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Spectrophotometric Determination of Meloxicam in Pure Form and its Pharmaceutical Formulation following Azo Dye Formation with 4-nitroaniline

Ali M. Atiyah[1*], Kameran S. Hussein[1], Abdul Majeed K. Ahmed[2]

[1]Department of Chemistry, College of Science, University of Kirkuk, Kirkuk, Iraq.
[2]Department of Chemistry, College of Education For pure sciences, University of Kirkuk, Kirkuk, Iraq.

Abstract: A fast, cheap, and straightforward spectrophotometric method has been proposed to determine meloxicam (MEL) in its pure form and pharmaceutical formulation. The technique involves diazotizing the (NH_2) group in 4-nitroaniline with $NaNO_2$ followed by a reaction with meloxicam to produce a stable and colored complex in a basic medium. This complex demonstrates maximum absorbance at 514 nm. The developed method's linearity ranges from 2.0 - 25 µg mL^{-1}, and the molar absorptivity is 1.5989×10^4 L mol^{-1} cm^{-1}. The RSD% is lower than 1.55%. Additionally, the limit of detection (LOD) is 0.2019 µg mL^{-1}. The method successfully determines the pharmaceutical preparation containing meloxicam (Loxim tablets) with a recovery rate of no less than 97.9%.

Keywords: Spectrophotometric, Diazotization coupling reaction, Meloxicam, 4-nitroaniline.

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***Corresponding author's E-mail:** alimohammed@uokirkuk.edu.iq

1. INTRODUCTION

Meloxicam is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carbox amide 1,1-dioxide (Figure 1), with the chemical formula $C_{14}H_{13}N_3O_4S_2$ a molecular weight of 351.4g mol^{-1}. Meloxicam is a pale-yellow crystalline powder. It is practically insoluble in water but shows higher solubility in strong acids and bases. It is also very slightly soluble in 96% aqueous ethanol (1).

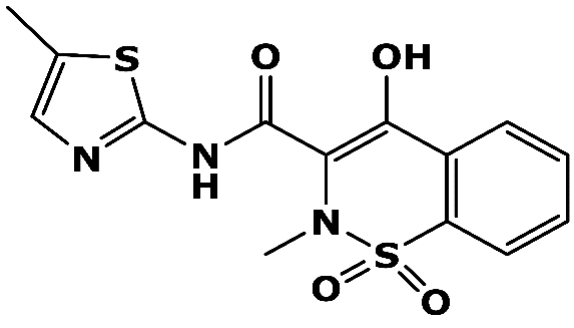


Figure 1: The structure of meloxicam.

An oxicam derivative called meloxicam is a nonsteroidal anti-inflammatory medication (NSAID) that selectively inhibits cyclooxygenase-2 (COX-2). MEL treats symptoms of ankylosing spondylitis, acute exacerbations of osteoarthritis, and rheumatoid arthritis. It is also used as a short-term symptomatic treatment. Moreover, juvenile idiopathic arthritis may be treated with it (2). MEL easily permeates the synovial fluid, suggesting that the active ingredient plays a role in eradicating the infectious process within the joint tissues. With a 20-fold selectivity towards COX-2 over COX-1, MEL exerts a beneficial influence on cartilage tissue metabolism and exhibits chondroprotective characteristics (3). Several methods have been applied for the estimation of meloxicam, such as spectrophotometric methods(4-12), high performance liquid chromatographic methods (HPLC) (13-19), ultra-high performance liquid chromatography (20), High-performance thin layer Chromatography (HPTLC) (21), polarography (22,23), voltammetry (24-26), and flow injection analysis (FIA) methods (27,28).

Azo dyes are synthetic compounds containing an azo bond (-N=N-) (29). Most azo dyes are produced by diazotization of an aromatic primary amine, followed by coupling with one or more electron-rich nucleophiles such as NH_2 or OH group (30). The spectrophotometric measurement of Meloxicam in this work is based on the drug's azo dye coupling with diazotized 4-nitroaniline in a basic medium.

2. EXPERIMENTAL

2.1. Apparatus

All spectrophotometric measurements were made using a T92+ spectrophotometer double beam, China, with a 1.0 mm quartz cell. Solution pH was measured using a Jenway 3310 pH meter, and all weight measurements were made using a Sartorius Balance BL210 SAG, Germany.

