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SPECTROPHOTOMETRIC DETERMINATION OF MELOXICAM IN PURE FORM AND ITS PHARMACEUTICAL PREPARATIONS VIA OXIDATIVE COUPLING REACTION

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A new sensitive, cheap, and simple spectrophotometric method was used for the determination of Meloxicam (MEL) by oxidative coupling reaction with metol in the presence of ferric chloride ($FeCl_3$) in the basic medium. This reaction yields a distinct purple-colored product that is water-soluble and exhibits maximum absorbance at 628 nm when compared to a blank solution. The method has obeyed Beer's Law within the concentration range of 3.0 to 20 µg ml^{-1}, characterized by a relative error ranging from -1.13% to 1.2% and a relative standard deviation of 0.96% to 1.55%, depending on the concentration level. Key analytical parameters were determined, including a molar absorptivity of 1.9959×10^4 L mol^{-1} cm^{-1}, Sandell's sensitivity of 0.0176 µg cm^{-2}, and a detection limit of 0.1959 µg ml^{-1}. The developed method was successfully validated and applied to the quantification of MEL in pharmaceutical preparations. This study demonstrates that the spectrophotometric method is efficient, precise, and suitable for routine analysis of MEL in quality control

***Keywords**: Loxim, Metol, Oxidative coupling, Spectrophotometric*

INTRODUCTION

MEL is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carbox amide 1,1-dioxide, (**Fig. 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[1] but shows higher solubility in strong acids and bases. It is also very slightly soluble in 96% aqueous ethanol[2].

An oxicam derivative called MEL is a nonsteroidal anti-inflammatory medication (NSAID) that selectively inhibits cyclooxygenase-2 (COX-2)[3]. 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[4]. Several methods have been applied for the estimation of meloxicam, such as spectrophotometric methods[5-12], High-Performance Liquid Chromatographic methods (HPLC)[13-19], High-performance Thin-Layer Chromatography (HPTLC)[20], polarography[21,22], voltammetry[23-25], and flow injection analysis (FIA) methods[26,27]. Oxidative coupling reactions are extensively utilized in analytical chemistry to ascertain and measure pharmaceutical compounds. The methodology entails the interaction of a pharmaceutical compound with an organic reagent, catalyzed by an oxidizing agent, resulting in a vividly pigmented complex that can be precisely analyzed using spectrophotometry. The underlying principle of this process lies in the

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oxidizing agent facilitating the coupling of the drug with the organic reagent typically leading to the generation of chromogenic substances. These reactions have been immensely beneficial in advancing analytical techniques due to their straightforwardness, sensitivity, and specificity. Employing oxidative coupling reactions proves to be highly beneficial when examining pharmaceuticals lacking intense chromophores or existing in low concentrations. By carefully selecting suitable organic reagents and oxidizing agents, a broad array of pharmaceutical compounds can be efficiently examined [28-31].

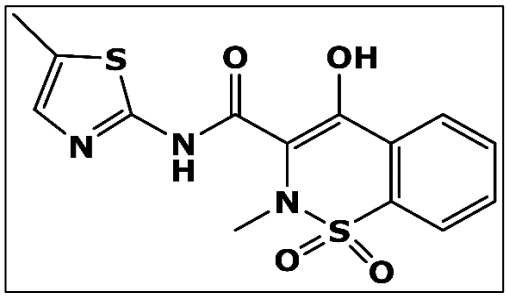


Fig. 1: The structure of meloxicam.

MATERIALS AND METHODS

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.

Reagents and chemical materials

The pharmaceutical and medical supplies company(SDI), Samarra-Iraq, provided the meloxicam (purity: 99.8%). Fluka and BDH provided all other analytical chemical reagents, including metol (purity: 99.0%), ferric chloride (purity: 97.5%), and sodium carbonate (purity: 99.5%). The company of Ajanta Pharma Limited, Mumbai, India, provided the pharmaceutical formulation tablet (Loxim® 15 mg). All materials were of the highest possible quality. Each solution was made from scratch using distilled water.

Preparation of solutions

Meloxicam solution (1000 µg ml^{-1})

It was prepared by dissolving 0.1g of MEL in 5.0 ml of sodium hydroxide at a concentration of 0.1N[32]. Then, it was completed to 100 ml with distilled water (DW) using a volumetric flask. Then, 25 ml of this solution is diluted to 100 ml with DW to obtain a solution (250 µg ml^{-1}, 7.1×10^{-4} M).

Metol reagent solution (1×10^{-3} M)

This solution was prepared by dissolving 0.0344 g of metol in distilled water, and the volume was completed to 100 ml in a volumetric flask. This solution was stable for at least five days.

Ferric chloride solution (1×10^{-2} M)

This solution was prepared by dissolving 0.162 g of ferric chloride in DW, and then the volume was completed to 100 ml with DW. This solution was stable for at least three days.

Sodium carbonate solution (approximate, 2×10^{-2} M)

This solution was prepared by dissolving 0.212 g of pure material in 100 ml of distilled water.

