CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

SIMULTANEOUS QUANTITATIVE ESTIMATION OF ETODOLAC AND PARACETAMOL IN TABLETS BY Q-ANALYSIS UV METHOD

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Abstract:
The developed method uses 0.1 N NaOH as solvent for estimation of etodolac and paracetamol in tablets by Q-analysis method, at wavelengths of 224.22 nm and 257.14 nm. The method resulted in linearity in the range 1-8µg/ml and 0.8125-6.5µg/ml for etodolac and paracetamol respectively. System precision and intra-day precision are determined. Percentage relative standard deviation are 1.36 and 0.25 for Etodolac, while 4.96 and 5.93 for Paracetamol. Method was found to be rugged as precision was found to be 3.5%, 5.63% for etodolac and paracetamol. Accuracy was performed and the values were found to be in the range of 90-110% by percentage method . Hence it can be concluded that, a cost effective assay method is developed and validated which can be used in various pharmaceutical industries.*

Keywords: *UV, Etodolac , Paracetamol, assay, Validation.*

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Please cite this article in press as Ashok Kumar et al, **Simultaneous Quantitative Estimation of Etodolac and Paracetamol in Tablets by Q-Analysis UV Method**, *Indo Am. J. Pharm. Sci, 2016; 3(4).*

INTRODUCTION:

Etodolac (**Figure 1**) is a NSAID and its IUPAC name is (*RS*)-2-(1,8-Diethyl-4,9-dihydro-3*H*-pyrano[3,4-b]indol-1-yl)acetic acid. This drug is used for the management of mild to moderate pain, fever, and inflammation. It works by reducing the levels of prostaglandins, which are chemicals that are responsible for pain and the fever and tenderness that occur with inflammation. Etodolac blocks the cyclooxygenase enzymes which form prostanoids, resulting in lower concentrations of prostaglandins. As a consequence, inflammation, pain and fever are reduced [1-3].

Paracetamol (**Figure 2**) is chemically N-(4-hydroxyphenyl) acetamide [4]. Etodolac is chemically 1,8-Diethyl-1,3,4,9-tetrahydropyrano (3,4-b)indole-1-acetic acid. Both these drugs belong to class of nonsteroidal anti-inflammatory drugs (NSAIDs). A combination of 325mg of Paracetamol and 400 mg of Etodolac is available commercially as tablet. This combination is used as analgesic and antipyretic.

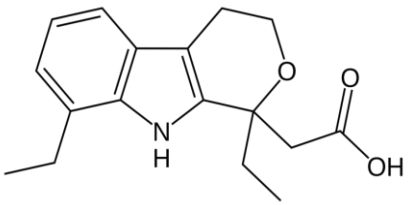

Fig 1: Structure of Etodolac

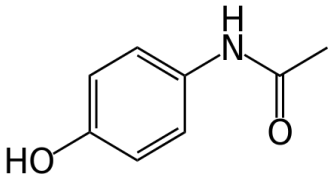

Fig 2: Structure of Paracetamol

Few UV methods are reported in the literature for the estimation of Paracetamol and Etodolac in combination using methanol [5], phosphate buffer pH 7.4 [6], triethyl ammonium phosphate pH 10 [7] as solvent. The present study was aimed at the simultaneous estimation of Paracetamol and Etodolac by absorbance ratio method or Q-analysis method using 0.1N NaOH as solvent.

MATERIALS AND METHODS:

Materials

Instrument

A double beam UV-visible spectrophotometer (Shimadzu, model 1800) having two matched quartz cells with 1 cm light path and loaded with UV probe software (version 2.41) was used for recording of spectra and measuring absorbance. An electronic analytical weighing balance (0.1 mg sensitivity, Shimadzu AY 220), digital pH meter (DELUX model 101) and a sonicator (sonica, model 2200 MH) were used in thisstudy.

Chemicals and Reagents

Analytically pure sample of Etodolac and paracetamol with purities greater than 99% was obtained as gift sample from Chandra labs, Hyderabad, India and tablet formulation [ETOVA-P] was procured from apollo pharmacy, Hyderabad, India with label claim of 400mg of Etodolac and 325mg of Paracetamol. Sodium hydroxide (AR Grade) is obtained from SD Fine chemicals (Hyderabad, India).

METHOD

Preparation of Solvent

4 grams of sodium hydroxide was added to 800ml of distilled water in a 1000ml volumetric flask and shaken to get a clear solution. This solution was made upto the mark using distilled water to get 0.1N NaOH.

