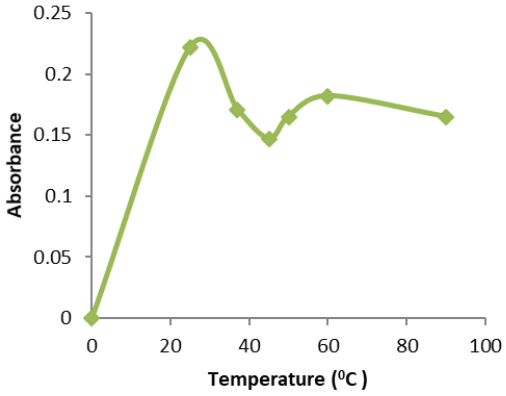

Figure 6: Effect of reaction time on the absorbance of meloxicam

Calibration plot for the pure meloxicam as shown in Figure 7 obeyed Beer's law and result for the recovery of meloxicam from the standard solution are as shown in the Table 1, while the results of the validation of the proposed analytical method are shown in Table 2. The results obtained from the recovery of meloxicam from the tablet dosage form using the developed method and the reported method are shown in Table 3.

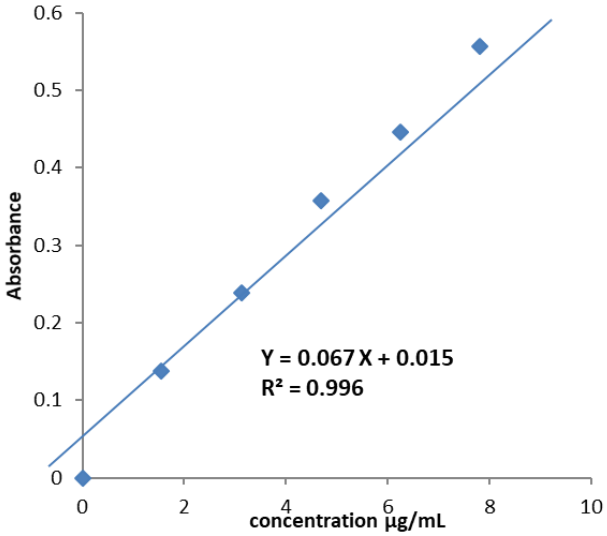

Figure 7: Calibration plot for pure meloxicam solution

Table 1: Result of the recovery of meloxicam from the standard solution for developed method

S/N	C/T (µg/mL)	Abs	C/F (µg/mL)	% Recovery
1	2.3438	0.185	2.4000	102.38
2	3.9063	0.293	3.9428	100.94
3	5.4688	0.404	5.5289	101.08
4	7.0312	0.522	7.2140	102.60
		MEAN ± S.D		101.75 ± 0.86

C/T: Concentration Taken, Abs: Absorbance, C/F: Concentration found, S.D: Standard deviation

Table 2: Regression analysis of the calibration curve of standard meloxicam solution

Parameters	Value
Wave length of maximum absorption (λ_{max}) (nM)	610
Regression equation	Y = 0.067X + 0.015
Correlation coefficient	0.996
Slope	0.0670
Intercept	0.015
Limit of Detection (µg/mL)	0.3238
Limit of Quantification (µg/mL)	1.0930
Molar Absorptivity	2.3820×10^4
Linearity range (µg/mL)	1.56 – 9.37

Table 3: Results of recovery of meloxicam from tablet dosage form using the developed and the proposed methods

S/N	BRAND CODE	% MEAN RECOVERY ± S.D		P-VALUE
		Proposed	Reported	
1	MLX_1	100.89 ± 0.99	99.90 ± 1.40	0.5825
2	MLX_2	100.60 ± 0.43	99.50 ± 0.50	0.4491
3	MLX_3	97.84 ± 0.32	96.80± 0.60	0.2860
4	MLX_4	97.11 ± 0.81	98.80 ± 0.40	0.5098

P > 0.05 no significant difference at 95% confidence interval, S.D: Standard Deviation

DISCUSSION

The developed method is based on the oxidation of the hydroxyl (OH) group in meloxicam by basified KMnO4. The oxidation of meloxicam results in the production of two peaks, firstly due to the oxidation of the enolic –OH with the formation of the corresponding free radical which can be deprotonated and the second step involves the oxidation of the deprotonated derivative with the formation of a carbonyl and a positive charge localized on a carbon atom, which is stabilized by the lone pair of the neighbouring nitrogen; this cation is susceptible to attack resulting in the formation of the second peak (Figure 8).

