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Fourth Derivative and Compensated Area under the Curve Spectrophotometric Methods Used for Analysis Meloxicam in the Local Market Tablet

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Abstract

Two Rapid, direct, ecological friendly and economical spectrophotometric methods were used for estimation of meloxicam in the market Tablet dosage form. The First method is based on the use the fourth order derivative spectrum (D4) and the second method is depended on the ratio of the area under the curve for the two peaks in the drug (Compensated area under the curve). The linear calibration graphs of the two methods were measured in the concentration range (5-35)mg/l and the average of recoveries for local market Tablet (AWA)® were 99.8% for D4 method and 100.2% for CAUC method which indicating a good accuracy and precision for these methods. In this study, the results obtained by these suggested methods have been successfully statistically compared by t-test and Mann-Whitney test showed a good agreement.

Keywords: meloxicam; D4; CAUC; spectrophotometric; Mann-Whitney test

الخلاصة

طريقتان طيفية مناسبة وملائمة للبيئة واقتصادية استخدمت لتقدير عقار ميلوكسيكام في المستحضرات الصيدلانية. تعتمد الطريقة الأولى على طيف المشتقة الرابعة والطريقة الثانية تعتمد على نسبة المساحة تحت المنحني للقمتان الموجودتان بالدواء. كانت الخطية ضمن التراكيز (٥-٣٥ مغم/ لتر) ومعدل النسبة المؤوية للاسترجاع للعقار من شركة ®(AWA) بلغت 99.8% للمشتقة الرابعة وبلغت ١٠٠,٢% لطريقة التعويض للمساحة تحت المنحني وهذا يدل على الدقة الجيدة لهذه الطرق. و تم مقارنة الطريقتين إحصائيا باستخدام اختبار تي واختبار مان وتني وأعطت نتائج جيدة.

Introduction

Meloxicam **Figure1**, is a newer non-steroidal anti-inflammatory drug (NSAID) in the enolic acid group found to inhibit cyclo- oxygenase -2(cox-2)[1], it is used to treatment of ankylosing spondylitis, osteoarthritis and rhenumatoid arthritis[2]. Meloxicam drug was used to prepare nano crystal formulation to increase transdermal delivery[3], also made films nano crystals from meloxicam[4] and using meloxicam as an analytical reagent for determination silver and vanadium[5,6]. There are many analytical methods were reported for the estimation meloxicam in biological and pharmaceutical samples they include: flow-injection chemiluminescence [7], liquid-chromatography- tandem mass spectrometry [8], polarographic [9], flow injection spectrophotometric [10, 11], fluorimetric[12] and derivative spectrophotometric methods[13]. In this paper, two precise, simple and nontoxic specrophotometric methods were used to estimation meloxicam in market Tablet formulation, the first method was based on recording the fourth derivative spectra and the second method was depended on the area of the absorption spectrum for the peaks, the data for these methods were successfully statistically compared using parametric t-test and non-parametric mann-whitny U-test.

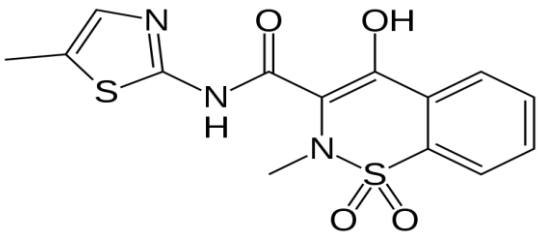

Figure1: structure of meloxicam

Materials and Methods

a. Apparatus : All the spectral measurements analysis were made by using spectrophotometric (VARIAN UV-visible) with 1cm path quartz cells with software program (originlab pro.2016) .
b. Material and standard solutions:

1. 1000 mg/l stock solution of pure meloxicam (M.Wt= 351.403) was prepared by dissolving (0.1gm) from this pure drug in 25 ml of distilled water and complete to 100 ml with the same solvent in 100 ml volumetric flask.
2. 100 mg/l standard solution was prepared by transferred 25 ml from 1000 mg/l standard solution to 250 ml volumetric flask and then complete the volume to the mark with distilled water.
3. Preparation of calibration graph was made up by preparation a series of 20 ml volumetric flask, (1,2,3,4,5,6 and7) ml of 100 mg/l meloxicam standard solution were transferred to obtained concentration (5,10,15,20,25,30 and 35) mg/l and then the volume of each flask was completed to the mark with distilled water.
4. Preparation of local market (AWA)® Tablet was made up by grinded ten Tablets and dissolving 0.1 gm from this powder in 100 ml distilled water to obtained concentration equal to 1000 mg/l , and then repeat the general procedure described under preparation of calibration graph.