Sample solution of meloxicam from tablets formulation 250 µg ml^{-1}

In the pharmaceutical formulation tablet, each tablet comprises 15 mg of MEL; the formulation process involves the precise weighing of ten tablets. After grinding and thorough mixing, the combined weight of the ten tablets was determined to be 2.477 g. Subsequently, a quantity of 0.413 g of this powder, equivalent to 0.025 g of the active pharmaceutical ingredient, was dissolved in a solution containing 5.0 ml of NaOH and distilled water. Following filtration to eliminate insoluble residues, the solution was topped with water to achieve a final volume of 100 ml.

RESULTS AND DISCUSSION

Results

General principle of the method

This spectrophotometric method is based on the oxidative coupling reaction between the metol reagent and the meloxicam drug in the presence of ferric chloride as an oxidizing agent and sodium carbonate as a catalyst (deprotonation of meloxicam). The reaction proceeds through a free radical mechanism. The oxidizing agent, ferric chloride, initially oxidizes the reagent to form a reactive radical intermediate. This radical then reacts with

meloxicam, producing a highly reactive species. The coupling between the oxidized reagent and the drug leads to the forming of a stable, colored complex that exhibits a maximum absorbance at 628 nm when compared to the blank solution. The color produced in the reaction indicates the formation of the final product, with the intensity of the color being directly proportional to the concentration of the drug in the solution. This technique, relying on oxidative coupling, provides a reliable and sensitive method for determining drug concentration based on measuring the absorbance of the colored complex at 628 nm.

Study of the typical circumstances for reaction

The impact of different variables on the absorbance intensity of the color dye formed from the reaction of MEL with metol reagent was investigated, and the optimum conditions have been selected as follows:

The impact of the amount of reagent

A study investigation was conducted to establish the ideal quantity of reagent solution (metol) necessary to achieve the highest absorption of the colored compound. This was achieved by adding varying volumes (ranging from 0.5 to 2.0 ml) of the reagent solution, 1.0 ml of an oxidizing agent solution, and 1.0 ml of the drug solution. Subsequently, 2.0 ml of sodium carbonate solution was introduced, followed by dilution to a total volume of 25 ml with distilled water. The findings revealed that the optimal amount of metol reagent required was 1.0 ml, utilized in subsequent experiments, with the outcomes depicted in **Fig. 2**.

Selection the best oxidizing agent

This study was conducted by testing various types of oxidizing agents such as N-Bromosuccinimide (NBS), Potassium persulfate ($K_2S_2O_8$), Potassium periodate (KIO_4), and Ferric Chloride ($FeCl_3$) to find the most suitable one for the formation of the colored product. A 2.0 mL volume of different types of oxidizing agents (1×10^{-2}M) was added. It was observed that ferric chloride ($FeCl_3$) was the best oxidizing agent, as it provided the highest absorbance for the colored product formed at a wavelength of 628 nm, as shown in **Fig. 3**. The selection of $FeCl_3$ was based on its moderate oxidizing properties, which effectively reduce the likelihood of undesirable side reactions and minimize the degradation of the pharmaceutical compound. In comparison to alternative agents, $FeCl_3$ demonstrated superior reproducibility and selectivity for the reaction in question. Therefore, $FeCl_3$ was determined to be the most appropriate oxidizing agent for the proposed method..

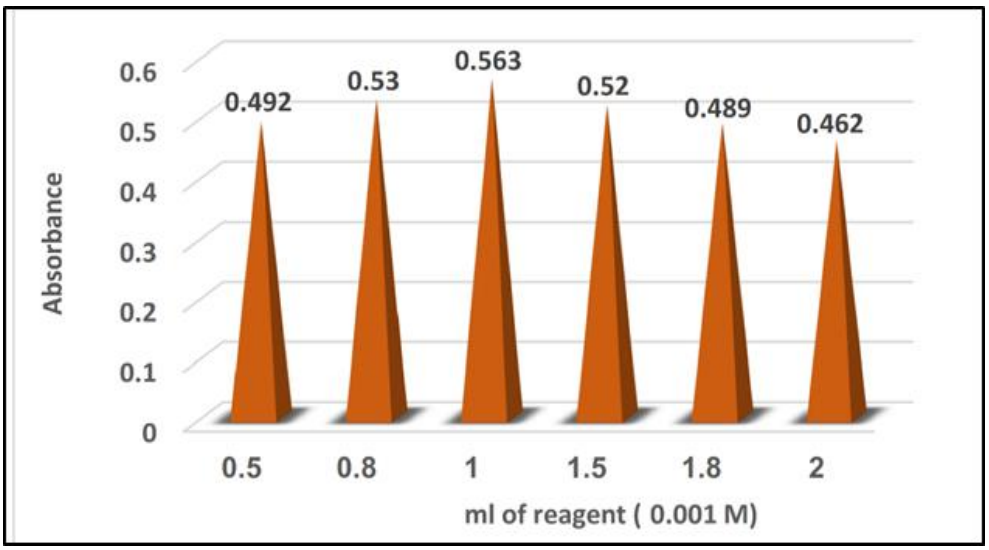


Fig. 2: Effect of the amount of reagent.

