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Ratio Derivative Spectrophotometric Method for the Determination of Some Oxicams in Presence of their Alkaline Degradation Products

Elham Anwer Taha *[1] , Eman Saad El- Zanfally [2] and Nahla Nour Salama [1]

[1] National Organization for Drug Control and Research,6 Abou Hazem Street, Pyramids Ave, P.O. Box 29 Giza, Egypt.

[2] Department of Analytical Chemistry, Faculty of Pharmacy, Cairo University, Kasr El-Eini Street,11562 Cairo, Egypt.

ABSTRACT

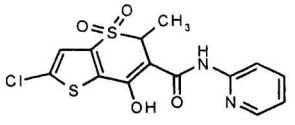
A new spectrophotometric method has been developed for the determination of some oxicams namely, lornoxicam (LX) , tenoxicam (TX) and meloxicam (MX), in the presence of their main alkaline degradation products, 2-aminopyridine (I) and 2-amino-5-methylthiazole (II) for (TX&MX), 2-aminopyridine and TX for lornoxicam. The method is based on the use of the first derivative of the ratio spectra (^{1}DD) of the mentioned compounds and their corresponding degradates. The procedure does not require any separation steps. Linear calibration graphs of ^{1}DD were obtained by measurement of the amplitudes at 316, 249 and 260nm for LX, 248.8 , 258.8 nm for TX and 287.2nm for MX. On carrying out measurements at the above mentioned wavelengths, the linearity range is found to be 2.5 - 35 μg ml^{-1} for LX and TX, 1.25 - 30 μg ml^{-1} for MX. The validity of the method was assessed by applying the standard addition technique. Statistical analysis of the results has been carried out revealing high accuracy and good precision. The suggested procedure could be used for the determination of the above mentioned drugs in pure and dosage forms as well as in presence of their degradation products.

Keywords

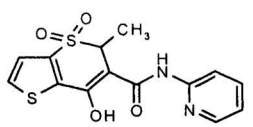
Ratio derivative spectrophotometry , Oxicams , 2-aminopyridine , 2- amino-5-methylthiazole, dosage forms.

Introduction

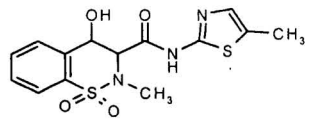
Lornoxicam (LX), 6-chloro-4-Hydroxy-2-methyl-N-2-pridinyl-2H-thieno[2,3-e]-1,2-thiazine- 3- carboxamide 1,1-dioxide [1] , tenoxicam (TX), 4-hydroxy-2-methyl-N-(pyridin-2-yl)-2H-thieno [2,3-e] 1,2-thiazine-3-carboxamide 1,1-dioxide [2] and meloxicam (MX), 4-hydroxy-2-methyl-N-(5-methyl-1.3-thiazol-2-yl)-2-H-1,2-benzothiazine-3-carboxamide 1,1-dioxide [2] are oxicam derivatives non-steroidal anti-inflammatory drugs ($NSAID_S$) Fig.1.They are used in the treatment of rheumatoid arthritis, osteoarthritis and related conditions [3] . The pharmacological actions of these oxicams are related to inhibition of cyclooxygenase (cox), a key enzyme of prostaglandine biosynthesis at the site of inflammation. Meloxicam is suggested to be a selective cox-2 inhibitor [4].



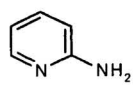
loronoxicam (LX)



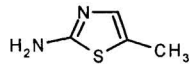
Tenoxicam (TX)



Meloxicam (MX)



2- Aminopyridine I



2-Amino-5-methylthiazole II

Fig. 1. Chemical structures and abbreviations of the studied oxicams and their degradations.