Procedure:

1. The fourth derivative spectra were accomplished in the range (300-400 nm), the absolute values for calibration graph were measured at 361 nm.
2. The area under the curve values for the meloxicam were recorded over the wavelength range for the first peak A1(264-277nm) and for the second peak A2(352-378nm), the calibration graph was constructed by the calculated the area under the curve ratios(ratio $\frac{AUC_{A1}}{AUC_{A2}}$) for the meloxicam standard solution (5-35mg/l).

Results and Discussion

Fourth derivative method D4

Derivative spectrophotometric methods were widely used for the analysis of pharmaceutical drugs, this technique is required less time for the analysis, cheaper and easily applied to analysis of pharmaceutical and raw material.

The zero order spectra that have the similar linear relationship between absorbance of the solutions and the corresponding concentration for all orders of derivative [14, 15]:

"A=Є BC" …. For zero order

$$"\frac{d\lambda}{dA} = \frac{d\epsilon}{d\lambda}\ bc"\ for\ all\ derivative\ order$$

So, for the fourth derivative order, the equation became as the following:

$$"\frac{d^4A}{d\lambda^4} = \frac{d^4\,\epsilon}{d\lambda^4}\ bc"$$

Where, A= is the Absorbance of the solution, ʎ= is the wavelength, Є= is the molar absorpivity, I= is the width of cell and C= is the concentration of the solution.

Figure 2 (a,b) show the zero order and fourth derivative spectra of pure meloxicam standard solution. The normal absorbance spectra is called zero order spectra, derivative spectrophotometry technique is based on derivative spectra of the zero-order spectrum, a fourth derivative and all other derivative order are passes through the same wavelength as ʎ max of the absorbance band for the zero order spectrum. **Figure 3** shows that the minimum bands for the fourth derivative at the same wavelength as (361 nm) ʎ max of the zero order absorbance bands.

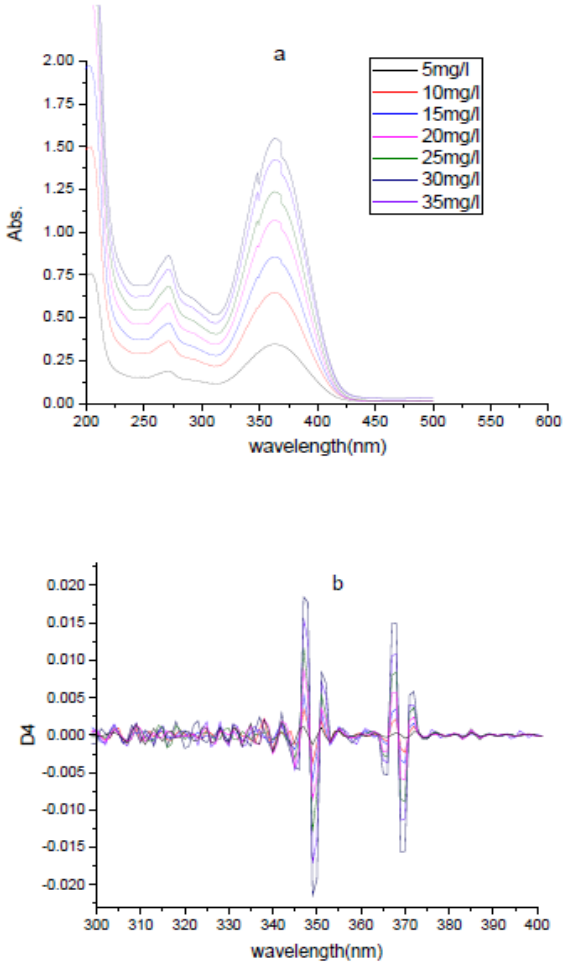

Figure 2: a- the zero order and b- the fourth derivative spectra of meloxicam standard solution