Preparation of Stock and Working Standard Solutions

10 mg of Etodolac is accurately weighed and taken in 100 ml clean and dry volumetric flask containing 80ml of solvent and then the solution was made up to the mark using the solvent. This is considered as standard stock solution (100µg/ml). 0.4 ml of the stock solution is pipetted out and made up to 10 ml to get a concentration 4µg/ml, it is treated as the working standard, 100% target concentration.

10mg of Paracetamol is accurately weighed and taken in 100 ml clean and dry volumetric flask containing 80ml of solvent and then the solution was made up to the mark using the solvent. This is considered as standard primary stock solution (100µg/ml). 6.5ml was pipetted out from the stock solution and diluted to 10 ml in 10ml volumetric flask to get secondary stock solution. 5ml solution is pipetted out from the secondary stock solution and diluted to 10ml to get a concentration of 3.25µg/ml of paracetamol, it is treated as the working standard, 100% target concentration.

Preparation of Stock and Working Sample Solution

Ten tablets were weighed separately. Tablet powder weight equivalent to 40mg of Etodolac and 32.5mg of Paracetamol was transferred to a 100 ml volumetric flask containing 80ml diluent and then subjected to intermittent shaking with sonication for 5minutes, followed by making up to the mark with the solvent and later filtration was done through 0.45µ nylon membrane filter. 0.1 ml of the above stock solution was pipetted out and made up to 10 ml to get working sample solution equivalent to a concentration of 4µg/ml of Etodolac and 3.25 µg/ml of Paracetamol.

Selection of Suitable Detection Wavelength

Suitable wavelength for the total experiment was determined by recording UV spectrum in the range

of 200-400 nm for Etodolac and Paracetamol. 224.22 nm for Etodolac (**Figure 3**) and 257.14nm for Paracetamol **(Figure 4)** were chosen as wavelength of maximum absorbances (λmax). 235.24nm is found to be the isobestic point as seen in the overlaid spectra (**Figure 5**). UV spectrum for the sample is given in **Figure 6**.