2.2. Reagents and Chemical Materials

The pharmaceutical and medical supplies company (SDI), Samarra, Iraq, provided the meloxicam (pure standard powder). Fluka and BDH provided all other analytical chemical reagents, including 4-nitroaniline, hydrochloric acid, sodium hydroxide, and sodium nitrite. The pharmaceutical formulation (tablets) was provided by the company of Ajanta Pharma Limited, Mumbai, India. All materials were of the highest possible quality. Each solution was made from scratch using distilled water.

2.3. Preparation of Solutions

2.3.1. Meloxicam solution (1000 µg mL^{-1})

It was prepared by dissolving 0.1g of meloxicam in 5.0 mL of sodium hydroxide at a concentration of 0.1N (31) and then completing the volume to 100 mL with distilled water using a volumetric flask. Then, 25 mL of this solution is diluted to 100 mL with distilled water to obtain a solution with a concentration of 250 µg mL^{-1} (7.1×10^{-4} mol L^{-1}).

2.3.2. Hydrochloric acid solution, approximate concentration 1.0 mol L^{-1}

This solution was prepared by diluting 8.5 mL of the concentrated acid (11.8 mol L^{-1}) with distilled water and then completing the volume to 100 mL in a volumetric flask.

2.3.3. Sodium Hydroxide solution, approximate concentration 0.1 mol L^{-1}

In a 100 mL volumetric flask, 0.4 g of sodium hydroxide was dissolved in the appropriate volume of distilled water, and the flask was then filled to the mark.

2.3.4. Diazotized 4-nitroaniline solution(D-4NA) 5×10^{-3} mol L^{-1}

These steps are carried out in a dark flask: in the beginning, defrost 0.0345g of 4-nitroaniline in 2.0 mL of hydrochloric acid, and in another beaker, dissolve 0.0172g of $NaNO_2$ in 5.0 mL of distilled water. Both beakers were placed in an ice bath for 10 minutes at a temperature of 0-5°C, then the sodium nitrite solution ($NaNO_2$) was added drop by drop to the reagent solution, then stirred for 5 minutes and completing the volume to 50 mL with water. The color dye product must be kept in the ice bath; the concentration of $NaNO_2$ (1×10^{-3} mol L^{-1}) in equimolar solution 1×10^{-3} mol L^{-1} of 4-nitroaniline, so we do not need to add sulfamic acid in this method to get rid of excess $NaNO_2$.

2.3.5. Sample solution of meloxicam from tablets formulation 250 µg mL^{-1}

In the pharmaceutical formulation tablet (Loxim), every tablet contains 15 mg of MEL; this solution was prepared as follows: Ten tablets were weighed accurately. After grinding and mixing well, the weight of ten tablets was equal to 2.477 g. Then, a weight of 0.413 g of this powder, which is equivalent to 0.025 g of the drug, was dissolved in 5.0 mL of NaOH with distilled water. The solution was filtered to remove any insoluble material, and then the volume was completed with water at 100 mL.

3. RESULTS AND DISCUSSION

3.1. The Fundamental Idea for the Method

The reaction involved the formation of the D-4NA, followed by reacting with MEL in the presence of NaOH to yield a reddish-orange colored azo dye that has the highest absorbance at 514 nm.

3.2. Study of the Typical Circumstances for Reaction

The effect of various variables on the absorbance intensity of the azo dye formed from the reaction of MEL with diazotized 4-nitroaniline was investigated, and the optimum conditions have been selected as follows:

3.2.1. The impact of acid-type

The impact of different types of acids used in the formation of diazonium salt (D-4NA) was investigated. First, 4-nitroaniline was diazotized as previously described (4-NA & $NaNO_2$) in the presence of 2 mL of various types of acids at a concentration of 1.0 mol L^{-1}. Then, 1.0 mL of the formed diazotized solution was added to volumetric flasks containing 1.0 mL of MEL. Finally, 1.5 mL of NaOH was added. The outcomes are indicated in Table 1.

Table 1: Impact of acid-type.

Acid type	Absorbance
HCl	0.564
H_2SO_4	0.505
HNO_3	0.509
CH_3COOH	0.415

To clarify: The optimal amount of NaOH was used when analyzing each acid in the study. The reason for this is that we will be measuring the absorption of the azo dye product formed in the last step, not the diazonium salt formed by the reaction of the amino group in the reagent in the presence of sodium nitrite and acid.

3.2.2. The impact of the quantity of acid

The congruent quantities and sequences of sodium nitrite were added to a diverse amount of hydrochloric acid (1.0 mol L^{-1}) used in the formation of D-4NA solution, and the diazotized was utilized as earlier indicated in the preparation of azo dye. At 514

nm, the absorbance of the colored azo dye was measured in comparison to the blank solution. According to Figure 2, 2.0 mL of HCl (1.0 mol L^{-1}) gives the maximum absorbance intensity for the azo dye. Therefore, this volume was adopted in the later experiments.