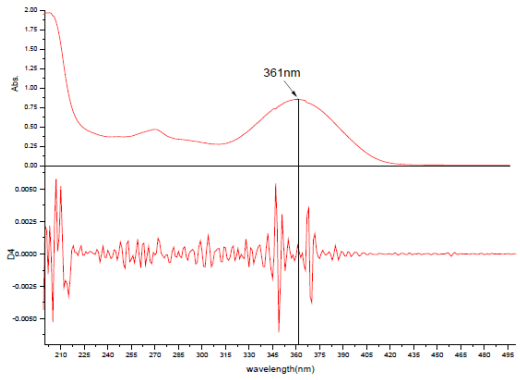

Figure 3: selected the wavelength 361 nm for fourth derivative order measurement at concentration 15mg/l

Compensated area under the curve method (CAUC)

This method is simple and providing better sensitivity and depended on measuring the area of the drug in the two range of wavelengths [(ʎ2-ʎ1) for peak A1 and (ʎ4-ʎ3) for peakA2] not only depending on the measuring the area at single wavelength, and then calculated the area under the curve ratio ($\frac{AUC_{A1}}{AUC_{A2}}$) for two peaks. **Figure4** is shown The AUC of meloxicam standard solution and the AUC was calculated from the following equations [16, 17, 18]:

$$"AUC_{A1} = \int_{ʎ1}^{ʎ2} A1\ dʎ = \int_{277}^{264} A1\ dʎ"$$
$$"AUC_{A2} = \int_{ʎ3}^{ʎ4} A2\ dʎ = \int_{378}^{352} A2\ dʎ"$$

Where; A1 and A2 = are the absorbance of meloxicam for the peak A1 and peak A2, respectively.

$\int_{ʎ1}^{ʎ2} A1\ dʎ$ and $\int_{ʎ3}^{ʎ4} A1\ dʎ$ = are the area under the curve between (264-277nm) for the peak A1 and (352-378nm) for the peak A2, respectively.

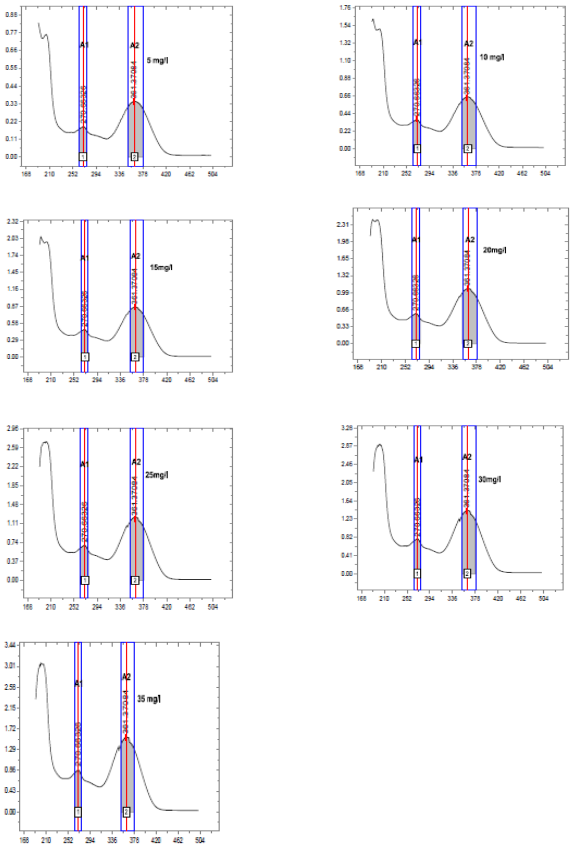

Figure 4: The CAUC at the selected wavelength ranges A1 (264–277 nm) and A2 (352–378 nm) for meloxicam standard solution

Calibration graph and validation parameters

the calibration graph for fourth derivative method was obtained by plotted the absorbance of the fourth derivative spectra vs. the concentration of the meloxicam standard solution **Figure 5** and the calibration graph for CAUC method **Figure 6** was obtained by plotted the AUC ratio vs. the concentration of the drug.