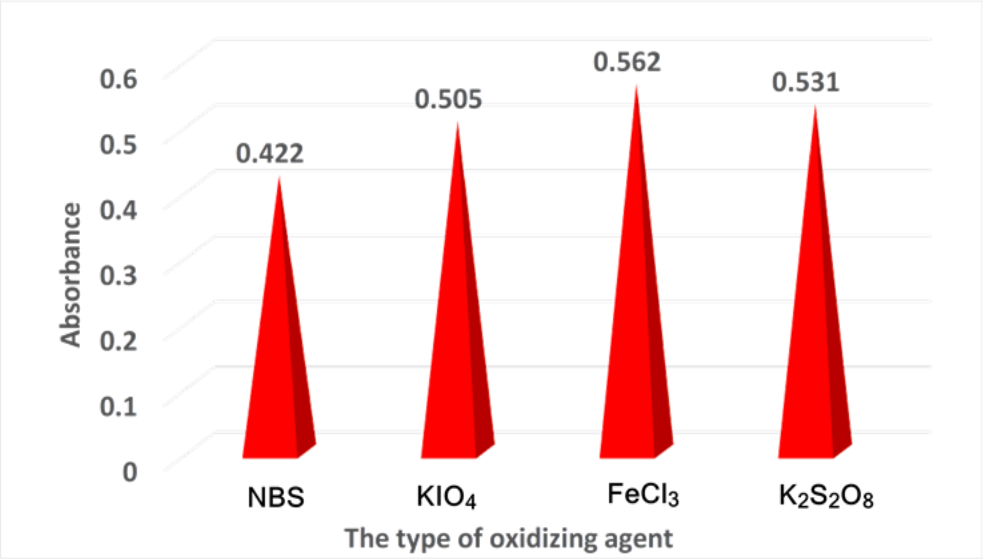


Fig. 3: Selection the best oxidizing agent.

The impact of amount of oxidizing agent

The impact of varying quantities of an oxidizing agent ($FeCl_3$) was examined by adding to a sequence of 25 ml volumetric flasks with 1.0 ml of MEL, followed by adding approximately 2.0 ml of sodium carbonate. Subsequently, the solution was supplemented with distilled water. The findings depicted in **Fig. 4** revealed that the most incredible intensity of colored dye absorbance was generated by 1.0 ml of the oxidizing agent solution.

Effect of the base type solution

The coupling reaction between MEL and the reagent (metol) occurs in an alkaline medium, so the effect of various bases and alkaline salts was investigated to determine which produced the higher absorbance. From the outcomes in **Fig. 5**, it is clear that sodium carbonate gives the highest absorbance. Therefore, it was adopted in subsequent experiments.

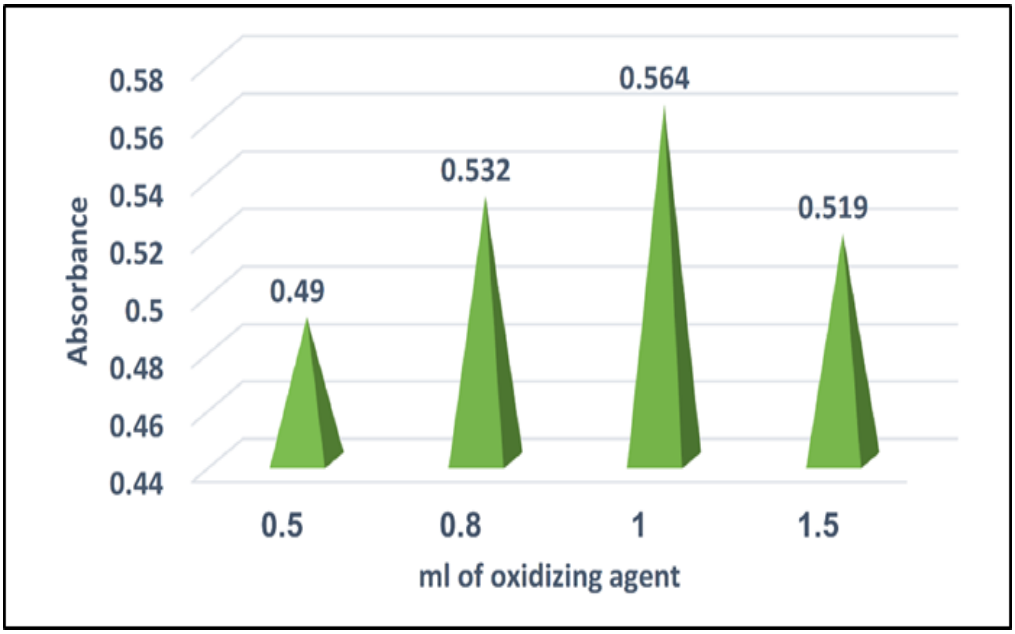


Fig. 4: The impact of amount of oxidizing agent.

