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ANALYTICAL METHOD DEVELOPMENT AND ITS VALIDATION FOR SIMULTANEOUS ESTIMATION OF ETORICOXIB AND PARACETAMOL IN BULK AND TABLET DOSAGE FORM BY UV- SPECTROSCOPIC METHOD

Yogesh Waghmare*, Vilas Kamble and Sonali Mahaparale

Department of Quality Assurance Technique, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India.

***Corresponding Author: Yogesh Waghmare**

Department of Quality Assurance Technique, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune-411044, Maharashtra, India.

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ABSTRACT

The two methods for simultaneous estimation of Etoricoxib and Paracetamol in combination of two drug tablet dosage form have been developed using Sodium Hydroxide (NaOH) as a solvent. The UV-visible Spectrophotometric method was a determination using the simultaneous or operating of the same time equation method was a determination using the simultaneous equation method at 234 nm and 254 nm. The second UV Spectrometric method is the Q-analysis (absorption ratio) method, which involves the formation of absorbance equation at 243 nm (isoabsorptive point) and at 254 nm the maximum absorption of Paracetamol. The accuracy of the methods was assessed by recovery studies was found to be 100.3 ± 0.53 and 100.4 ± 0.80 for simultaneous equation method and 96.8 ± 0.55 and 98.18 ± 0.58 for Q analysis (absorption ratio) method for Etoricoxib and Paracetamol respectively. These methods are no complicated involved also corrected and rapid those require no in preparation of the more important separation and can therefore be used for routine analysis of both drugs. The linearity ranges for Etoricoxib and Paracetamol were 4-12µg/ ml and 2-18µg/ml respectively. The linearity ranges for Etoricoxib and Paracetamol were 2-18 µg/ml and 2-10 µg/ml respectively.

KEYWORDS: Etoricoxib, Paracetamol, UV Spectrophotometry, Q-Analysis Spectroscopic method.

INTRODUCTION

The Etoricoxib is chemically 5-chloro-6'-methyl-3-[4-(methyl sulfonyl) phenyl] - 2, 3'-bipyridine. It is mainly used for the osteoarthritis, rheumatoid arthritis and acute gouty arthritis. The drug is available in tablet form and is not official in any pharmacopoeia. Spectrophotometric solid phase extraction liquid chromatography–tandem mass spectrometry methods have been reported for the estimation of ETO in dosage forms and in plasma. PARA, chemically 4-hydroxy acetanilide is a centrally and peripherally acting non-opiod analgesic and antipyretic drug. It is official in Indian Pharmacopoeia, British Pharmacopoeia and United States Pharmacopoeia. ETO in combination with PARA is widely used in arthritis associated with fever condition in aged patient because ETO has anti-inflammatory analgesic action while PARA has antipyretic-analgesic action. In the present paper we describe the utilization of simultaneous equation and Q-Analysis method for the simultaneous estimation of ETO and PARA in the presence of each other as well as of the excipients. Etoricoxib (Figure a) is a Non Steroidal Anti-Inflammatory drug (NSAID) and a specific type of an anti-inflammatory drug most commonly used for the relief of the pain and highly COX-2 inhibitor. Produces dose dependent inhibition of COX-2 without inhibition of COX-1. COX-2 inhibition provides anti-inflammatory and analgesic effects. It is an off-white crystalline powder relatively insoluble in water, and freely soluble in alkaline aqueous solution. Molecular formula is C18H15C1N2O2S. Molecular Weight is 358.842g/mole Etoricoxib is available in tablet dosage forms (60, 90, 120mg and 325mg) and is not official in any pharmacopoeia. It is used for symptomatic management of Osteoarthritis, rheumatoid arthritis and also indicated in primary dysmenorrheal postoperative dental pain, acute gouty arthritis, cancer treatment and prevention and migraine. It was found that some analytical methods such as Visible, UV, HPLC other methods were reported for Etoricoxib. Paracetamol is chemically N-(4-hydroxyphenyl) acetamide (Figure b). It has analgesic and antipyretic activity the objective of the present study is to develop simple and accurate method for the determination of Etoricoxib and Paracetamol by UV VIS method in bulk drug and tablet dosage form.

MATERIALS AND METHODS

Instrument

A Shimadzu UV-1700 UV/VIS Spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm

and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions.

Materials

The Standard gift sample of etoricoxib and paracetamol was procured from Emcure Pharma. Ltd. Bhosari, Pune. Tablets of Etoricoxib and Paracetamol combination were procured from marketed commercial brand that is Nucoxia-P.