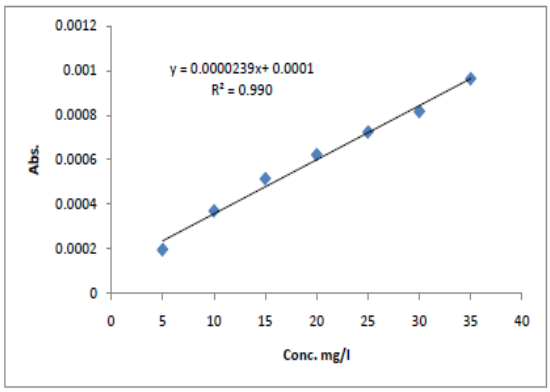

Figure5: the calibration graph of the fourth derivative for meloxicam standard solution

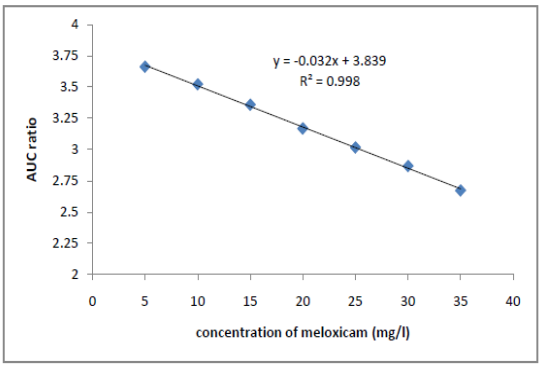

Figure 6: the calibration graph of the CAUC for meloxicam standard solution

Correlation of determination of the fourth derivative was 0.990 and 0.998 for the CAUC, the other statistical parameters analysis of the data was given from calibration graph are listed in Table 1.

Table 1: The validation parameters obtain from the calibration graph of meloxicam

	D4 at peak 361 nm	CAUC
Wavelength nm	361 nm	A1=(264-277nm) A2= (352-378 nm)
R^2	0.990	0.998
Linearity range(mg/L)	5-35	5-35
Equation	Y=0.0000239x+0.0001	Y= -0.032 x+3.839
b	0.0000239	-0.032
a	0.0001	3.839
Conf. limit for slope b± t_{sb}	0.0000239 ± 18.911	-0.032± -58.689
Conf. limit for Intercept a ± t_{sa}	0.0001± 4.212	3.839± 306.032

"b = Slope, a = intercept, S_b = Standard deviation of the slope, S_a = Standard deviation of intercept"

Accuracy and precision

The good recovery percentage indicate a high accuracy and the small values of relative standard deviation refer to a good precision, all the results are listed in Table 2.

Table (2): Accuracy and precision for this study

methods	Pure meloxicam Conc. (taken) mg/l	Pure meloxicam Conc. (Found) mg/l	Rec.* %	Avg of Rec.%	RSD* %
D4	15	15.091	100.606	100.619	2.664
	25	25.158	100.632		3.479
CAUC	15	14.881	99.206	99.847	1.442
	25	25.124	100.488		1.852

Application and statistical analysis

The proposed methods are successfully applied to estimation of meloxicam (AWA)® Tablet. Figures (7a, b) and 8 shows the spectra of market meloxicam(AWA)® Tablet was analysis by the two suggested methods, the results in Table 3 are shown the robustness and reliability of this study.

The recoveries results were statistically compared by using parametric t-test and non-parametric mann-whitny U-test as shown in Table 4. The results of the t-test at (95% confidence level) and Mann –Whitney test U did not exceed the theoretical t value 4.303 and theoretical U value 3 for the two suggested methods, which indicate that there is no difference between fourth derivative and CAUC spectrophotometric methods and reported method [19] and refer to a good accuracy and precision in estimation meloxicam in pure and local market Tablet (AWA)®.