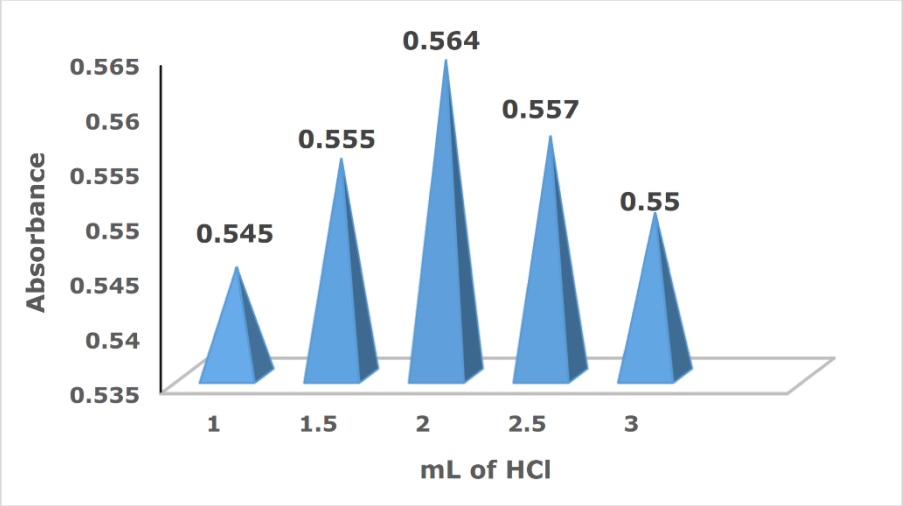


Figure 2: The impact of the quantity of acid.

3.2.3. Effect of amount of diazotized agent

The effect of different amounts of diazotized 4-nitroaniline(D-4NA) was studied by adding it to a series of 25 mL volumetric flasks containing 1.0 mL of MEL, followed by adding about 1.5 mL of sodium hydroxide. Then, the solution was completed with water. The results shown in Table 2 indicated that 1.0 mL of the diazotized agent solution produced the highest azo dye absorbance intensity.

3.2.4. The impact of the base type solutions

The coupling reaction between D-4NA and MEL occurs in an alkaline medium, so the impact of various bases and alkaline salts was probed to determine which produced the highest absorbance. From the results in Figure 3, it was clear that sodium hydroxide gives the highest absorbance. Therefore, it was used in subsequent experiments.

Table 2: Effect of amount of diazotized agent.

Amount of diazotized agent	Absorbance
0.5	0.552
1.0	0.563
1.5	0.556
2.0	0.544
2.5	0.532

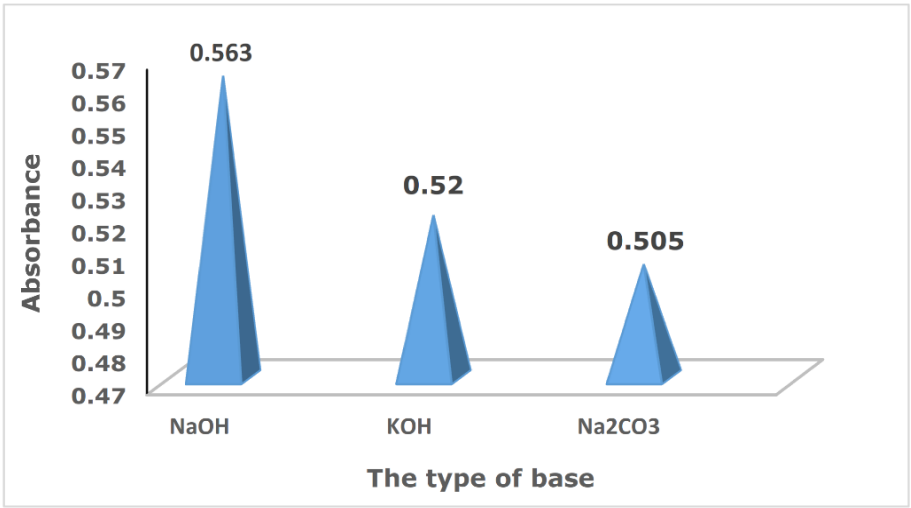


Figure 3: The impact of the base type solutions.