The official methods for the determination of TX and MX are non aqueous titration with perchloric acid, determining the end point potentiometrically [2] . Lornoxicam is not official in any pharmacopoeia and no method has been reported in the literature for the determination of LX in presence of its degradation products. Only few HPLC [5,6] methods were reported for its determination. For TX, different methods were reported including spectrophotometric [7-9] , infra-red [10] , HPLC [11] , polarographic [12,13] and electrochemical[14] .For MX, spectrophotometric [9,15,16], HPLC [5,17] and electrochemical [18,19] methods were reported. The aim of this work was to develop sensitive, selective and validated stability

indicating method for determination of the three studied drugs in presence of their degradation products using first derivative of ratio spectrum.

EXPERIMENTAL

Apparatus

A double- beam shimadzu (Japan) UV- VIS Spectrophotometer , model UV1601 PC connected to an IBM compatible computer and a HP600 inkjet printer was used .The bundle software was UVPC personal spectroscopy software version 3.7 (Shimadzu). The spectral bandwidth was 2nm and the wavelength scanning speed was 2800 nm min^{-1} . The absorption specra of a test and reference solutions were recorded in 1cm quartz cells over the range 450 - 200 nm.

Materials

Lornoxicam (LX); was kindly supplied by October Pharm. Co. (Egypt). The purity of the sample was found to be 99.97± 0.67 , according to the manufacture non aqueous method [20] . Xefo tablets (October Pharm. Co.) are labeled to contain 8mg / tablet . Tenoxicam (TX) was kindly obtained from Epico Co. (Egypt) , its purity was found to be 99.74 ± 0.86 , according to the official method [2] . Epicotil tablets and vials Epico Co.(Egypt) are labeled to contain 20mg /tablet or vial. Meloxicam (MX) was kindly supplied by Adwia Co. (Egypt). The purity of the sample was found to be 99.94 ±0.76 , according to the official method [2] . Anticox II tablets ,ampoules and capsules (Adwia Co., Egypt) are labeled to contain 15mg / tablet or ampoule and 7.5 mg / capsule . 2-Aminopyridine was purchased from Reidel - 36685 (99.9 %) . 2-Amino-5-methylthiazole was purchased from Fluka- 08652 (98.0%).

Reagents

All reagents and solvent used were of analytical grade. Methanol (Lab - Scan) and sodium hydroxide 0.1 N aqueous solution.

Stock solution

Standard stock solutions (1mg ml^{-1}) were prepared by transfering accurately weighed 25mg of LX , TX, and MX in 25 ml volumetric flask then dissolved in 3ml of 0.1 N NaOH and completed to the volume with methanol. These stock solutions were subsequentely used for the preparation of working standards in concentration range of 2.50- 35 µg ml^{-1} for LX and TX, and 1.25 - 30µg ml^{-1} for MX by further dilution with 0.1N NaOH.

General Procedure

The UV absorption specra of standard solutions of LX, were divided by the UV absorption spectrum of 10 µg ml^{-1} of TX and 5 µg ml^{-1} of (I) (in 0.1 N NaOH as solvent). For TX, the UV absorption spectra of standard solutions were divided by 5 µg ml^{-1} of (I) (in 0.1 N NaOH as solvent). For MX , the UV absorption spectra of standard solutions were divided by the normalized spectrum of (II) (in 0.1 N NaOH as solvent). The first derivative was calculated for the obtained ratio specra with $\Delta \lambda = 4$ nm and scaling factor = 10. The amplitudes at 249nm, 260nm (divisor 5 µg ml^{-1} of I) and at 316nm (divisor 10 µg ml^{-1} of TX) were measured and found to be proportional to the concentration of LX .The amplitudes at 248.8 nm and 258.8nm were measured and found to be proportional to the concentration of TX. As for MX, the amplitudes at 287.2nm were measured and were found to be proportional to the concentration of MX.

Procedure for Determination of the studied compounds in Dosage Forms

An accurately weighed amount of the tablets , capsules or vials powder and equivalent milliliters of ampoules , equivalent to 25mg of the cited drugs were dissolved in 3 ml of 0.1N NaOH and 15 ml methanol . The solutions were stirred with magnetic stirrer for 30 mins., for tablets and capsules and shaked for 15mins for vials and ampoules. The solutions were transferred quantitatively to 25ml volumetric flask , the volume was completed with methanol and filtered .Then completed as under general procedure.