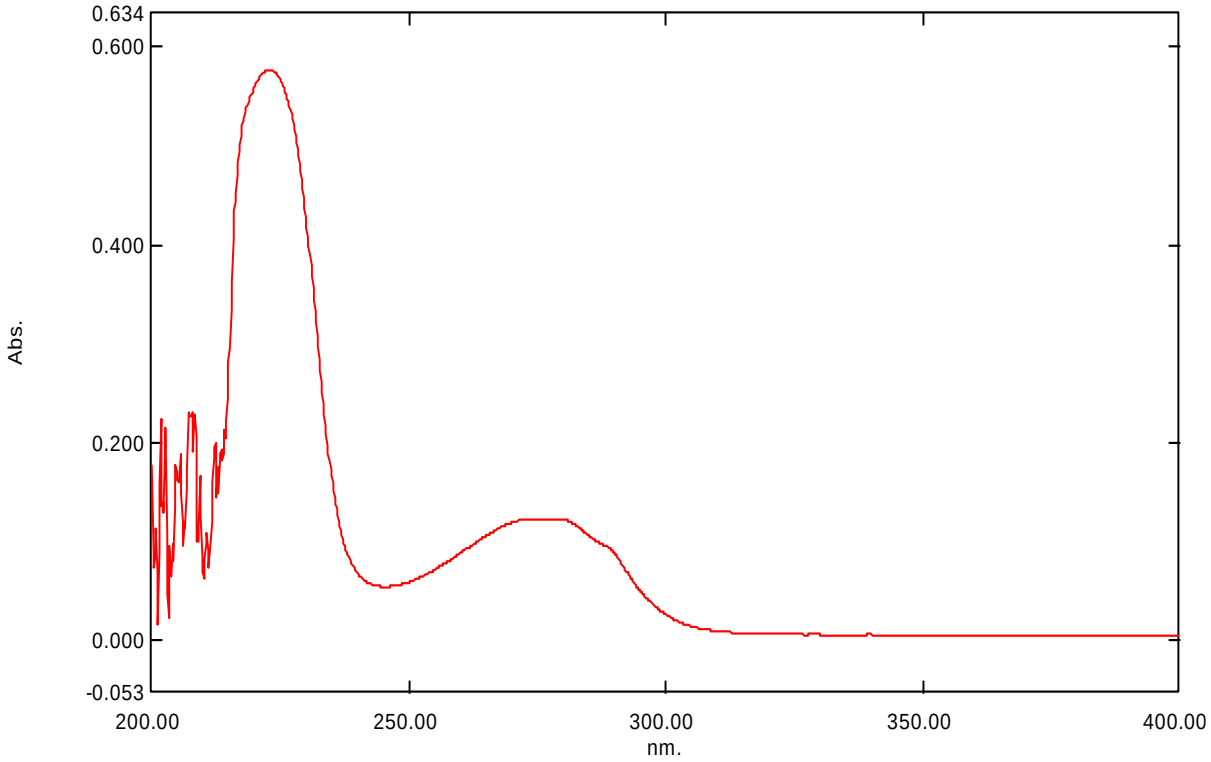

Fig 3: UV Spectrum of Etodolac Standard

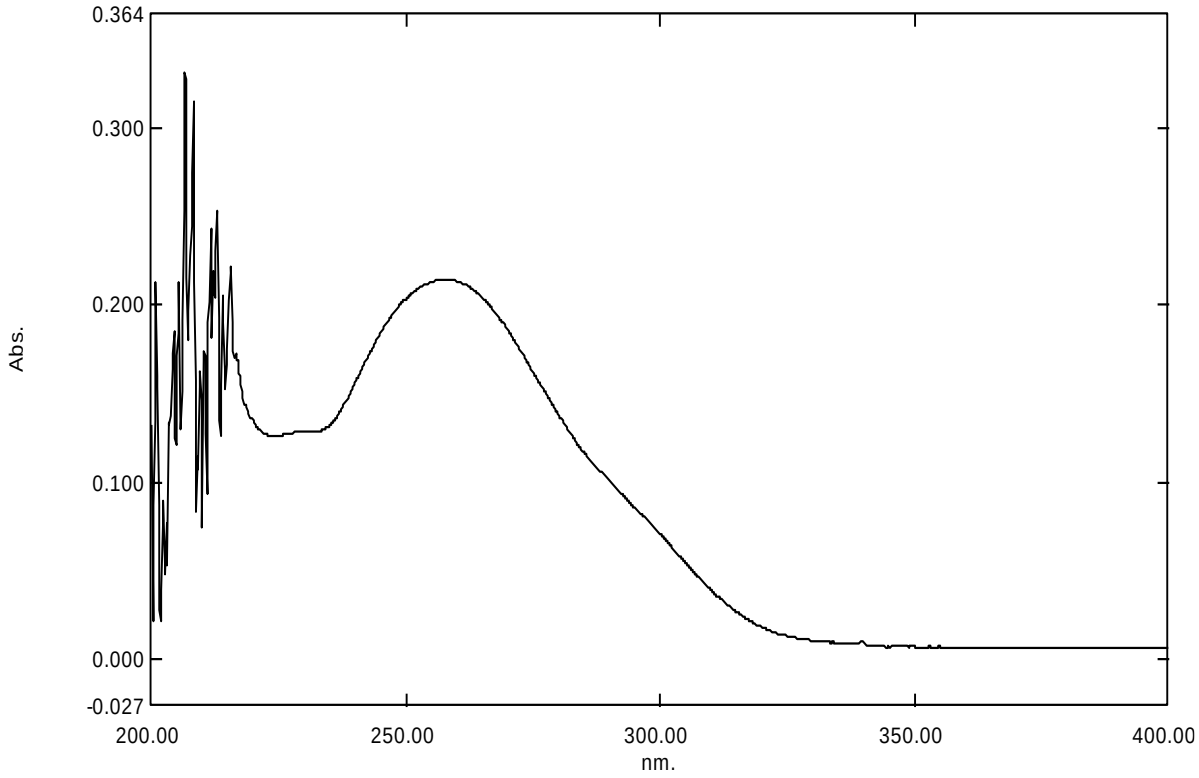

Fig4: UV Spectrum of Paracetamol Standard