3.2.5. The impact of the amount of base

A study was carried out to establish the typical amount of base solution by adding diverse volumes (0.5-2.5 mL) of sodium hydroxide. It was found that 1.5 mL of NaOH gives the highest absorbance at pH=10.9. From the results listed in Table 3, it is clear to us that the relationship is a positive one at the beginning. Then, after the added quantity reaches 1.5 mL (pH 10.9), we will obtain the highest absorption of the dye formed, and then it may plateau or decrease. The reason for an increase, in the beginning, is that the sodium ion originating from the sodium hydroxide displaces the chloride ion in the diazonium salt. Consequently, a positively

charged diazonium ion is formed, which functions as an electrophile and undergoes a reaction with the MEL, resulting in the formation of an azo dye. The reason for the decrease in absorbance after that is due to the ionization of MEL.

3.2.6. The impact of time on the stability of the dye formed

The stability of the produced dye was investigated by examining how time affected the absorbance of three different concentrations (5.0, 10, and 15 μg.ml^{-1}) of MEL, following the suggested method procedure. The outcomes in Table 4 show that the reddish-orange dye remains stable for 50 minutes.

3.3. The Eventual Absorption Spectrum

After selecting the optimum conditions shown in Table 5, the eventual absorption spectrum was measured using 1.0 ml of MEL, 1.0 mL of D-4NA, and 1.5 mL of NaOH. The reaction was carried out in an ice bath (0-5°C), and then the solution was left for 5.0 minutes to complete the reaction. The volume was then finished with water to 25 mL. The absorption was measured against the blank solution. It was found to give a higher absorbance at 514 nm, while its blank gave a little absorption at the same wavelength. The results are shown in Figure 4.

Table 3: The impact of the amount of base.

Amount of NaOH (0.1 M)	Absorbance	pH
0.5	0.482	5.9
1.0	0.541	8.2
1.5	0.563	10.9
2.0	0.554	11.1
2.5	0.513	11.6

Table 4: The impact of time on the stability of the dye formed.

Time (min)	Absorbance		
	5.0 μg mL^{-1}	10 μg mL^{-1}	15 μg mL^{-1}
5	0.261	0.563	0.734
10	0.261	0.563	0.734
15	0.261	0.563	0.733
20	0.261	0.562	0.733
25	0.260	0.562	0.733
30	0.260	0.562	0.732
35	0.260	0.561	0.732
40	0.260	0.561	0.731
45	0.258	0.560	0731
50	0.258	0.559	0.730
55	0.251	0.552	0.725
60	0.242	0.522	0.686

Table 5: Summary of optimum conditions.

Parameter	Optimum conditions
λmax	514 mL
Amount of 7.1×10^{-4} mol L^{-1} (MEL)	1.0 mL
Amount of 5×10^{-3} mol L^{-1} (D-4NA)	1.0 mL
Amount of HCl (1.0 mol L^{-1})	2.0 mL
Amount of NaOH (0.1 mol L^{-1})	1.5 mL
Solvent	Water

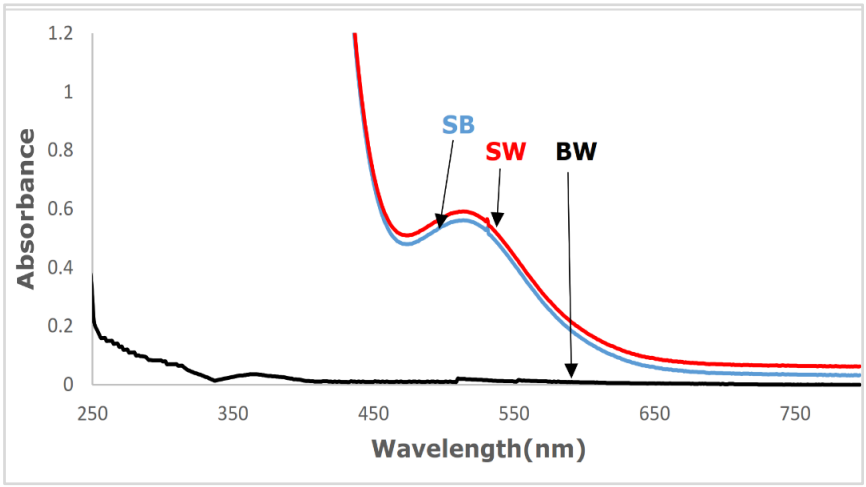


Figure 4: The eventual absorption spectrum for the determination of MEL (10µg mL^{-1}) versus water (SW), MEL vs. blank solution (SB), and blank solution vs. water (BW).