Solvent Used

The 0.1N Sodium Hydroxide (NaOH) and Distilled Water.

Stock Solution Preparation

An accurately weighed quantity of etoricoxib (10 mg) and paracetamol (10mg) were transferred to a separate 100 ml volumetric flask and dissolved and diluted to the mark with distilled water to obtain standard solution having concentration of etoricoxib (100 µg/ml) and paracetamol (100 µg/ml).

Standard used	Wt. taken	% Potency	Diluted	Pipeted	Diluted	Dilution Factor	Final Conce.ug/ml
Etoricoxib	10.00	100.00	10	5	50	0.10000	100.00
Paracetamol	10.00	100.00	10	5	50	0.10000	100.00

Method I

The standard solutions of etoricoxib 10 µg/ml and the paracetamol 10 µg/ml were scanned separately in the UV range of 400 nm to 200 nm to determine λ-max of both the drugs it is the λ-max of the etoricoxib and paracetamol was found to be 234 nm to 254 nm respectively in given figure 1. The one or more standard solutions having 2, 4, 6, 8, 10 and 12 µg/ml concentration for etoricoxib and paracetamol will be prepared in 0.1 M sodium hydroxide (NaOH) that this solution using the concentration 100 µg/ml. it is measured absorbance or wavelength at 234 nm and 254 nm the calibration curves the plotted at these λ-max and the Absorptivity coefficient and the percent standard deviation of etoricoxib and paracetamol these drugs the determined using this plotted graph. The simultaneous equation generated by using Absorptivity coefficient the absorbance values of etoricoxib and paracetamol at these wavelength the particular wavelength have been substituted in the given equation.

$$Cx = \frac{A2ay1 - A1ay2}{ax2ay1 - ax1ay2} \quad \text{----------(1)}$$

$$Cy = \frac{A1ax2 - A2ax1}{ax2ay1 - ax1ay2} \quad \text{----------(2)}$$

Where,

A1, A2 — absorbance of the mixture,
ax1, ax2 – denotes absorptivity's of the X at 234 nm and 254 nm respectively,
ay1, ay2 — denotes absorptivity's of Y at 234 nm and 254 nm respectively,
Cx = concentration of Etoricoxib.
Cy = concentration of Paracetamol.

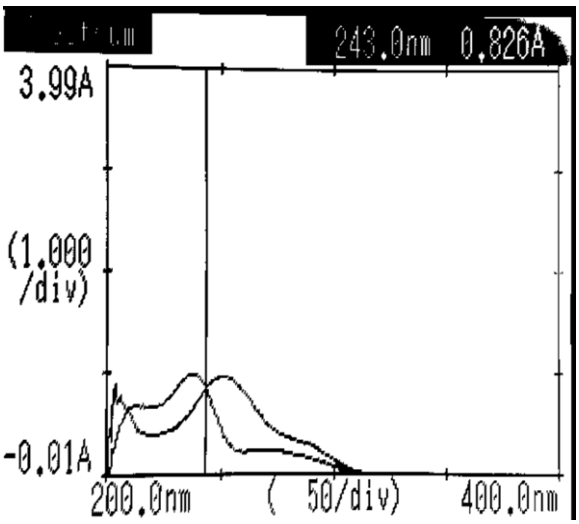

Figure.1: Overlain Spectra of Etoricoxib and Paracetamol.

Method II

The pure solution of etoricoxib and paracetamol both are same 10 µg/ml and these drugs sample solution is run in UV range of 400nm to 200nm to the determined isoabsorptive point and the isoabsorptive point was found to be 243.0 nm in given below figure 1. The given standard solutions having concentration 4, 6, 8, 10 and 12 µg/ml the etoricoxib and paracetamol was prepared in 0.1 M Sodium Hydroxide using the solution concentration 100 µg/ml. The absorbance of resulting solution is measured at 243 nm isoabsorptive point and 234 nm the λ-max of the etoricoxib and calibration curve was be plotted at this wavelength. This etoricoxib and paracetamol are determined Absorptivity at following calibration equation the etoricoxib and paracetamol in drug concentration determined by using the respective Q-analysis method. The determination of absorbance and Absorptivity value using the following formula in given that.