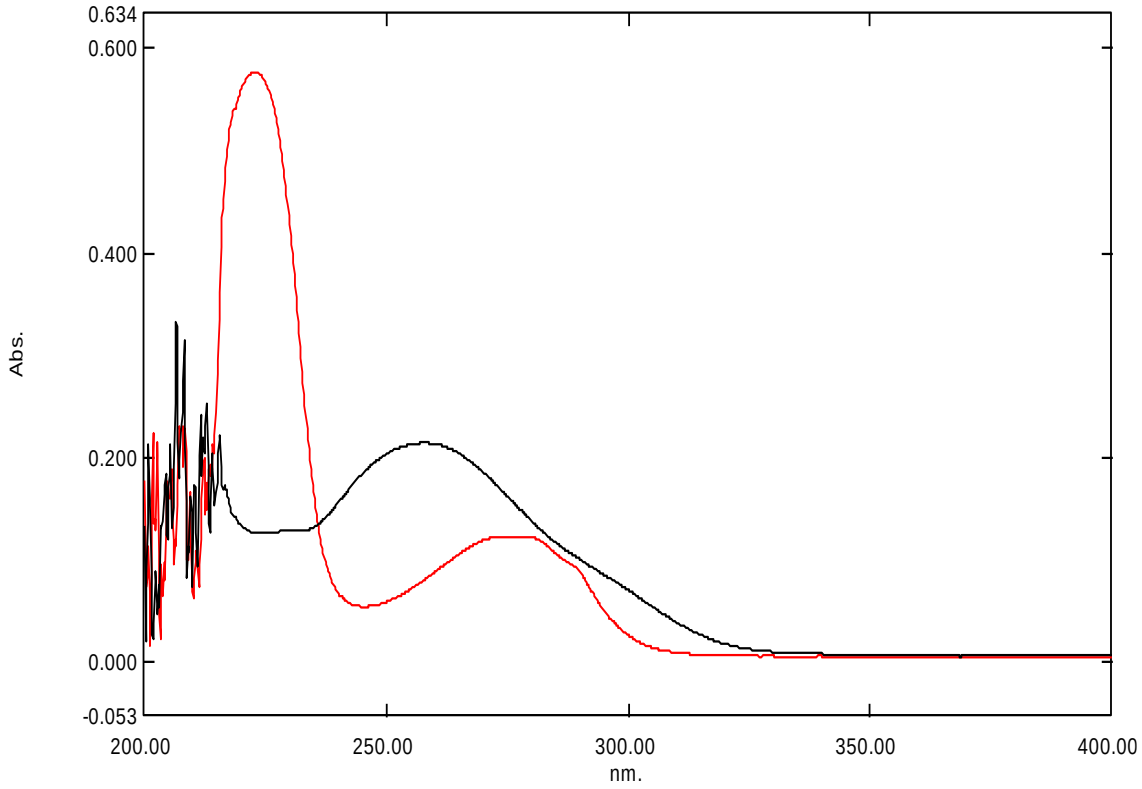

Fig 5: Overlaid UV Spectra of Etodolac and Paracetamol Standards.

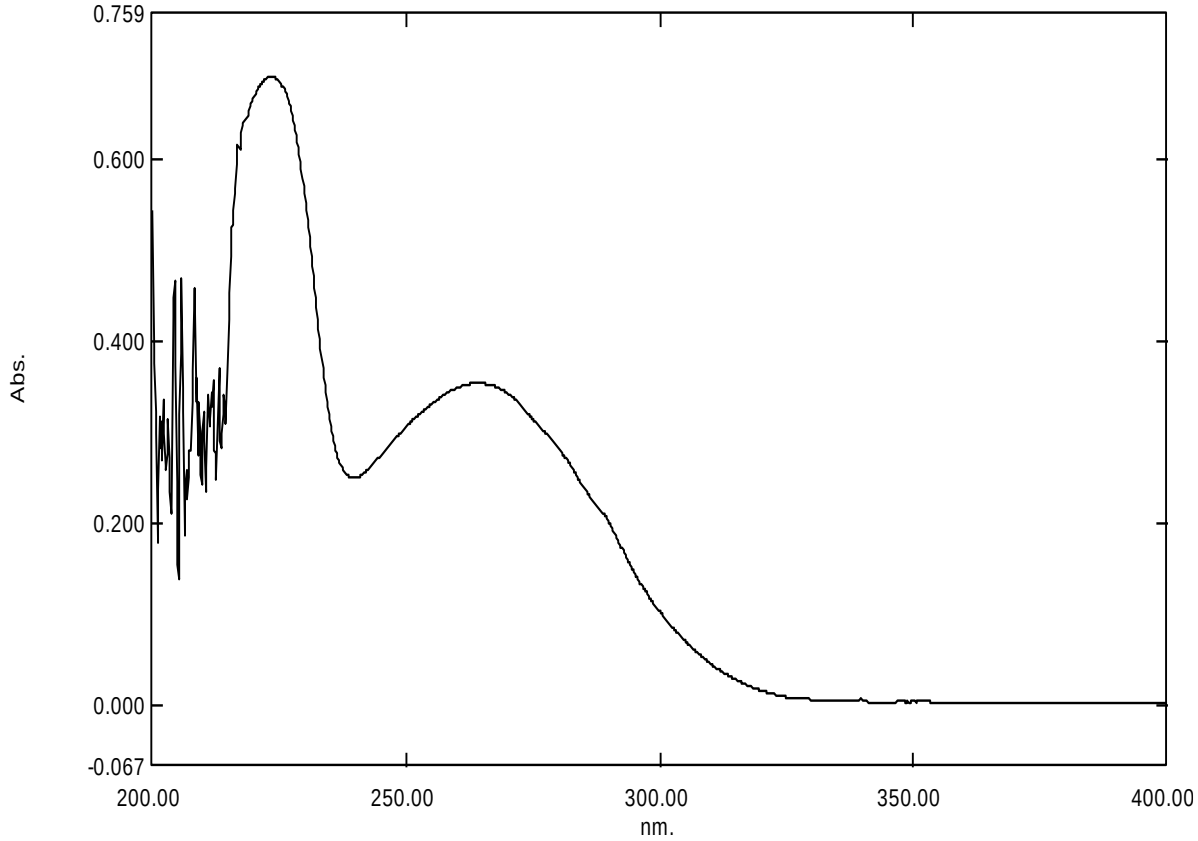

Fig 6: UV Spectrum of Sample

RESULTS AND DISSCUSSION:

Preliminary Solubility Studies: Solubility studies were explored for Eplerenone in various solvents ranging pH of 1 to 7.5.

1. Distilled water: 10mg of drugs each were added to 10ml of distilled water and found to be insoluble even after sonication. Similar solubility procedure was followed using other solvents.

2. **0.1N HCL**: 8.33 ml of concentrated HCl was made up to 1000ml using distilled water.

3. **0.1N NaOH**: 4 grams of sodium hydroxide was added to 800ml of distilled water in a 1000ml volumetric flask and shaken to get a clear solution. This solution was made upto the mark using distilled water to get 0.1N NaOH.

4. **0.05N NaOH**: 2 grams of sodium hydroxide was added to 800ml of distilled water in a 1000ml volumetric flask and shaken to get a clear solution. This solution was made upto the mark using distilled water to get 0.1N NaOH.

It was concluded from the preliminary solubility studies that both the drugs were found to be freely soluble in both 0.05N NaOH and 0.1NNaOH and hence was taken forward for performing stability studies.

Stability Studies

Etodolac and Paracetamol standards were found to be stable for minimum of 1 hour at room temperature using both 0.05N NaOH and 0.1N NaOH having percentage degradation less than 2% and hence this solvent was used for the preparation working standards and determination of assay of both the drugs in tablets.

Method Development

Q-analysis or absorbance ratio method is used for the determination of assay of both the drugs in tablets. In this method isobestic point is considered as one of the wavelength (λ1) and of paracetamol λmax is considered as (λ2). The following formula is used for determining the assay, where A1 and A2 are absorbances of sample at 235.24nm and 257.14nm respectively, ax1, ax2 and ay1, ay2 are absorptivities of Etodolac and Paracetamol at 235.24nm and 257.14nm respectively. Qx and Qy are the ratios of absorptivities of Etodolac and Paracetamol respectively at wavelengths as per formula given below. Qm is the ratio of absorbances of the sample at both wavelengths as below. Cx and Cy are the practically observed concentrations of Paracetamol and Etodolac in the formulation respectively.

$$C_X = \frac{Q_m - Q_y}{Q_x - Q_y} \times \frac{A_1}{a_{X1}}$$

$$C_Y = \frac{Q_m - Q_x}{Q_y - Q_x} \times \frac{A_1}{a_{Y1}}$$

$$Q_m = A_2/A_1, Q_x = ax_2/ax_1 \text{ and } Q_y = ay_2/ay_1$$

Percentage assay of a drug in the sample or formulation was determined by the formula as:

Practically observed concentration (Cx or Cy) X assay of standard / Expected concentration of the standard (4 or 3.25 based on drug)

Assay of ETOVA-P tablets were studied at working concentration using both 0.1N NaOH and 0.05N NaOH. Assays were in the acceptance limits (90-110%) by using the solvent 0.1 N NaOH while failing in the acceptance criteria using 0.05N NaOH and hence 0.1N NaOH has been the optimized solvent for the determination of assay of both the drugs in the formulation.

Method Validation

Validation of the analytical method is the process that establishes by laboratory studies in which the performance characteristics of the method meet the requirements for the intended analytical application. UV spectrophotometric dissolution method was developed and validated according to International Conference on Harmonization (ICH) guidelines [8] for validation of analytical procedures. The method was validated for the parameters like linearity, accuracy, system precision, intra-day precision, inter-day precision / intermediate precision/ruggedness and specificity.

Precision

System Precision

Six replicate recording of absorbances at 235.24 nm and 257.14 nm of both the standard solutions individually at working concentration showed % RSD (Relative Standard Deviation) of absorbances less than 2, which indicates acceptable reproducibility and there by the precision of the system (**Tables 1 and 2**).