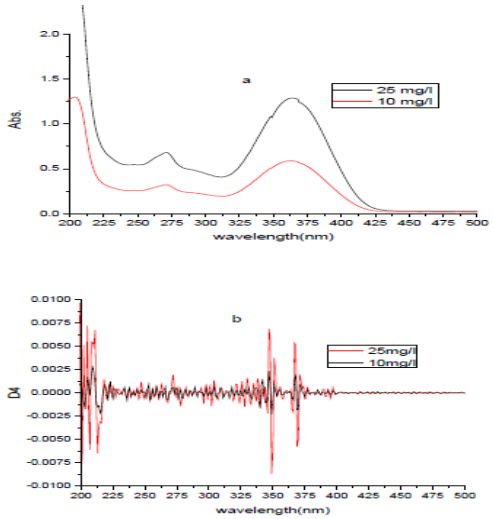

Figure 7: a- the zero order and b- the fourth derivative spectra of market meloxicam (AWA)® Tablet at concentration 10 and 25 mg/l

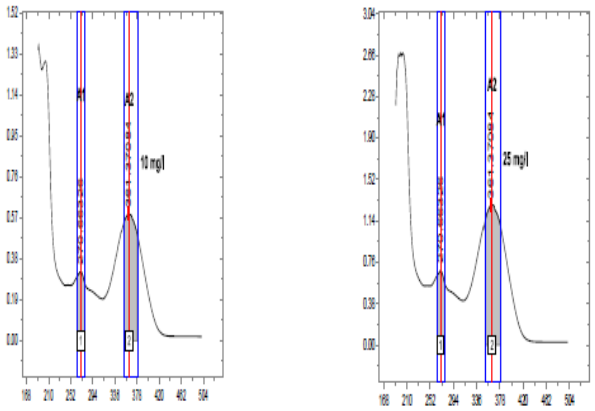

Figure 8: The CAUC for the market meloxicam(AWA)® Tablet at concentration 10 and 25 mg/l

Table 2: The recovery and relative standard deviations of the local marcet market meloxicam (AWA)® Tablet at 12 and 20 mg.l^{-1}.

method	Meloxicam (AWA) Awamedica 15mg. Tablet		Rec.* %	Average of Rec.%	RSD*%
	(taken) mg/l	(Found) mg/l			
D4	10	9.965	99.650	99.785	1.269
	25	24.980	99.920		0.560
CAUC	10	9.977	99.770	100.249	1.758
	25	25.182	100.728		0.932

"*Average of three determination"

Table 4: The comparison of theD4 and CAUC Spectrophotometric methods with reported method

		Statistical Parameters	Tablet Pharmaceutical preparation	
			meloxicam pure	Meloxicam (AWA)® 15 mg Tablets
Present work	D4 At peak 361 nm	Rec.%	100.619	99.785
		S**	0.418	
		t*	0.530	
		s_1^2	0.347	
		∑ Rank	5	
		U	2	
	CAUC	Rec.%	99.847	100.249
		S**	0.204	
		t*	0.331	
		s_1^2	0.080	
		∑ Rank	5	
		U	2	
Reported method[19]		Rec.%	99.940	100.020
		s_2^2	0.0032	
		∑Rank	5	

"Where, S**= pooled standard deviation $= \sqrt{\frac{(n1-1)s_1^2+(n2-1)s_2^2}{n1+n2-2}}$, (n_1-1) and (n_2-1)= number of degrees of freedom for this study and standard method, respectively, t*= parametric t-test, $T_{theoretical}$ = 4.303, $T_{calculated} < T_{theortical}$ at 95% confidence level, S^2_1 = *variation* $= \frac{\Sigma(xi-\bar{x})_1^2}{n1-1}$, $S^2_2 = \frac{\Sigma(xi-\bar{x})_2^2}{n2-1}$, $t^* = \frac{|\bar{x}1-\bar{x}2|}{s^{**}\sqrt{\left(\frac{1}{n1}+\frac{1}{n2}\right)}}$

U= Mann - Whitney non parametric test(n1=n2=2), $U = \sum Rank - \frac{n(n+1)}{2}$, $U_{theoretical}$=3 , $U_{calculated} < U_{theortical}$."

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