3.4. The Calibration Graph

After selecting the optimized experimental conditions, ranging from 0.2 to 2.5 mL of MEL drug solutions were transferred to a series of volumetric flasks (25 mL). These volumes corresponded to concentrations ranging from 2.0 µg mL^{-1} to 25 µg.mL^{-1}. Subsequently, 1.0 mL of diazotized 4-nitroaniline solution was added, followed by the addition of 1.5 mL of NaOH. The volumes were then completed with water, and the absorbance was measured against the blank solution at 514 nm. Figures 5 and 6 demonstrate that the calibration graph adheres to Beer's law in the range of 2.0 to 25 µg.mL^{-1}, while higher concentrations appear to show a negative deviation from Beer's law. The molar absorptivity was determined to be 1.5989×10^4 L.mol^{-1}.cm^{-1}, and Sandall's index value was 0.02198 µg.cm^{-2}.

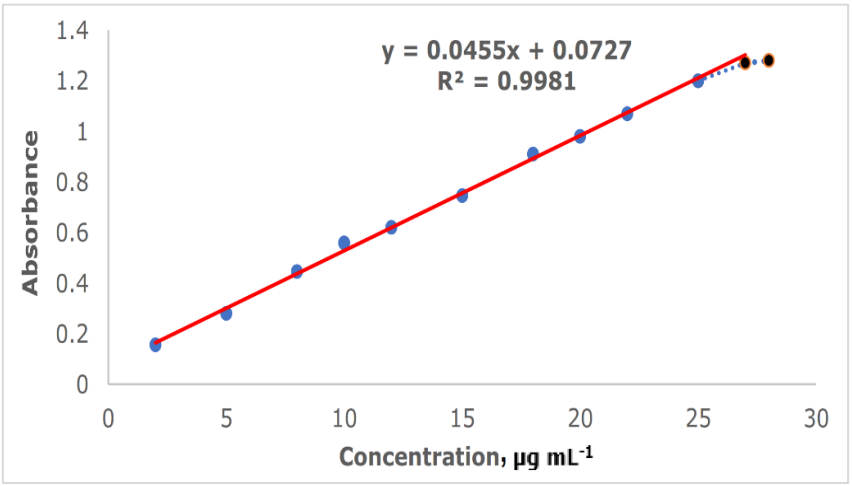


Figure 5: The calibration graph for the estimation of MEL using the suggested method.

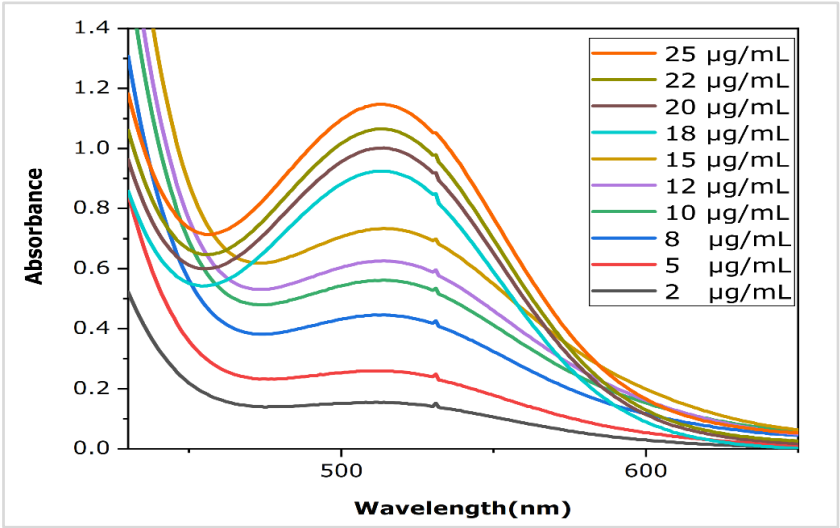


Figure 6: The calibration graph spectra for the estimation of MEL using the suggested method.

3.5. The Precision & Accuracy

The precision and accuracy of the method were examined by measuring the recovery percentage, as well as the relative standard deviation (RSD%) and the relative error (RE%). This was done for three different concentrations (5.0, 10, and 15) μg ml^{-1}, with the absorbance being measured six times at a wavelength of 514 nm for each concentration. The average was then taken. The findings in Table 6 showed that the method for determining MEL had acceptable precision and accuracy.

Table 6: The results of precision and accuracy.