Table 1: System Precision Results of Etodolac

n	235.24nm	257.14nm
1	0.583	0.26
2	0.580	0.258
3	0.570	0.258
4	0.577	0.258
5	0.561	0.259
6	0.580	0.259
Average	0.5765	0.2589
SD	0.007868	0.000816
%RSD	**1.364**	**0.315656**

Table 2: System Precision Results of Paracetamol

n	235.24nm	257.14nm
1	0.251	0.614
2	0.252	0.617
3	0.251	0.61
4	0.251	0.614
5	0.250	0.615
Average	0.251	0.613
SD	0.000632	0.613833
%RSD	**0.251974**	**0.002317**

Method precision

Method precision was determined by performing assay by Q-analysis method of sample under the tests of (i) repeatability (Intraday precision) and (ii) Intermediate precision (Inter day precision or ruggedness) performed during 2 consecutive days by two different analysts, at working concentration.

Repeatability (Intraday precision)

Six consecutive recording of absorbances at 235.24 nm and 257.14 nm of the sample from the same homogeneous mixture of the sample at working concentration showed % RSD less than 5 concerning % assay of both the drugs by Q-analysis method, which indicate that the method developed is method precise by the test of repeatability and hence can be understood that the method gives consistently reproducible results (**Table 3**).

Intermediate precision (Inter day precision/Ruggedness)

Percentage Assay precision between two consecutive days performed by different analysts of the sample showed % RSD less than 5, which indicate the method developed is inter day precise/rugged (**Table 4).**

Table 3: Intraday Precision Results

n	A2	A1	% Assay of Etodolac	% Assay of Paracetamol
1	0.320	0.276	97.90	90.53
2	0.342	0.292	101.06	97.75
3	0.348	0.293	99.19	100.85
4	0.322	0.299	100.83	90.33
5	0.331	0.310	109.9	100.85
6	0.355	0.312	108.812	104.20
Average	0.3395	0.297	102.9487	97.4183
SD	0.01532	0.013266	4.606312	4.7788
%RSD	**4.512495**	**4.466835**	**4.960057**	**4.8038**

Table 4: Inter day Precision/ Ruggedness Results

n	A2	A1	% Assay of Etodolac	% Assay of Paracetamol
1	0.306	0.275	98.78	97.07
2	0.339	0.289	94.78	110.00
3	0.341	0.299	103.10	109.85
4	0.313	0.282	101.7	99.14
5	0.323	0.287	101.20	103.20
6	0.338	0.289	95.30	110.00
Average	0.32667	0.28683	99.1433	104.88
SD	0.0014922	0.00801	3.474	4.8906
%RSD	**4.567965**	**2.792705**	**3.50460**	**4.9**

Linearity

Standard solutions of Etodolac and Paracetamol at different concentrations level (25%, 50%, 75%, 100%, 125%, 150%, 175% and 200%) were prepared. Calibration curves (**Figure 6-9**) were constructed by plotting the concentration level of drug versus absorbance at 235.24 nm and 257.14nm for both the drugs. The results show an excellent correlation between absorbance and concentration level of Etodolac within the concentration range (1-8µg/ml) for the Etodolac (**Table 5**) and for Paracetamol within the concentration range (0.8125-6.5µg/ml) (**Table 5**). The correlation coefficient was greater than 0.995 for both the drugs at both wavelengths, which meet the method validation acceptance criteria and hence the method is said to be linear across the above mentioned concentration ranges.

Accuracy

Accuracy was determined by means of recovery experiments, by the determination of % mean recovery of sample by percentage method at three different levels (50-150%). At each level, three determinations were performed. Percentage mean recovery was calculated as shown in **Table 7.** The accepted limits of recovery are 90%-110% and all observed data are within the required range which indicates good recovery values and hence the accuracy of the method developed.

Table 5: Calibration Data for Etodolac

S.NO	% Concentration Level	Concentration (µg/ml)	Absorbance at 257.14nm	Absorbance at 235.24nm
1	25	1	0.033	0.065
2	50	2	0.048	0.102
3	75	3	0.065	0.126
4	100	4	0.08	0.169
5	125	5	0.097	0.203
6	150	6	0.116	0.238
7	175	7	0.123	0.26
8	200	8	0.144	0.306
Regression coefficient			**0.9961**	**0.9966**
Slope (m)			**0.015738**	**0.0338**
Intercept (c)			**0.017429**	**0.0311**
Regression equation y = mx + c			**y=0.0157x +0.0174**	**y=0.0338x+0.0311**

Table 6: Calibration Data for Paracetamol

S.NO	% Concentration Level	Concentration (µg/ml)	Absorbance at 257.14nm	Absorbance at 235.24nm
1	25	0.8125	0.074	0.054
2	50	1.625	0.134	0.083
3	75	2.4375	0.19	0.116
4	100	3.25	0.26	0.154
5	125	4.0625	0.321	0.184
6	150	4.875	0.389	0.227
7	175	5.6875	0.437	0.25
8	200	6.5	0.513	0.301
Regression coefficient			**0.9989**	**0.9955**
Slope (m)			**0.0768**	**0.04092**
Intercept (c)			**0.00871**	**0.013821**
Regression equation y = mx + c			**y=0.0768x +0.00871**	**y=0.04092x+0.013821**