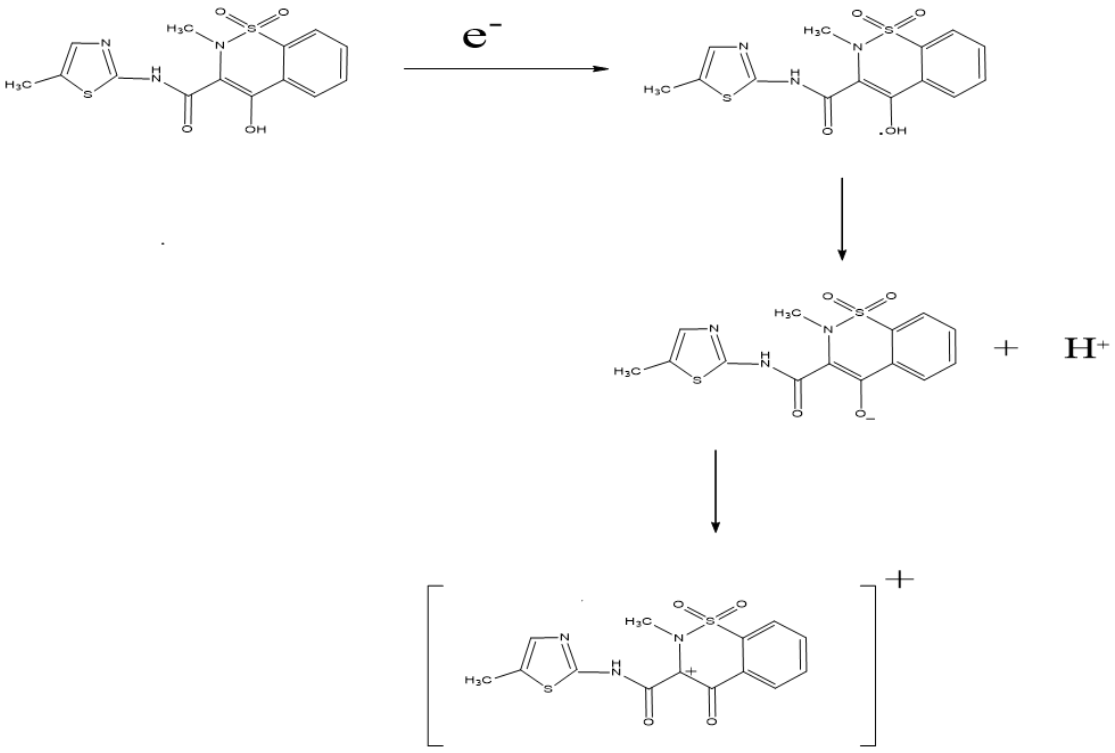

Figure 8: Proposed reaction mechanism of meloxicam with potassium permanganate

The green solution of the manganate ion had an absorption maximum at 610 nm for meloxicam and the calibration plot obtained was linear (A=0.067C + 0.015. R^2 = 0.996) and obeyed Beer's law over 1.56 – 9.37 µg/mL concentration range hence, it is suitable for the estimation of the drug. The slope, intercept and correlation coefficient summarised in Table 2 states a good correlation.

The optimum conditions were fixed by varying one parameter at a time while keeping other parameters constant and observing the effect on absorbance at 610 nm. It was found that 0.02 N was the optimum concentration for potassium permanganate and 0.1 N for sodium hydroxide as shown in Figure 5 and 6, respectively.

The effect of temperature and reaction time on the absorbance of the oxidized meloxicam showed that absorbance was highest at room temperature and increase in temperature led to decrease in absorbance while 30 minutes was the optimum reaction time for the study as shown in Figures 5 and 6, respectively.

The developed method was validated using the ICH guidelines. The precision was measured in terms of repeatability which was determined by sufficient aliquots of homogenous sample. The recovery technique was carried out to study the accuracy and reproducibility of the developed method. The results of the recovery studies from the standard solutions using optimum conditions as shown in Table 1 reveals that the method is accurate and precise. The developed method was found to be sensitive due to its high molar absorptivity and slope as shown in Table 2. The developed method, applied to the tablet dosage form of meloxicam is shown in Table 3.

The results were also compared to results obtained using an established colorimetric method. The results showed no statistically significant difference between the results of the developed and the colorimetric method. However, the developed method is more sensitive when compared to the reported method as shown by the higher value of the molar absorptivity and slope compared to that of the reported method.

Conclusion

A colorimetric method was developed and validated for the analysis of meloxicam in bulk and pharmaceutical dosage form using potassium permanganate. The developed method is simple, cost-effective, sensitive, precise and accurate and it is comparable to the reported method for quantitative assay of meloxicam.

Thus, this method can be effectively used as alternative for rapid and routine determination of meloxicam in bulk and tablet formulation.

Conflict of Interest

No conflict of interest is associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities on claims relating to the article's content will be borne by the authors. Henry Okeri and Uyi Ogbeide designed the study, Chinwe Nduecheche carried out the laboratory work and managed the data and Uyi Ogbeide wrote the manuscript which Henry Okeri reviewed. All the authors read and approved the final manuscript.

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