Results and discussion

The UV absorption spectra of LX and its degradation products TX and 2-aminopyridine (I) in 0.1N NaOH display complete overlap with TX and considerable overlap with (I) , that the conventional spectrophotometry failed to resolve , as shown in Fig. 2. However , this spectral overlapping was sufficient enough to demonstrate the resolving power of the ^{1}DD method to be used as a stability indicating method.

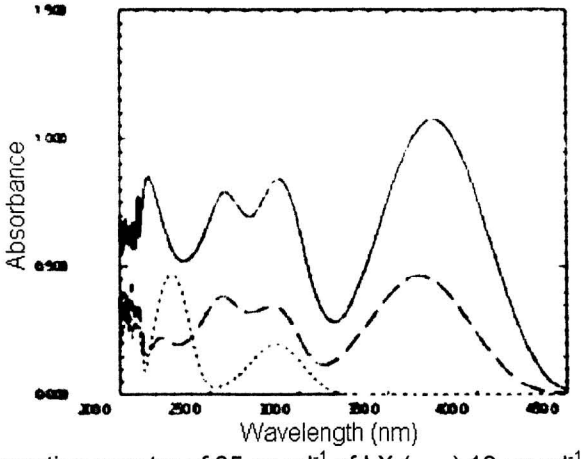


Fig. 2. UV absorption spectra of 25 μg ml^{-1} of LX (___),10 μg ml^{-1} of TX (-----) and 5 μg ml^{-1} of 2-aminopyridine (.....) in 0.1N NaoH.

The main advantage of the derivative of the ratio spectra method may be the chance of doing measurements in correspondence of peaks , hence there is a potential for greater sensitivity and accuracy. While the main disadvantages of the zero crossing method in derivative spectrophotometry for resolving a mixture of component with overlapped spectra one the risk of small drifts of the working wavelengths and the circumstance that the

working wavelengths generally do not fall in correspondence of peaks of the derivative spectrum. This may be particularly dangerous when the slope of the spectrum is very high with consequent loss of accuracy and precision , and the working wavelength is proximity of the base of the spectrum , which causes poor sensitivity [21].

To optimize the ^{1} DD method for determination of LX, TX and MX in presence of their degradation products , it is necessary to test the influence of the variable : divisor concentration , $\Delta\lambda$ and smoothing function [22] . All these variables were carefully studied . The influence of the $\Delta\lambda$ for obtaining the ^{1} DD was tested and $\Delta\lambda$ = 4 nm was selected as optimum value. A correct choice of the divisor concentration is fundamental for several reasons. Among these , is the wavelength range where the absorbance of the spectrum used as divisor is zero , bad choice of the divisor concentration may lead to great noise of ratio spectra. If the concentration of divisor is increased or decreased , the resulting derivative ratio values are proportionally decreased or increased with consequent variation of both sensitivity and linearity range. From several tests ,The best results in terms of signal to noise ratio , accuracy , sensitivity and repeatability were obtained upon using 10 μg ml^{-1} of TX and 5 μg ml^{-1} of (I) as divisor for LX. Fig. 3 ,4. For TX , 5 μg ml^{-1} of (I) was used as a divisor Fig. 5,6 . For MX, normalized spectrum of (II) was used Fig. 7, 8 . The first derivative was calculated for the ratio spectra obtained with $\Delta\lambda$ = 4nm.The ^{1} DD showed several peaks at different wavelengths. The best results were obtained upon using 316nm for determination of LX in presence of TX and 249 , 260 nm in presence of (I). The concentration range obtained was 2.50 - 35 μg ml^{-1} for all the above mentioned wavelengths. As for TX , ^{1} DD showed peaks at 248.8 and 258.8 nm in presence of its degradation products (I).