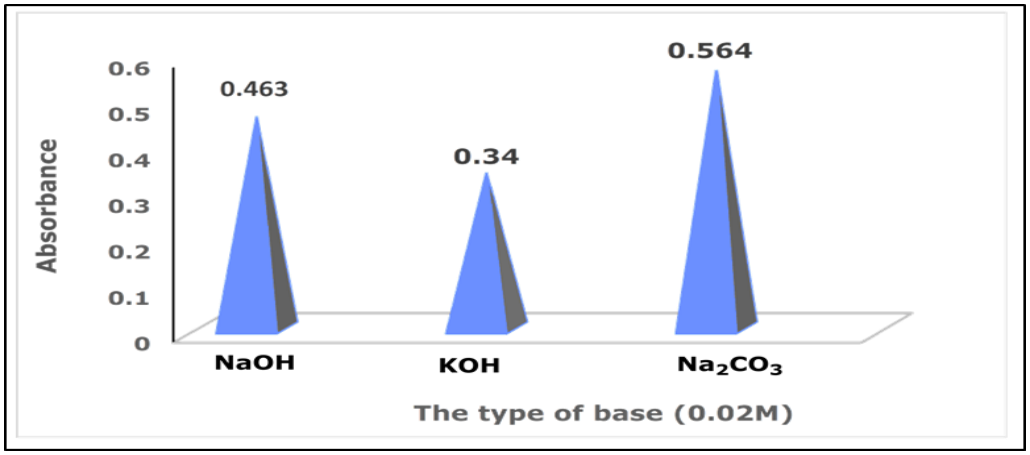


Fig. 5: Effect of the base type solution.

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 carbonate solution. It was found that 2.0 ml of Na_2CO_3 gives the highest absorbance at pH=12.20, the outcomes listed in **Table 1**.

The impact of order of addition

The impact of various orders on choosing the utmost sequence in addition to the reactants was found from the results that order No. 2 (O + M+ B + R) is the best order to form a colored product with maximum absorbance. Therefore, it was chosen in the later experiments, as outlined in **Table 2**.

Table 1: The impact of the amount of base.

Amount of Na_2CO_3 2×10^{-2}M	**Absorbance**	**pH**
0.5	0.428	10.94
1.0	0.450	11.10
1.3	0.489	11.26
1.5	0.505	11.55
1.8	0.533	11.81
2.0	0.562	12.20
2.5	0.541	12.43

Table 2: The impact of order of addition.

Order number	***Order of addition**	**Absorbance**
1	O + R + M + B	0.544
2	O + M+ B + R	0.563
3	M + R + O + B	0.512
4	M + O + R + B	0.527
5	R + B + M + O	0.532
6	O + B + M + R	0.540
7	O + R + B + M	0.466

*(M) MEL, (R) metol, (O) $FeCl_3$, (B) Na_2CO_3.

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, 10, and 15 µg ml^{-1}) of MEL, following the suggested method procedure. The outcomes in **Fig.6** show that the purple-colored dye remains stable for 50 minutes.

The impact of Temperature

The influence of temperature within the range of 5 to 50°C on the absorbance of the resultant colored dye compound has been examined; it was determined that a temperature of 20°C yielded the highest absorbance. Consequently, subsequent trials were conducted at this specific temperature, with the outcomes presented in **Fig. 7**.

The eventual absorption spectrum

The ultimate absorption spectrum was determined utilizing 1.0 ml of MEL, 1.0 ml of metol, and 1.0 ml of $FeCl_3$ in the presence of a sodium carbonate solution at a temperature of 20°C. Subsequently, the solution incubated for 5.0 minutes to finalize the reaction, followed by adjusting the volume to 25 ml in a volumetric flask. The absorption values were recorded relative to the blank solution, revealing a heightened absorption at the wavelength of 628 nm, in contrast to minimal absorption observed in the blank solution at the same wavelength. These outcomes have been visually represented in **Fig. 8.**