For Etoricoxib

$$Cy = \frac{Qm - Qx}{Qy - Qx} \times \frac{A1}{Ax1} \quad \text{..... (3)}$$

For Paracetamol

$$Cx = \frac{Qm-Qy}{Qx-Qy} \times \frac{A1}{Ax1} \quad \ldots\ldots\ldots (4)$$

Where,

$$Qm = \frac{\text{Absorbance of sample at 254nm}}{\text{Absorbance of sample at 234nm}}$$

$$Qx = \frac{\text{Absorbance of ETO at 234nm}}{\text{Absorbance of ETO at 234nm}}$$

$$Qy = \frac{\text{Absorbance of PARA at 254nm}}{\text{Absorbance of PARA at 243nm}}$$

A_1 = Absorbance of sample at isoabsorptive point, Ax_1 = Absorptivity of Paracetamol at isoabsorptive point.

Validation of the Proposed Method

The proposed methods were validated according to the International Conference on Harmonization (ICH) guidelines.

LINEARITY (CALIBRATION CURVE)

The linearity of Etoricoxib and Paracetamol was found to be in the concentration ranges of 5-50 µg/ml and 5-60 µg/ml, respectively, at their respective maximas. The calibration curves were plotted over a concentration range of 4-12 µg/ml and 2-18 µg/ml for Etoricoxib and Paracetamol respectively for Simultaneous equation and 4-12 µg/ml and 3-15 µg/ml for Etoricoxib and Paracetamol respectively for Q - analysis. Accurately measured standard solutions of Etoricoxib (4, 6, 8, 10 and 12) and Paracetamol (2, 6, 10, 12, 14 and 18) were transferred to a series of 100 ml of Volumetric flasks and diluted to the mark with Sodium Hydroxide Solution for Simultaneous equation method. Accurately measured standard solutions of Etoricoxib (4,6,8,10 and 12 ml) and Paracetamol (3, 6, 9, 12 and 15 ml) were transferred to a series of 100 ml of volumetric flasks and diluted to the mark with Sodium Hydroxide for Q- analysis method. The absorbance of the solutions was measured at 254 and 234 nm against Sodium Hydroxide as blank for Q – analysis method. The calibration curves were constructed by plotting absorbance versus concentrations and the regression equations were calculated.

ACCURACY and PRECISION (RECOVERY STUDY)

The Agreement between true value and the value founded opinions or option (degree of scatter) between a series of measurements repeat ability different time (same test) Intermediate Precision (different tests), Recovery studies were carried out by applying the method to drug content present in tablet dosage form to which known amount of mixed standard of Etoricoxib and Paracetamol was added at 50%, 100% and 150% levels. At each of the levels, three determinations were performed. The precision of repeat ability was studied by six replicate analyses of tablet solutions containing 12µg/ml of Paracetamol. This both methods are investigated by assay and observational this concentrations of Etoricoxib 80%,100% and 120% of 60 mg Etoricoxib tablet preparation In the different days and same days consecutive days. The data evaluated was summarized in. Intra-day and Inter-day relative standard deviation recovery of standard deviation values and also the low RSD values obtained from the analysis of the pharmaceutical formulation in given table indicated good intermediate precision of method. To validate prediction ability of suggested method, different concentrations of Etoricoxib at 50% (30µg/ml), 100% (60µg/ml) and 150% (90µg/ml), respectively in sample solution. The % recovery of these different concentrations was found to be 100%, indicative of high accuracy. The intra-day and Inter-day precision of the proposed methods was determined by analyzing the corresponding responses 3 times on the same day and on different days this different drugs concentrations of the standard solutions of this both methods. The analyzed samples were spiked with, 100 and 150% of the standard Etoricoxib and the mixtures were reanalyzed by proposed method. The experiment was conducted three times. This was done to check for the recovery of the drug at different levels in the formulation. The accuracy of the method was determined by calculating recovery of ETO and PARA by the standard addition method. Known amounts of standard solutions of ETO and PARA were added at 80, 100 and 120% level to quantified and pre-quantified sample solutions of Etoricoxib and Paracetamol. (5000 µg/ml and 150µg/ml for PARA) The amounts of ETO and PARA were estimated by applying obtained values to the respective regression line equations. The experiment was repeated for five times for both methods.

LIMIT OF DETECTION AND LIMIT OF QUANTIFICATION

The limit of detection (LOD) and the limit of quantification (LOQ) of the drug were derived by calculating the signal-to-noise ratio (S/N) using the following equations designated by International Conference on Harmonization (ICH) guidelines.

$$LOD = \frac{3.3 \times \sigma}{S}$$

$$LOQ = \frac{10 \times \sigma}{S}$$

Where, σ = the standard deviation of the Intercept of Calibration curve and S = slope of the calibration curve.