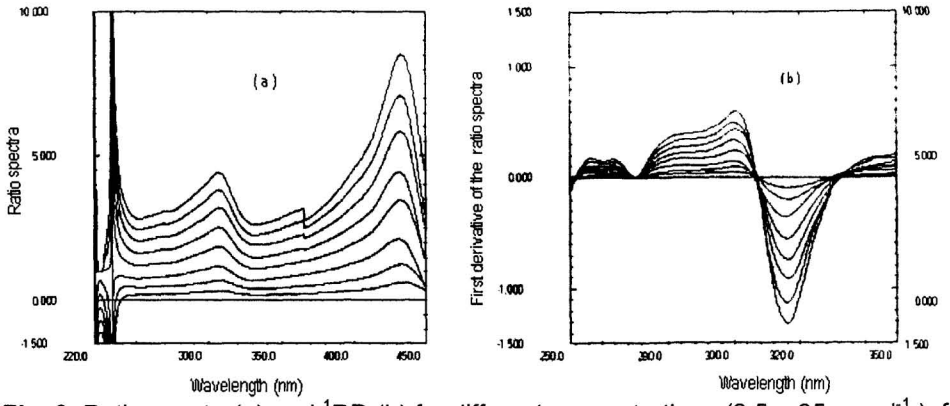


Fig. 3. Ratio spectra(a) and ^{1}DD (b) for different concentrations (2.5 – 35 µg ml^{-1})of LX , using 10 µg ml^{-1} of TX as a divisor .

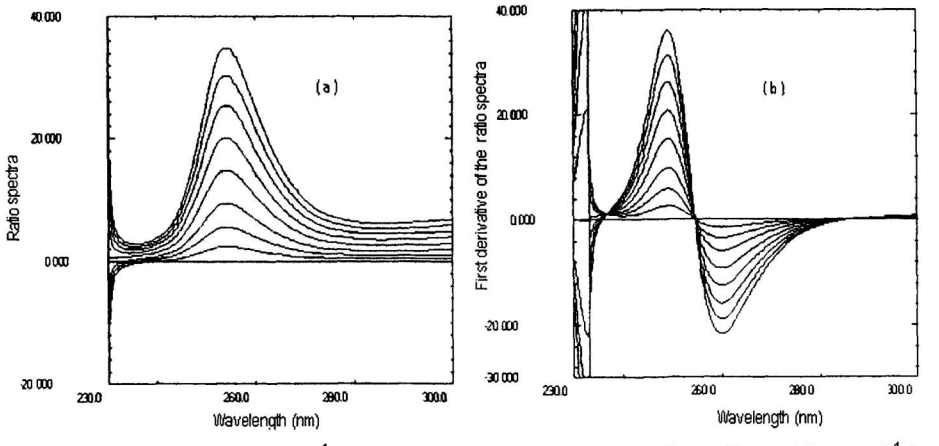


Fig. 4. Ratio spectra (a) and ^{1}DD (b) for different concentrations (2.5 - 35 µg ml^{-1}) of LX , using 5 µg ml^{-1} of 2-aminpyridine as a divisor .

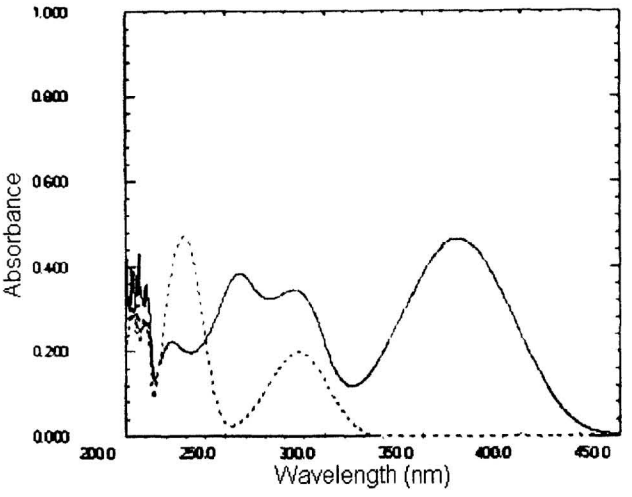


Fig. 5. UV absorption spectra of 10 μg ml^{-1} of TX (——) and 5 μg ml^{-1} of 2-aminopyridine (.....) in 0.1 N NaoH .