Amount of MEL (μg mL^{-1})		*RE%	*Recovery%	*RSD%
Taken	Measured			
5	5.05	1.0	101	1.42
10	10.12	1.2	101.20	1.55
15	14.83	-1.13	98.86	0.96

*Average of six times

3.6. The Limit of Detection

The limit of detection was calculated by measuring the absorption of the blank solution (32) under optimized conditions (six times) at a wavelength of 514 nm using Equation: LOD=3.3 SD/b (33,34), where (SD) is the standard deviation and (b) is the slope of the calibration curve. The limit of detection of the method was found to be 0.2109 μg mL^{-1}.

3.7. Studying the Ratio of MEL and Diazotized 4-Nitroaniline in Forming Azo Dye

The stoichiometry of the product was investigated through the employment of the continuous variation method, also known as Job's method. This method was utilized to determine the characteristics of the resulting product and the proportion of the drug's ability to bind with the diazotized agent (35). The outcomes in Figure 7 indicate that the ratio of azo dye formed between diazotized 4-NA and MEL is 1:1.

Scheme 1 shows the suggested mechanisms for the reddish-orange dye formed by the reaction of MEL with the diazotized 4-NA in the basic medium.

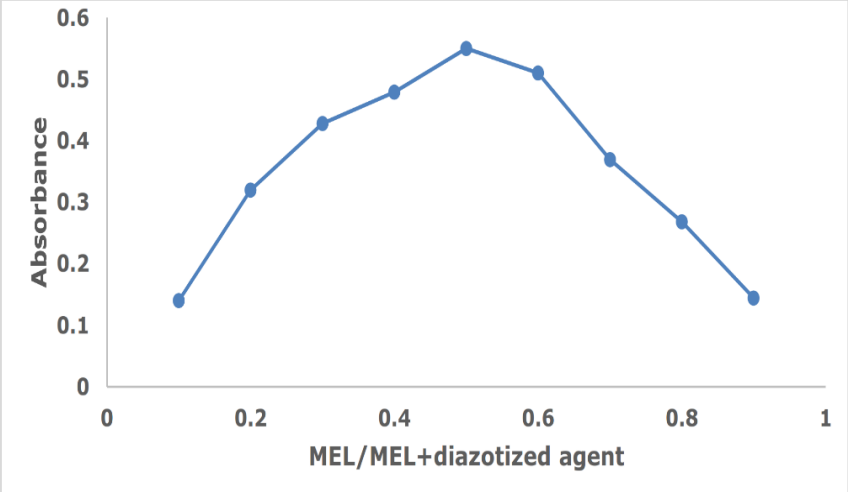
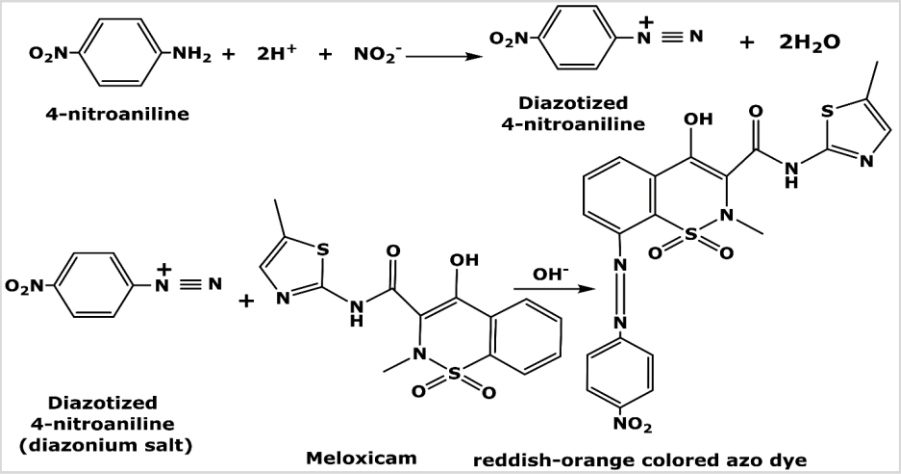


Figure 7: Continuous variation method of azo compound.



Scheme 1: The suggested mechanisms for the reaction.

3.8. Stability Constant of the Dye Formed (K_s)

To determine the stability constant for the 1:1 formed product (MEL and diazotized 4-NA), we utilized the outcomes of the Job's method as detailed in Section (3.7). Solutions were prepared containing equimolar quantities of MEL and diazotized 4-NA, each having a concentration of $7.1X10^{-4}$ mol L^{-1}. The absorbance of each solution was measured in comparison to its respective blank and denoted as (As). Furthermore, solutions were also prepared with the same quantity of MEL but with an excess amount (2 mL) of the diazotized agent, and their absorbance was denoted as (Am). The degree of dissociation (α) was determined using Equation 1. Subsequently, the stability constant of the reddish-orange dye produced in the aqueous solution was calculated using Equation 2. The results shown in Table 7 indicate that the product is highly stable.

$$\alpha = \frac{Am-As}{Am} \quad (1)$$

$$K_s = \frac{1-\alpha}{\alpha^2 C} \quad (2)$$

Table 7: Stability constant.