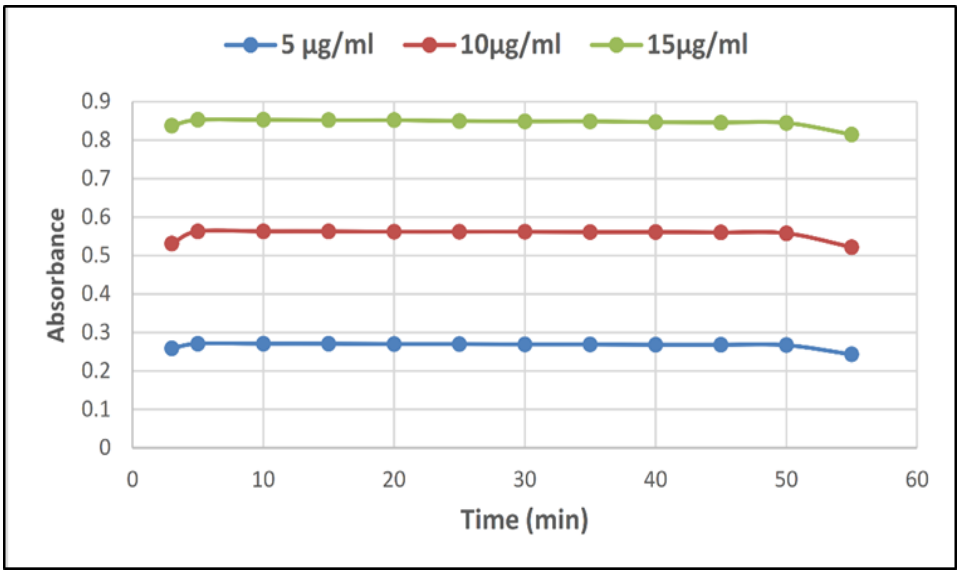


Fig. 6: The impact of time on the stability of the dye formed.

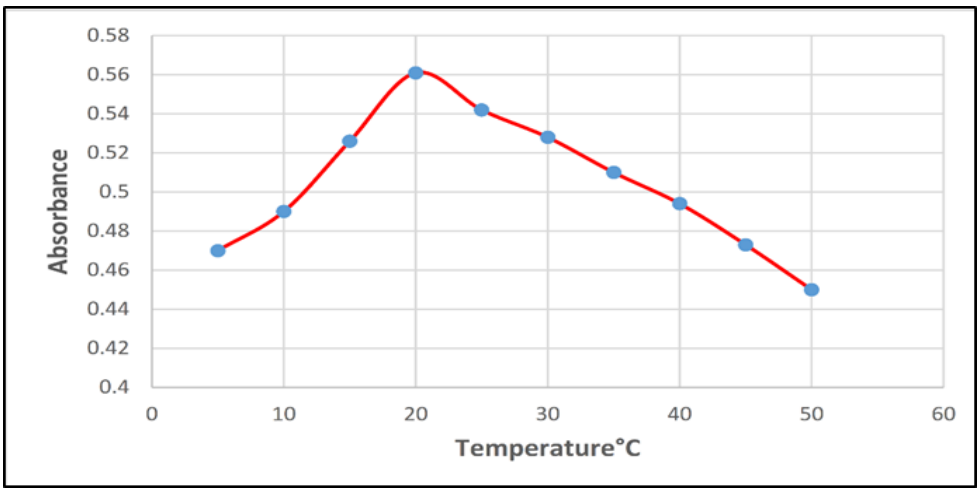


Fig. 7: The impact of Temperature.

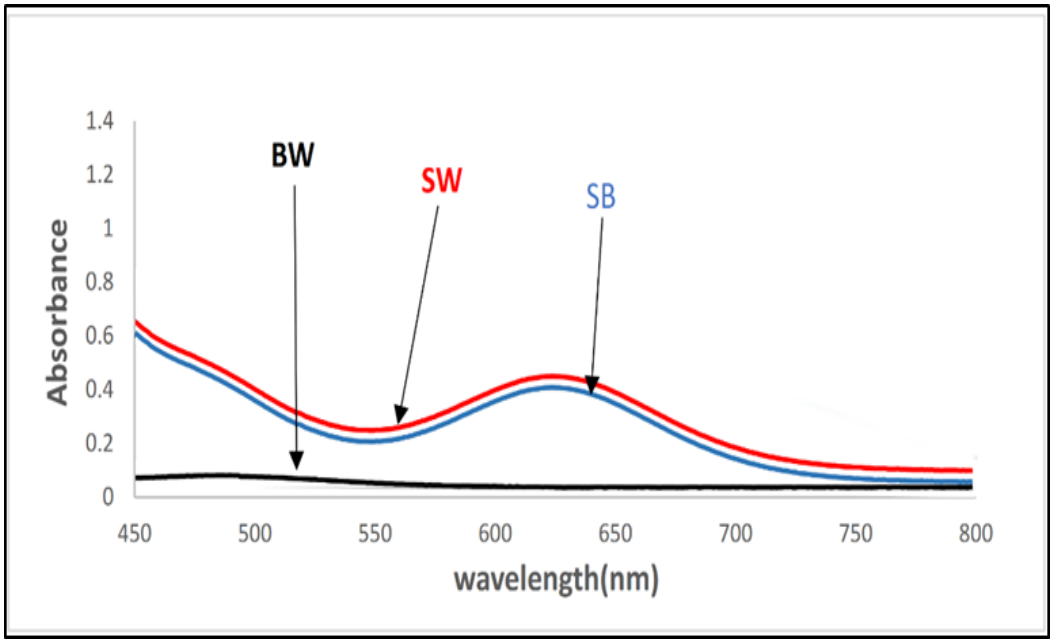


Fig. 8: The eventual absorption spectrum for the determination of MEL versus water (SW), MEL versus blank solution (SB), and blank solution versus water (BW). The concentration of MEL was 10 µg ml^{-1}.