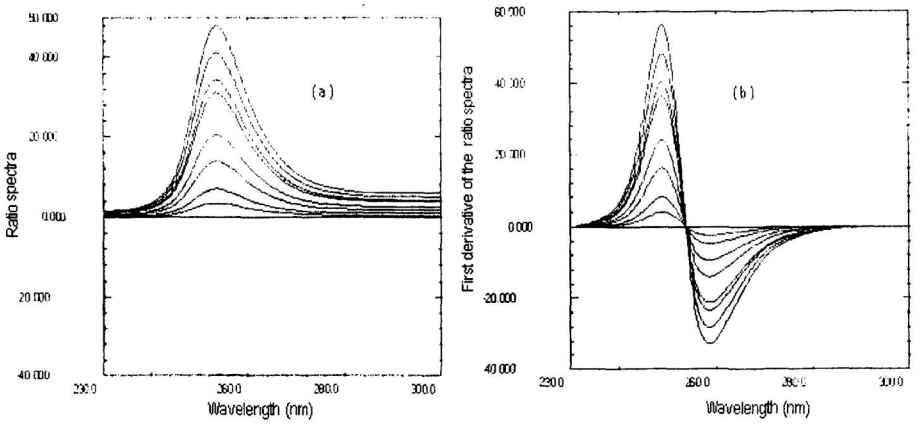


Fig. 6. Ratio spectra (a) and ^{1}DD (b) for different concentrations (2.5 – 35 μg ml^{-1}) of TX , using 5 μg ml^{-1} of 2-aminopyridine as a divisor .

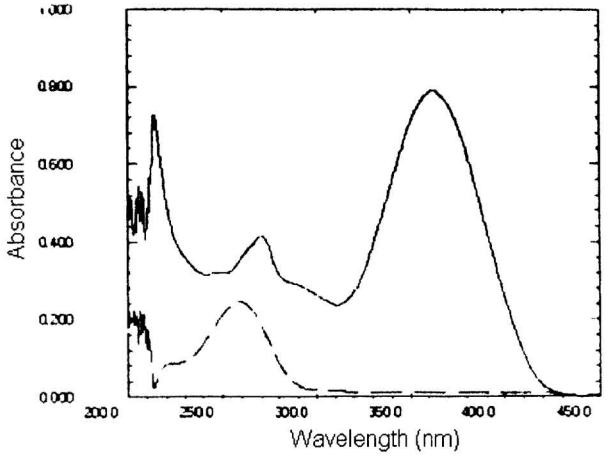


Fig. 7: UV absorption spectra of 10 μg ml^{-1} of MX (___) and 5 μg ml^{-1} of 2-amino-5-methylthiazole (-----) in 0.1 N NaoH .

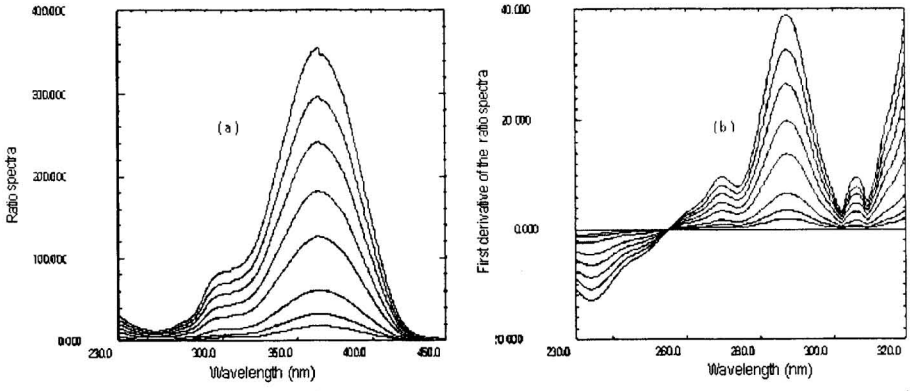


Fig. 8. Ratio spectra (a) and ^{1}DD (b) for different concentrations (1.25 – 30 μg ml^{-1}) of MX , using normalized spectrum of 2-amino-5-methylthiazole as a divisor .