*Concentration (C) mol L^{-1}	Absorbance		α	K_S, L.mol^{-1}
	A_s	A_m		
$7.1X10^{-4}$	0.568	0.580	0.02069	3.2×106

*(C) The concentration of the colored product.

3.9. The Applications Part

The methods were applied to a pharmaceutical formulation containing MEL drug, which is the pharmaceutical formulation (Loxim) produced by Ajanta Pharma Limited, Mumbai, India, in the form of tablets, and each tablet contained 15 mg of MEL.

3.9.1. Direct method

In order to demonstrate the validity of the suggested method in the estimation of MEL in the form of tablets with three different concentrations, the results are summarized in Table 8. The assay results indicated that the proposed method is applicable.

3.9.2. The standard addition method

To demonstrate that the method was free from interferences, the standard additions method was used to determine the concentration of MEL in its pharmaceutical preparation. Two series of six 25 mL volumetric flasks were prepared, with constant volumes (0.5 and 1.0 mL) of the pharmaceutical preparation added, equivalent to a concentration of (5.0 and 10 μg.mL^{-1}). Increasing volumes of MEL solutions were added, and then the absorption was measured against the blank solution at the wavelength of 514 nm. Table 9 and Figure 8 show the accordance of the standard addition method with the suggested method.

Table 8: The results of the direct method for the determination of MEL in pharmaceutical preparations.

Amount of MEL (μg mL^{-1})		*RE%	*Recovery%	*RSD%
Taken	Measured			
5	5.10	2.0	102	1.91
10	9.92	-0.8	99.2	1.13
15	15.02	0.13	100.13	1.61

*Average of six times

Table 9: The results of standard-addition method for the identification of MEL in tablets

Amount of MEL (μg mL^{-1})		*RE%	*Recovery%	*RSD%
Taken	Measured			
5	5.10	2.0	102	1.86
10	9.79	-2.1	97.9	1.12

*Average of six determinations

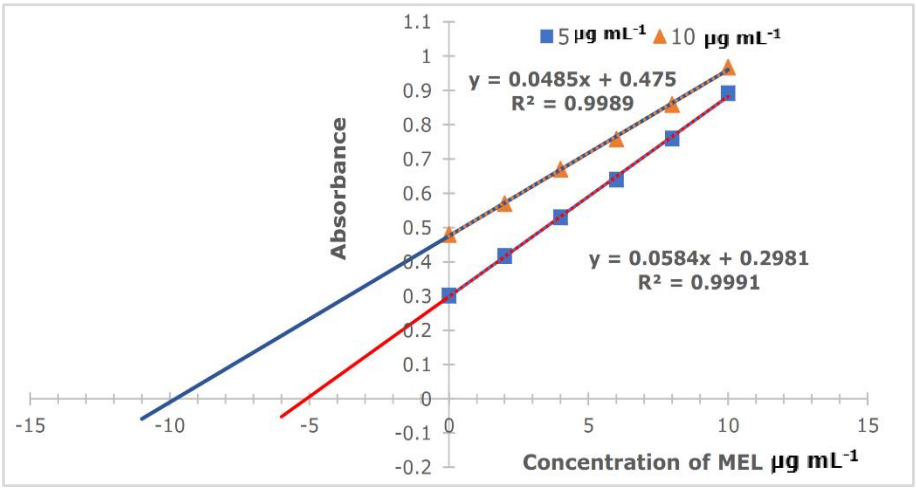


Figure 8: The standard addition curve for the identification of MEL in tablets.

3.10. Advantages of Our Spectrophotometric Method Compared to Other Analytical Technique

In this section, a comprehensive analysis is provided to elucidate the advantage of our spectrophotometric approach in contrast to other frequently employed analytical methodologies, including high-performance liquid chromatography (HPLC), polarography, and flow injection analysis. Emphasizing crucial factors such as precision, expenditure, temporal efficacy, usability, and instrumental prerequisites.

Accuracy: The current method offers high accuracy and consistent results. HPLC also provides very high accuracy, precise analysis, and separation but demands intricate preparation. Electrochemical conditions and impurities in the sample influence accuracy in polarography. Flow injection analysis delivers good accuracy but is susceptible to changes in flow rate and environmental factors.