The calibration graph

After selecting the optimized experimental conditions in **Table 3**, ranging from 0.3 to 2.0 ml of MEL drug solutions were transferred to a series of volumetric flasks (25 ml). These volumes corresponded to concentrations ranging from 3.0 µg ml^{-1} to 20 µg ml^{-1}. Subsequently, 1.0 ml of metol solution was added, followed by adding 1.0 ml of $FeCl_3$. Finally, 2.0 ml of Na_2CO_3 was added. The solutions were allowed to react for 5.0 minutes to achieve a complete reaction. The volumes were then completed with water, and the absorbance was determined by comparing it to the blank solution at 628 nm. **Fig. 9** and **10** demonstrate that the calibration graph adheres to Beer's law in the range of 3.0 to 20 µg ml^{-1}; higher concentrations seem to exhibit a deviation from Beer's law that is negative. The molar absorptivity and Sandell's index were determined, which were found to be 1.9959×10^4 L mol^{-1} cm^{-1} and 0.0176 µg cm^{-2}, respectively.

Table 3: Summary of optimum conditions.

Parameter	Optimum conditions
λmax	628nm
Amount of 7.1×10^{-4} M (MEL)	1.0 ml
Amount of 1×10^{-3}M metol	1.0 ml
Amount of 1×10^{-2} M $FeCl_3$	1.0 ml
Amount of 2×10^{-2} M Na_2CO_3	2.0 ml
Solvent	Water

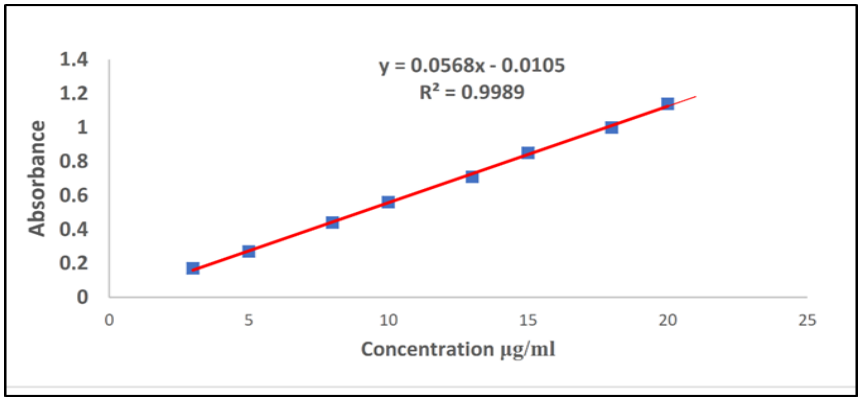


Fig. 9: The calibration graph for the estimation of MEL using the suggested method.

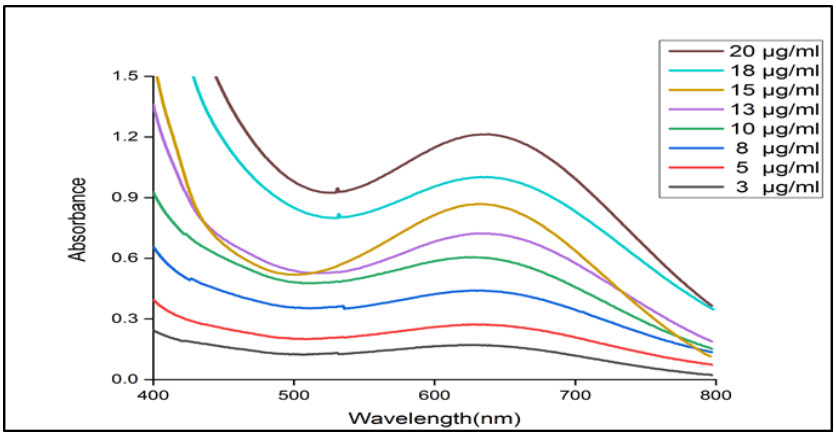


Fig. 10: The calibration graph spectra for the estimation of MEL using the suggested method.

The precision and accuracy

The examination of the precision and accuracy of the approach involved the assessment of the recovery percentage, as well as the relative standard deviation (RSD%) and the relative error (RE%) across three distinct concentrations (5, 10, and 15) µg ml-1, with the absorbance being assessed six times at a wavelength of 628 nm for each concentration. Subsequently, an average was computed. The results presented in **Table 4** indicated that the methodology employed to determine MEL exhibited satisfactory precision and accuracy.

The detection limit

The detection limit (DL) was calculated by measuring the absorption of the blank solution[33] under optimized conditions (six times) at a wavelength of 628 nm using **Equation 1**[34]. The DL of the method was found to be 0.1959 µg ml^{-1}.

$$DL = \frac{3.3 \times SD}{b} \ldots\ldots\ldots\ldots \quad Eq.\,1$$

Where (SD) is the standard deviation and (b) is the slope of the calibration curve

Statistical Parameters of the Method

The linear regression analysis was conducted to ascertain the accuracy and precision of the method employed. The statistical parameters show in **Table 5**,

Table 4: 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.

Table 5: Statistical Parameters of the Calibration Curve.