TX could be determined in concentration range 2.5 - 35 μg ml^{-1} . For MX ^{1}DD peak obtained was at 287.2 nm and the concentration range of the method was

1.25 -30 µg ml^{-1}. The characteristic parameters for regression equations are given in table 1.

	Lornoxicam			Tenoxicam		Meloxicam
	λ_{316nm}	λ_{249nm}	λ_{249nm}	$\lambda_{248.8nm}$	$\lambda_{248.8nm}$	$\lambda_{248.8nm}$
Calibration range (µg ml^{-1})	2..5 - 35	2..5 - 35	2..5 - 35	2..5 - 35	2..5 - 35	1.25 - 30
Precision						
Intraday*	0.29	0.45	0.28	0.75	0.5	0.4
Interday*	0.39	0.79	0.52	1.07	0.63	0.35
Accuracy						
Mean±RSD%	100±0.78	100.02±0.73	100.23±0.97	100.08±0.46	100.13±0.86	100.28±0.83
Regression equation						
. Slope	$3.68x10^{-2}$	1.0411	0.63	1.6053	0.9372	1.3016
. S E of slope	$1.57x10^{-4}$	$1.02x10^{-2}$	$6.9x10^{-3}$	$3.4x10^{-3}$	$1.84 x10^{-3}$	$6.1 x10^{-3}$
. Intercept	$2.88x10^{-2}$	- 0.1641	-0.1587	0.0201	0.0418	0.2731
. S E of intercept	$3.31x10^{-3}$	0.227381	0.154	$7.1 x10^{-2}$	$3.9 x10^{-2}$	0.103
Correlation coeffient	0.99995	0.9997	0.9997	1	1	0.99995
.SE of estimation	$4.87x10^{-3}$	0.285	0.193	0.105	$5.7 x10^{-2}$	0.17

*n=9

Tab.1. Results of assay validation obtained by applying the proposed method .

The proposed method was compared with those of the reported [20] or official methods [2]. Statistical comparison of the results was performed with regard to accuracy and precision using student's t - test and F- ratio at 95% confidence level. Table 2, shows that there is no significant difference between the proposed method and the reported or official method.

	Lornoxicam Recovery* %				Tenoxicam Recovery* %			Meloxicam Recovery* %	
	λ316nm	λ249nm	λ260nm	manufacturer method [20]	λ 248.8nm	λ 258.8nm	Official Method [2]	λ 287.2nm	Official Method [2]
Mean	100.17	100.02	100.23	99.97	100.08	100.13	99.74	100.28	99.94
SD	0.78	0.73	0.97	0.67	0.46	0.86	0.86	0.83	0.76
RSD	0.78	0.73	0.97	0.67	0.46	0.86	0.86	0.83	0.76
SE	0.35	0.33	0.43	0.30	0.17	0.33	0.38	0.34	0.34
Variance	0.60	0.53	0.94	0.45	0.21	0.74	0.74	0.69	0.58
n	5	5	5	5	7	7	5	6	5
t-test	0.43	0.11	0.50	(2.306)**	0.82	0.77	(2.228)**	0.71	(2.306)**
F	1.33	1.78	2.09	(6.4)**	3.52	1.0	(6.2)**	1.19	(6.3)**

* Mean of three experiment .

** Theoritical values for t and F (P=0.05) .

Tab.2. Statistical comparison between the results of the proposed [1]DD method and the manufacure or official method for the determination of lornoxicam, tenoxicam and meloxicam in their pure powder form .