The cost: The current method is cost-effective because it requires minimal equipment and no expensive reagents. In contrast, HPLC is expensive due to its complex instruments and costly chemicals. Polarography has moderate costs involving specialized electrochemical equipment. Flow injection analysis has medium to high costs due to precise flow control and fluid handling systems.

Time Efficiency: The current method provides fast results within minutes. HPLC is slow, taking hours for preparation and analysis. Polarography is moderately time-consuming, contingent on electrochemical response time. Flow injection analysis is quick but needs a pre-analysis setup.

The simplicity of utilization: Our method is user-friendly and does not necessitate sophisticated technical competencies, rendering it appropriate for regular laboratory assessments conducted by skilled technicians. Conversely, HPLC demands advanced technical proficiency and practical know-how to manage and uphold the intricate machinery. Polarography necessitates a grasp of electrochemical examination but is comparatively less intricate than HPLC, whereas flow injection analysis mandates technical expertise to supervise flow systems and calibrate the equipment.

Equipment Requirements: The utilization of the spectrophotometric approach necessitates solely a basic spectrophotometer and an illuminating source, rendering it feasible for the majority of laboratory settings. Conversely, the application of HPLC mandates sophisticated chromatographic apparatus and equipment for sample preparation. Polarography, on the other hand, calls for a polarograph and supplementary electrochemical devices, whereas flow injection analysis necessitates a precise continuous flow mechanism and linked control instruments.

This comparison clearly illustrates the superiority of our spectrophotometric method in terms of simplicity, cost-effectiveness, and rapid analysis, making it an ideal choice for routine laboratory analysis compared to the more complex and expensive alternatives.

3.11. Comparison of the Method

Table 10 displays a comparison of various analytical variables between the current method and alternative methods found in the literature.

3.12. Statistical Agreement t-Test

Both the current method and the method described in the literature (36) were simultaneously utilized in the calculation of the t-test, with the obtained value then compared against statistical tables for eight degrees of freedom at a 95% confidence level. The findings presented in Table 11 demonstrate that there is no significant discrepancy between the two methodologies.

Table 10: The comparison study between the suggested method and other techniques reported in the literature.

	Method	λmax nm	Linear range µg mL^{-1}	RSD%	Recovery%	LOD µg mL^{-1}	Literature method Ref.
Current method		514	2	0.96-1.42	98.86-101.2	0.2109	-
Literature method	Spectroscopy	708	0.1-11	0.25-0.73	98.7-99.5	0.0092	7
	HPLC	290	1.0-50	< 3.9	100.4	0.25	13
	Polarography	-	0.38-15.0	0.27	99.20	0.02	23
	Voltammetry	-	10-90 in both *SWV & **DPV	2.72 for SWV & 3.06 for DPV	98.5 for SWV 98.7 for DPV	1.50 in both SWV & DPV	26
	FIA	530	10-160	1.2	97.0-104	6.0	28

*(SWV) Square wave voltammetric method, **(DPV) Differential pulse voltammetry.

Table 11: The results of t-test analysis.

Drug	Pharmaceutical preparation	*Recovery%		t. exp
		Current method	Literature method (36)	
Loxim	Tablet	99.95	98.4	0.77

*Average of five determinations

4. CONCLUSION

A robust spectrophotometric method was developed and validated for determining meloxicam in pure form and its pharmaceutical formulation through azo dye formation. Key performance metrics highlighted method efficacy. The linear range was 2.0-25 µg mL^{-1} with a high correlation coefficient, showing excellent linearity for quantitative analysis. Molar absorptivity was 1.5989×10^4 L mol^{-1} cm^{-1}, and Sandell's sensitivity was 0.02198 µg cm^{-2}, indicating high sensitivity to detect small meloxicam quantities. LOD was 0.2109 µg mL^{-1}, demonstrating the method's capability to identify low concentrations accurately. The recovery rate was 98.86% - 101.20%, ensuring accuracy and reliability with common excipients. Relative standard deviation values were 0.96% to 1.55%, highlighting method precision and reproducibility. The stability constant of the azo dye complex was 3.2×10^6, which indicates that it is a highly stable complex suitable for routine analysis. The method's applicability to the pharmaceutical formulation Loxim was confirmed, showing that common excipients did not interfere with the determination of meloxicam. This validation suggests that the proposed method is robust and versatile for quality control purposes in the pharmaceutical industry.

5. CONFLICT OF INTEREST

The authors declare that there is no conflict of competing financial interests.

6. ACKNOWLEDGMENTS

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