Parameter	Value
Slope	0.0568
Intercept	0.0105-
Standard deviation	0.003373
Correlation coefficient	0.99945
Determination coefficient	0.9989

Studying the ratio of MEL and reagent of metol in forming colored 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 reagent[35]. The outcomes in **Fig. 11**, indicate that the ratio of color dye formed between reagent and MEL is 1:1. The concentration of each standard MEL solution and metol reagent solution were equal to 7.1×10^{-4}M.

Stability constant of the dye formed (K_s)

We used the outcomes of Job's method to determine the stability constant for the 1:1 formed product (MEL and reagent). Solutions were prepared to contain equimolar quantities of MEL and reagent (metol), each having a concentration of 7.1×10^{-4} M. The absorbance of each solution was measured and compared to its respective blank, denoted as (As). Furthermore, solutions were prepared with the same quantity of MEL but with an excess amount (2 ml) of the regent, and their absorbance was denoted as (Am). The degree of dissociation (α) was determined using **Equation 2**. Subsequently, the stability constant of the reddish-orange dye produced in the aqueous solution was calculated using **Equation 3**. The outcomes shown in **Table 6** indicate that the product is highly stable.

$$\alpha = \frac{\mathrm{Am} - \mathrm{As}}{\mathrm{Am}} \ldots\ldots\ldots\ldots \text{Eq. 2}$$

$$\mathrm{K}_S = \frac{1-\alpha}{\alpha^2 C} \ldots\ldots\ldots\ldots\ldots \text{Eq. 3}$$

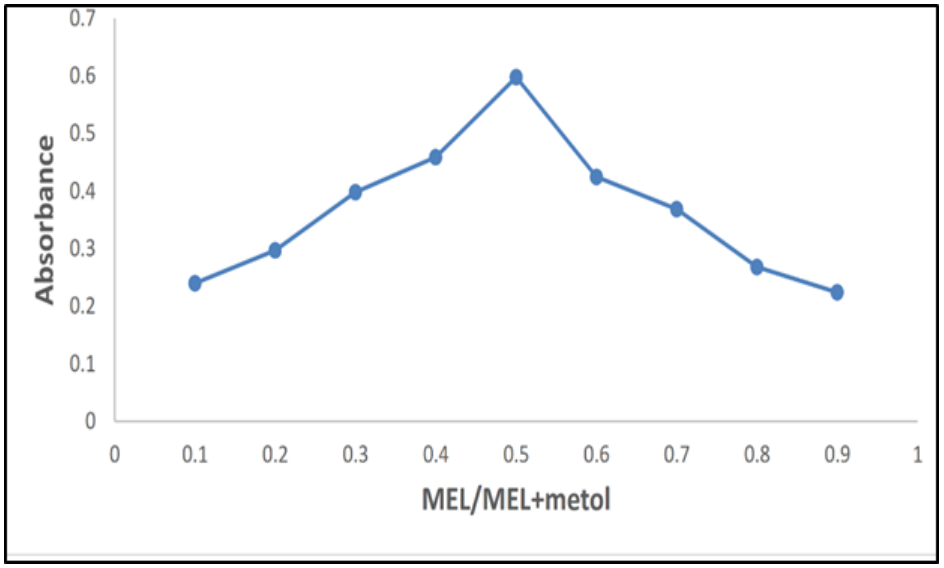
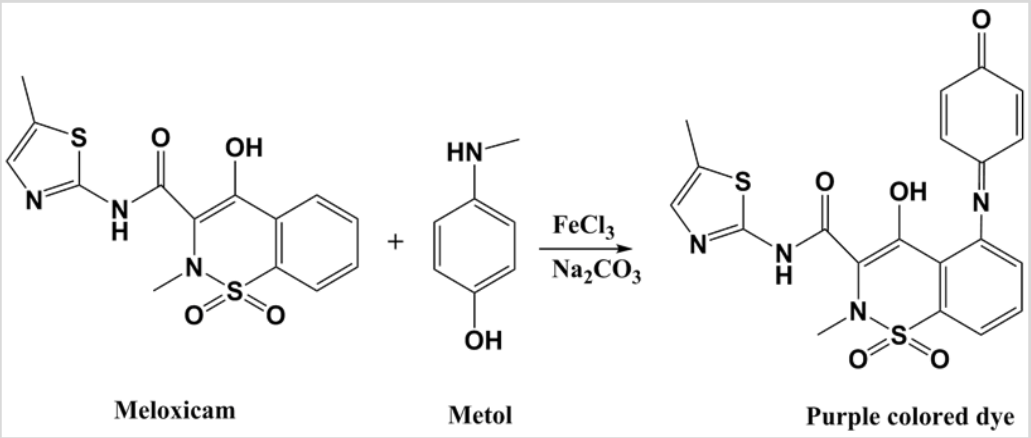


Fig. 11: Continuous variation method of purple-colored product.

(**Scheme 1**) shows the suggested mechanisms for the purple colored dye formed by the oxidative coupling reaction.