To assess the stability indicating efficiency of the proposed method , the degradation products of LX , TX and MX were mixed with their intact samples in different ratios (10 - 90 %) and mixtures were analysed by the proposed method as shown in table 3.

	Lornoxicam Concentration(µg ml^{-1}						Temoxicam Concentration(µg ml^{-1}				Meloxicam Concentration(µg ml^{-1}		
% Deg.	Intact drug	tenoxicam	2-amino pyridine	Intact drug recovery* %			Intact drug	2-amino pyridine	Intact drug recovery* %		Intact drug	2-amino-5-methyl thiazole	Intact drug recovery* %
				λ 316nm	λ 249nm	λ 260nm			λ 248.8nm	λ 258.8nm			λ 287.2nm
10	22.5	2.5	2.5	100.7	98.82	98.79	22.5	2.5	101.12	98.69	22.5	2.5	99.57
20	20.0	5.0	5.0	98.6	99.26	98.9	20.0	5.0	99.55	99.1	20.0	5.0	99.8
40	15.0	10.0	10.0	98.2	99.2	99.38	15.0	10.0	100.79	98.76	15.0	10.0	99.1
60	10.0	15.0	15.0	98.15	98.13	101.12	10.0	15.0	99.06	101.5	10.0	15.0	99.02
80	5.0	20.0	20.0	-	99.48	101.5	5.0	20.0	98.5	100.52	5.0	20.0	-
90	2.5	22.5	22.5	-	98.26	98.7	2.5	22.5	100.5	98.61	2.5	22.5	-
Mean ±RSD				98.66 0.73	98.86 0.56	99.06 0.33			99.63 0.94	99.2 0.73			99.37 0.38

* Mean of five determinations

Tab.3. Determination of laboratory prepared mixtures of the studied oxicams by the proposed ^{1}DD method .

It is clear that the accuracy of the proposed method is not affected by up to 90% of 2- aminopyridine as degradation product for LX and TX, and up to 60 % of TX and 2-amino -5 -methylthiazole as degradation products for LX and MX respectively.

Application of the proposed method for the determination of dosage forms

The proposed procedure was successfully applied for the analysis of LX , TX and MX in their pharmaceutical dosage forms. No interference due to excipients was detected in the spectra produced . Table 4, shows statistical comparison of the results obtained by the propoed method and those of the reported or official methods. Furthermore , the validity of the proposed procedure was assessed by applying standard addition technique , as shown in table 5.

	Proposed [1] DD method Recovery* % ± c.v.	Reported[a&b] or official [2] method Recovery* % ± c.v.
Lornoxicam[a]		
Xefo 8 mg / tablet	λ_{316nm} 102.5 ± 0.02 λ_{249nm} 98.6 ± 0.26 λ_{260nm} 100.18± 0.46	100.56 ± 0.83
Tenoxicam [2]		
Epicotil 20 mg / tablet	$\lambda_{248.8nm}$ 102.11± 0.1 $\lambda_{258.8nm}$ 101.5 ± 0.06	99.96 ± 0.83
Epicotil 20 mg / vial	$\lambda_{248.8nm}$ 99.13 ± 0.16 $\lambda_{258.8nm}$ 100.18± 0.09	97.4 ± 0.46
Meloxicam[b]		
Anticox II 15 mg / tablet	$\lambda_{287.2nm}$ 99.14± 0.82	99.82 ± 1.17
Anticox II 15 mg / ampoule	$\lambda_{287.2nm}$ 102.76±0.35	101.1 ± 0.38
Anticox II 7.5 mg /capsule	$\lambda_{287.2nm}$ 98.74 ± 0.21	101.1 ± 0.38

* Mean of five experiments .

[a] HPLC manufacture procedure supplied by October Pharm Co. Egypt .

[b] Spectrophotometry manufacture method supplied by Adwia Co. Egypt .