ANALYSIS OF ETORICOXIB AND PARACETAMOL IN COMBINED DOSAGE FORM (TABLET)

The accurately weight of 20- tablets and this tablet average weight is calculated then this tablets were triturated to a fine powder with the help of mortar and pestle. An accurately weighed quantity of powder equivalent to 500 mg of Etoricoxib and 150 mg Paracetamol then dissolved in 10 ml methanol in volumetric flask and sonicate for 20 min and make up the volume up to 100 ml. The solution was filtered through Whitman filter paper No. 41 and liquor portion of filtrate was diluted to produce solution having concentration of 10µg/ml of ETO and 3µg/ml of PARA.

The absorbance of sample solution was measured at selected wavelengths and the concentrations of the two drugs using by following formula No.(1) and (2) then calculating the simultaneous equation method are given equation No. (3) And (4) for absorbance ratio method. This analysis procedure was repeated up to the six times and the results are represented to the table No.2.

RESULTS AND DISCUSSION

The overlain spectra of ETO and PARA exhibit λ max of 234.0 nm and 254.0 nm for etoricoxib and paracetamol respectively which are quite separated from each other. Additionally one is absorptive point was observed at 234.0 nm. This wavelength was selected for simultaneous estimation of these two drugs for Q value analysis and it is assumed to be sensitive wavelength. The criteria for obtaining maximum precision by Simultaneous equation method were calculated and lodging was provided to the ranges and for Q-analysis ratios of absorbance at two different wavelengths were given that constant. Standard calibration curves for etoricoxib and paracetamol were linear with correlation coefficients (r2) values in the range of 0.998 – 0.9974 at all the selected wavelengths and the values were average of three readings with standard deviation in the range of 0.0057 – 0.0254. The measured these plotted graph were the standard sample solution repeated three times in that day and the total percent recovery ranges of this two drugs is given that 2.0 and 2.5 similarly the method was repeated for three different days and average percent recovery range of etoricoxib is 6.6 and the range for paracetamol is 7.9. The accuracy of the methods was confirmed by recovery studies.

TABLE-1 Regression Analysis Data and Summary of Validation Parameter of the Calibration Curves.

Parameters	Method 1				Method 2			
	ETO		PARA		ETO		PARA	
Wavelength (nm)	234.0	254.0	234.0	254.0	234.0	243.0	234.0	243.0
Beer's law limit (µg/ml)	4 - 12	4 - 12	2 - 18	2 - 18	4 - 12	4 - 12	3 - 15	3 - 15
Regression equation (y=a+bc)	y = 0.106x - 0.0057	y = 0.0077x + 0.0001	y = 0.0425x - 0.0004	y = 0.0902x + 0.0254	y = 0.106x - 0.0057	y = 0.0619x + 0.073	y = 0.0425x - 0.0004	y = 0.0689x + 0.0087
Slope (b)	0.106	0.077	0.0425	0.0902	0.106	0.0619	0.0425	0.0689
Intercept (a)	0.0057	0.0001	0.0004	0.0254	0.0057	0.073	0.0004	0.0087
Correlation coefficient (r^2)	0.998	0.9978	0.9973	0.9974	0.998	0.9904	0.9973	0.997
LOD (µg/ml)	1.38	1.4	0.58	0.29	0.66	0.53	0.34	0.21
LOQ (Mg/ml)	4.20	4.26	1.76	0.88	2.00	1.61	1.05	0.65
Precision (%RSD,n=3) Interday	2.0-6.6	2.0-8.0	2.6-7.8	2.5-7.9	1.3-2.3	1.0-6.5	0.6-6.1	0.97-4.0
Intraday	0.3-2.1	0.9-2.9	0.6-2.6	0.79-2.0	0.2-1.5	0.4-1.0	0.1-1.3	0.6-1.7

TABLE-2 Results of the recovery Studies.

Level of recovery	Amount of pure drug added (ml)		Simultaneous equation method % recovery	Q-Absorbance method % recovery		
	ETO (100µg/ml)	PARA (100µg/ml)	ETO	PARA	ETO	PARA
80	8	2.4	105.6	100.02	102.5	100.7
100	10	3	102.46	101.07	99.5	99.33
120	12	3.6	98.05	99.69	99.25	98.19
Mean % recovery			102.03	98.93	100.4	99.4
SD*			3.79	0.9	1.8	1.25
CV**			3.76	0.91	1.8	1.26

Table-3 Results of Analysis studies.