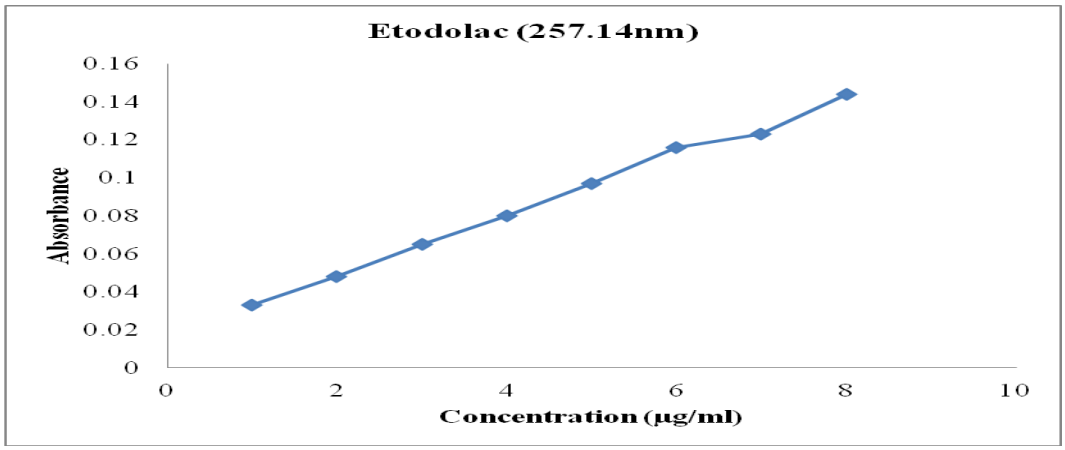

Fig 6: Linearity Graph of Etodolac at 257.14nm

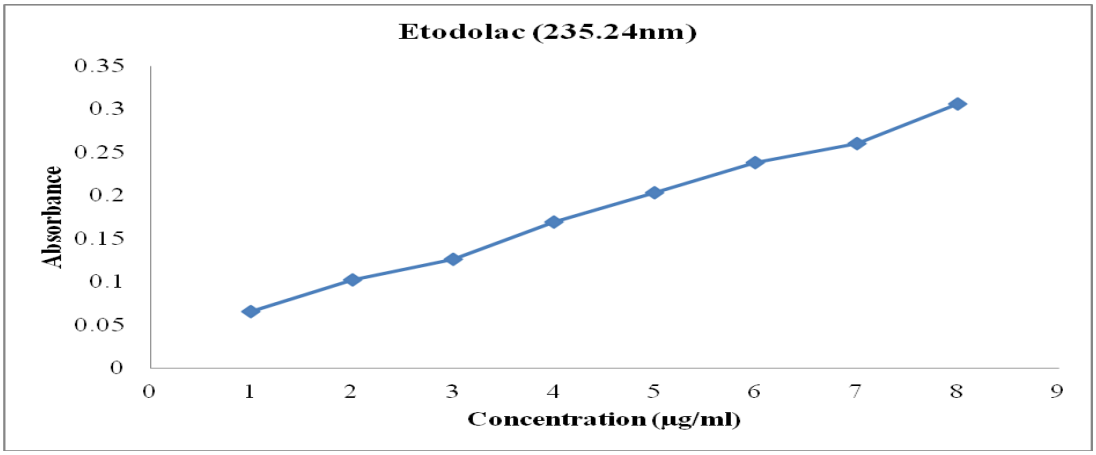

Fig 7: Linearity Graph of Etodolac at 235.24nm

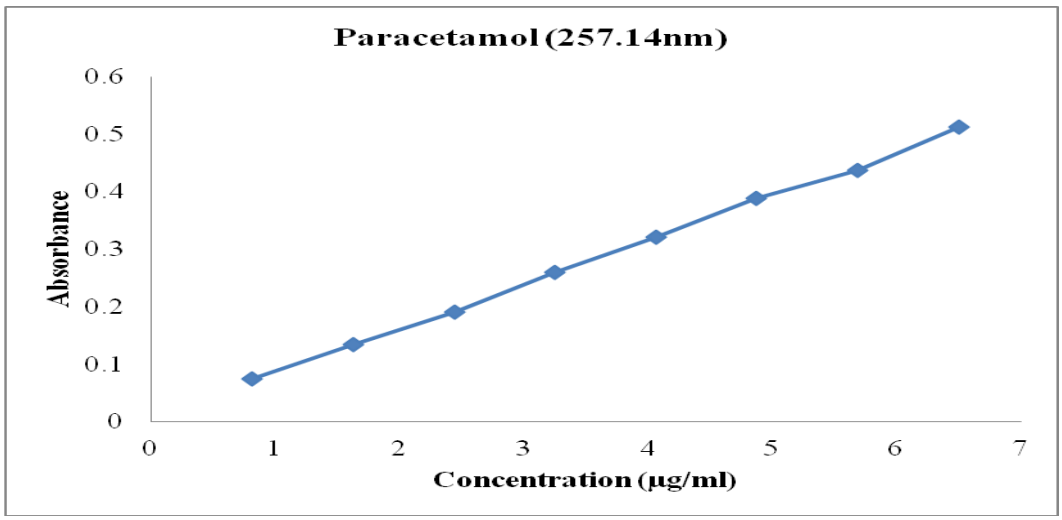

Fig 8: Linearity Graph of Paracetamol at 257.14nm

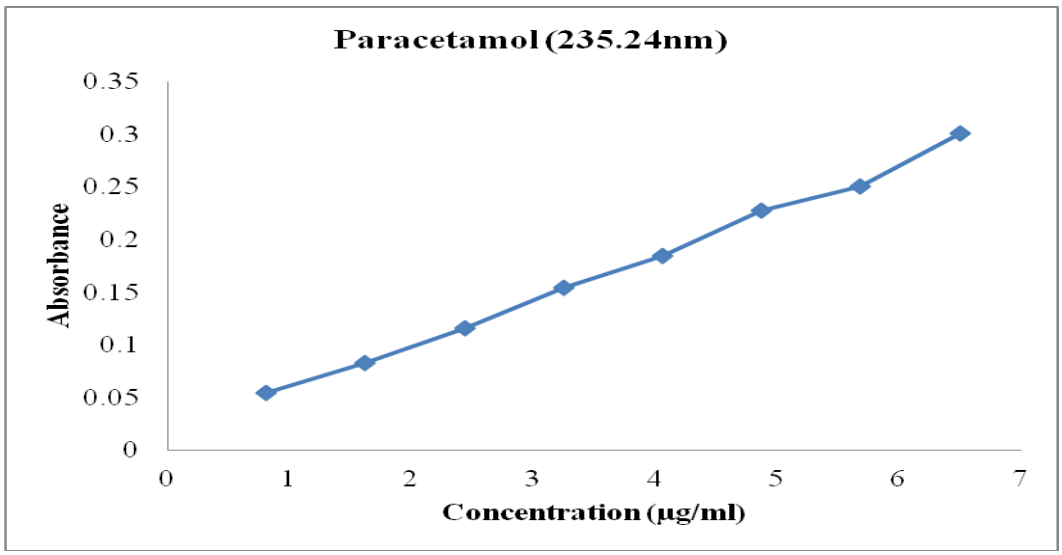

Fig 9: Linearity Graph of Paracetamol at 235.24nm

Table 7: Results of Accuracy Studies

% Level	% Recovery of Etodolac	% Recovery of Paracetamol	% Mean recovery of Etodolac	% Mean recovery of Paracetamol
50-1	100.09	107.46	**102.18**	**105.22**
50-2	98.42	99.57		
50-3	108.37	108.49		
100-1	97.9	90.53	**99.38**	**96.37**
100-2	101.06	97.75		
100-3	99.19	100.85		
150-1	92.12	96.71	**94.5**	**96.53**
150-2	100	95.19		
150-3	91.63	97.717		

CONCLUSION:

A simple and a cheap assay method was developed and validated for the simultaneous estimation of Etodolac and Paracetamol in tablets as per ICH guidelines by Q-analysis or absorbance ratio method. The optimized method uses 0.1N NaOH as a solvent for the estimation at a detection wavelength of 235.24 nm and 257.14nm resulting linearity in the range 1-8µg/ml for Etodolac and 0.8125-6.5µg/ml for Paracetamol. System precision, intra-day precision, inter day precision and accuracy results fulfill the acceptance criteria for both the drugs. Accordingly it is concluded that the developed UV spectrophotometric assay method is simple, accurate, precise, linear and rugged and therefore the method can be used for the routine analysis of Etodolac and Paracetamol in tablets in various pharmaceutical industries.

ACKNOWLEDGEMENT:

The authors thank the management of Vijaya College of pharmacy (VJYH), Hyderabad, for providing the necessary facilities to carry out of this research work. The authors are grateful to Chandra labs, Hyderabad for providing drugs in form of gift sample.

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