Tab.4. Comparison between the proposed method and the manufacture or official method for the determination of the studied drugs in their pharmaceutical dosage forms.

	Amount taken ($\mu g\ ml^{-1}$)	Authentic added ($\mu g\ ml^{-1}$)	Found recovery* % ± RSD
Lornoxicam			
Xefo 8 mg / tablet			
at 316 nm			99.25 ± 0.36
at 249 nm	10	5.0 – 20.0	100.84 ± 0.52
at 260 nm			100.17 ± 0.94
Tenoxicam			
Epicotil 20 mg / tablet			
at 248.8 nm	10	5.0 - 20.0	98.71 ± 0.72
at 258.8 nm			99.14 ± 0.3
Epicotil 20 mg / vial			
at 248.8 nm	10	5.0 – 25.0	98.9 ± 0.46
at 258.8 nm			98.65 ± 0.79
Meloxicam			
at 287.2nm			
Anticox II 15 mg / tablet	10		100.22 ± 0.59
Anticox II 15 mg / ampoule	10	5.0 – 20.0	100.03 ± 0.42
Anticox II 7.5 mg /capsule	10		101.4 ± 0.75

* Mean of five experiments .

Tab.5. Results of application of standard addition technique for the determination of lornoxicam , tenoxicam and meloxicam by the proposed [1]DD method .

Validation of the method

Linearity

The linearity of the proposed method was evaluated by analysing a series of different concentrations of LX , TX and MX .According to the ICH guidelines [23] , at least five concentrations must be used . In this study seven concentrations were chosen ranging between 2.5 - 35 μg ml^{-1} for LX and TX and 1.25 - 30 μg ml^{-1} for MX. Each concentration was repeated three times , the repeated runs were genuine repeats and not just repetitions at the same reading ; this approach will provide information on the variation in ^{1} DD values between samples of the same concentration . The assay was performed according to the experimental conditions previousely established. The linearity of the calibration graphs and adherence of the system to Beer ' s law were validated by the high value of the correlation coefficient, Table 1.

Precision

For evaluation of the precision intraday precision of the method were evaluated by assaying freshly prepared solutions in triplicate at concentrations of 10, 15 and 25 μg ml^{-1} of the three drugs . RSD are shown in table 1. The interday precision of the method calculated from assaying freshly prepared solutions in triplicate for three days . The RSD of the studied drugs are shown in table 1. This demonstrated the ruggedness of the method and its suitability for use in routine analysis , quality control of the three drugs in bulk substances as well as in pharmaceutical formulations.

Selectivity

Method selectivity was achieved by preparing different mixtures of LX, TX and MX within the linearity range concentration and their degradation

products. The synthetic mixtures were analysed according to the proposed method described under general procedure. Satisfactory results were obtained in table3,indicating the high selectivity of the proposed method for determination of LX , TX and MX in the presence of their degradation products.

Accuracy

This study was performed by addition of known amounts of LX, TX and MX each to a known concentration of the commercial preparations (standard addition method). The resulting mixtures were assayed and results obtained for LX, TX and MX were compared with expected results. The excellent recoveries of the standard addition method ,shown in table 5 indicate good accuracy of the proposed method and there is no interference from the excipients .

Robustness

The robustness of a method is its ability to remain unaffected by small change in parameters. To determine robustness of the proposed method, experimental conditions such as strength of sodium hydroxide were purposely altered and ^{1}DD characteristic was evaluated . Variation of strength of NaOH did not have a significant effect on ^{1}DD amplitude in the proposed method

The proposed ^{1}DD method provides simple , accurate and reproducible quantitative analysis for the determination of LX , TX and MX in pure form , in pharmaceutical dosage forms and in the presence of their degradation products This method was validated in comparison with the official or manufacturer HPLC methods. Although HPLC methods have a higher selectivity , they require complicated pretreatment and use of expensive apparatus and solvents. The advantages of the proposed method are low cost , rapidity and environmental protection. It is suitable for quality control laboratories , where economy and time are essential.

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