Scheme 1: The suggested mechanisms for the reaction.

Table 6: Stability constant.

*Concentration (C) M	Absorbance		α	K_S, L mol^{-1}
	A_s	A_m		
7.1X10^{-5}	0.563	0.712	0.2093	2.54×10^5

*(C) the concentration of the colored product.

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.

Direct method

To demonstrate the validity of the suggested method in estimating MEL in tablet form with three different concentrations, the results are summarized in **Table 7**. The assay results indicate that the proposed method is applicable.

The standard addition method

To establish that the technique was devoid of any interferences, standard addition was applied to determine MEL in its pharmaceutical preparation. The addition of constant volumes (0.5 and 1.0 ml), equivalent to (5.0 and 10 µg ml^{-1}) of the pharmaceutical preparation, was done in two series of six volumetric flasks of 25 ml. Then, increasing volumes of MEL solutions were added, and the absorption was measured against the blank solution at a wavelength of 628 nm. **Table 8** and **Fig. 12** illustrate the standard addition method in accordance with the suggested method.

Comparison of the method

Table 9 displays a comparison of various analytical variables between the current method and alternative methods found in the literature.

Table 7: The outcomes of the direct method for the determination of MEL tablet.

Amount of MEL (µg ml^{-1})		*RE%	*Recovery%	*RSD%
Taken	Measured			
5	4.98	-0.4	99.6	1.41
10	9.81	-1.9	98.1	1.63
20	19.63	-1.85	98.15	0.84

*Average of six times.

Table 8: 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	4.81	-1.8	98.2	1.76
10	10.10	1.3	101.3	1.22

*Average of six determinations.

Table 9: 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		628	3-20	0.96-1.42	98.86-101.2	0.1959	-
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	22
	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	25
	FIA	530	10-160	1.2	97.0-104	6.0	27

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

Statistical Agreement t-test

Both the current method and the method described in the literature [36] were simultaneously utilized in the t-test calculation, with the obtained value then compared against statistical tables for eight degrees of freedom at a 95% confidence level. The calculated T-statistic (0.2885) is less than the critical T-value (2.306), we have not found sufficient evidence to reject the null hypothesis, indicating that there is no statistically significant discrepancy between the averages of the reported and current approaches at a significance level of 5%.

Conclusion

A sensitive and accurate spectral method was developed for the estimation of escitalopram oxalate by the oxidative coupling reaction. The method is based on the reaction of MEL with the metol reagent in the presence of oxidizing agent ($FeCl_3$) in a basic medium, where a purple-colored product is formed, and the highest absorption is given at the wavelength of 628 nm. The method was successfully applied to determine the pharmaceutical preparation (loxim) with a recovery of no less than 98.1%. The results of this study underscore the potential of the developed spectrophotometric method as an efficient and precise analytical tool for the routine analysis of MEL in pharmaceutical settings. Its simplicity, cost-effectiveness, and high sensitivity make it a valuable addition to existing analytical techniques for MEL determination. Future work may explore the application of this method to other pharmaceutical compounds and expand its utility in various analytical scenarios. Overall, this study contributes to enhancing the analytical methodologies available for the quality control of pharmaceutical products containing meloxicam.

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التقدير الطيفي للميلوكسيكام في شكله النقي وفي مستحضراته الصيدلانية عن طريق تفاعل الاقتران التأكسدي

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تم استخدام طريقة طيفية جديدة وحساسة ورخيصة وبسيطة لتقدير الميلوكسيكام (MEL) من خلال تفاعل الاقتران التأكسدي مع كاشف الميتول في وجود كلوريد الحديديك ($FeCl_3$) في وسط قاعدي. ينتج عن هذا التفاعل منتج ذو لون بنفسجي مميز قابل للذوبان في الماء ويظهر أقصى امتصاص عند الطول الموجي ٦٢٨ نانومتر، بالمقارنة مع المحلول الصوري. تطيع الطريقة قانون بير ضمن نطاق تركيز يتراوح بين ٣,٠ إلى ٢٠ ميكروغرام مل−١، ويتمثل ذلك بخطأ نسبي يتراوح بين −١,١٣٪ إلى ١,٢٪ وانحراف معياري نسبي يتراوح بين ٠,٩٦٪ إلى ١,٥٥٪، حسب مستوى التركيز. تم تحديد المعايير التحليلية الرئيسية، بما في ذلك الامتصاصية المولارية بقيمة ١,٩٩٥٩×١٠٤ لتر مول−١ سم−١، وحساسية ساندل بقيمة ٠,٠١٧٦ ميكروغرام سم−٢، وحد الكشف بقيمة ٠,١٩٥٩ ميكروغرام مل−١. تم التحقق بنجاح من الطريقة المطورة وتطبيقها في تقدير الميلوكسيكام في المستحضرات الصيدلانية. تُظهر هذه الدراسة أن الطريقة الطيفية فعّالة ودقيقة ومناسبة للتحليل الروتيني للميلوكسيكام في مراقبة الجودة.