Drugs	Simultaneous equation method % ± SD (n=5)	Q-Absorbance method % ±SD (n=5)
ETO	100.3 ± 0.53	100.4 ± 0.80
PARA	96.8 ± 0.55	98.18 ± 0.58

ANALYSIS OF TABLET FORMULATION

For the preparation of formulation of Nucoxia-P in tablet the accurately about weight of the 20-tablets in weighing balance and triturated to the small semi aquatic of the fine powder. Equal volumes about 20 µl/ml of the blank solution standard solution and the test solution were separately injected into the chromatography and chromatograms were recorded and areas were measured for the major peak. The quantity of Etoricoxib and Paracetamol was calculated in comparison with the

standard solution and the results are presented. Tablet powder equivalent to 10 mg of Nucoxia-P was weighed and dissolved in 0.1 N Sodium Hydroxide (NaOH). then this standard solution is ultrasonic for 20 minute and the volume make up with the using distilled water then after this solution is filtered with the help of Whitman filter paper then this tablet solution of the concentration of 100 µg/ml. then this standard solution of tablet stock is examine for the carefully of the two or more time to the different process and concentrations of Nucoxia-P in tablet concentration is calculated by the three process in given table 4. Then the recovery studies will be carried out at three different levels that is 80%, 100% and 120% by adding the pure drug (8 mg, 10 mg and 12 mg respectively) to previously examined tablet powder sample 10 mg as per ICH guidelines and percentage recovery is calculated in given table 5 all the given methods are validated.

Table-4 Estimation of Nucoxia-P formulation tablet

Method	Tablet Formulation	Label claim	Amount found	% mean	S.D	%SD	S.E
A	T_1	80	79.90	99.74	0.1179	0.118	0.0482
B	T_1	80	79.10	99.67	0.1644	0.165	0.06712
C	T_1	80	79.84	99.69	0.246	0.244	0.096

Table-5 Recovery study data.

Method	Tablet Formulation	Level of % Recovery	Amount present (mg/tab)	Amount of std drug added	Total amount recovered (mg)*	% Recovery*	SD	% SD	S.E
A	T1	80	10	8	17.98	99.90	0.0602	0.118	0.0348
		100	10	10	19.98	99.92	0.0611	0.164	0.0352
		120	10	12	21.90	99.83	0.1150	0.198	0.0664
B	T1	80	10	8	17.82	99.91	0.09074	0.1824	0.05239
		100	10	10	19.98	99.93	0.1401	0.08036	0.08090
		120	10	12	21.97	99.90	0.08505	0.155	0.04910
C	T1	80	10	8	17.98	99.89	0.0953	0.350	0.055
		100	10	10	19.98	99.90	0.0624	0.258	0.036
		120	10	12	21.97	99.89	0.0953	0.269	0.055

RESULTS AND DISCUSSION

The examination of different thing for the suitable method is selected the chemical characterized by this two drugs etoricoxib and the paracetamol Initial spectroscopic analysis of compounds showed that Etoricoxib and Paracetamol showed a maximum UV absorbance (λmax) at 234 nm, 254 nm respectively. Statistical evaluation of analysis and recovery study was carried out. The values of standard deviation and measure of some property of this process being difference the pour satisfactory. The standard percent recovery is 99.99% to 100% is designate the correctness value. All methods A, B and C for the estimation of Nucoxia-P in tablet dosage form were found to be simple, accurate, precise, specific and reproducible. Beer-Lambert's law was obeyed in the concentration range of 5-50 µg/ml. The values of standard deviation were satisfactory low and the recovery studies were close to 100%. Nucoxia-P absorbing having great broad like peaks the derivative spectroscopy method applied has the advantage that it locates the not accessible peaks in the normal spectrum when the peaks is not sharp or its eliminates the obstructing caused by the only imperfectly present in the solution preparation. The AUC method has advantage that it is applicable to be drug which shows the broad spectra without a sharp peak. Hence these methods can be useful in the routine analysis of Nucoxia-P in bulk drug and formulation.

CONCLUSIONS

The results of this study it can be concluded that the proposed first order derivative spectrophotometric method can be used for simultaneous determination of Etoricoxib and Paracetamol. This method is simple, rapid, practical, reliable, economical and inexpensive and can be used for routine analysis of simultaneous determination of these compounds without any prior separation in quality control laboratories. The developed UV spectrophotometric method for the determination of Nucoxia-P has the advantage of being fast, simple, inexpensive, and applicable over a wide concentration range with high precision and accuracy. Then this method is validated as per the ICH guidelines and its regulation. The results of the validation tests were found to be satisfactory and therefore this method can be applied successfully to analyze drug formulations.

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