New Analytical Methods and Their Validation for the Estimation of Etodolac in Bulk and Marketed Formulations

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Abstract

Etodolac is non-steroidal anti-inflammatory drug. It is used for the management of mild to moderate pain, fever and inflammation.

Purpose: Analytical methods are required to characterize drug substances and drug products composition during all phases of pharmaceutical development. Development of methods to achieve the final goal of ensuring the quality of drug substances and drug products must be implemented. This determination requires highly sophisticated instruments and methods like HPLC, HPTLC and Spectrophotometer. Hence there was a need for the development of newer, simple, sensitive, rapid, accurate and reproducible analytical methods for the routine estimation of etodolac in bulk and pharmaceutical dosage form.

Methods: Two simple, sensitive, specific and validated methods (method A and method B) have been developed for the quantitative estimation of etodolac in bulk and pharmaceutical dosage form. Method A is based on reaction of etodolac with p-dimethylaminocinnamaldehyde to produce orange colour chromogen which showed λmax at 526.8 nm. In method B, etodolac oxidizes in presence of ferric chloride and hydrogen peroxide which absorbs at λmax at 537.2 nm.

Reults: The linearity was found in concentration range of 5-30µg/ml and 2-12µg/ml for method A and method B respectively. The correlation coefficient was found to be 0.9990 and 0.9966 for method A and method B respectively. The methods were validated as per ICH guidelines. The LOD and LOQ for estimation of etodolac were found as 0.0824, 0.0230 for method A and 0.2498, 0.0699 for method B respectively.

Conclusions: Proposed methods were successfully applied for the quantitative estimation of etodolac in marketed formulations.

Keywords: etoodolac, p-dimethylaminocinnamaldehyde, ferric chloride hexahydrate, hydrogen peroxide.

Introduction:

Etodolac is a non-steroidal anti-inflammatory drug (NSAID) and are used for the management of mild to moderate pain, fever, and inflammation. They work by reducing the levels of prostaglandins, which are chemicals that are responsible for pain and the fever and tenderness that occur with inflammation.[1] A survey of the literature reveals that there are very few reported methods for the determination of etodolac. Of those studies reported, the techniques used include chromatography, RP-HPLC [2,3], GC [4,5] and spectrophotometric methods [6-11]. However, an extensive survey of the literature revealed that there is no method available for the determination of ETD in pure form and pharmaceutical formulations by condensation and oxidation reactions. The aim of this study was to apply condensation and oxidation reactions in developing simple, accurate, sensitive and reproducible assays to analyse etodolac in pure form and pharmaceutical formulations, by employing p-dimethylaminocinnamaldehyde (PDAC), ferric chloride and hydrogen peroxide. This study describes spectrophotometric methods that can be used in laboratories where modern and expensive equipment, such as that required for GC or HPLC, is not available.

Materials and Methods:

Etodolac was obtained in highly pure form (pharmaceutical grade) from the local pharmaceutical industry. Its pharmaceutical preparations obtained from different commercial sources. All other reagents were of analytical grade. Distilled water was used for preparation of all solutions. Ultraviolet and visible spectrophotometry were carried out through Systronics UV – Visible Double beam spectrophotometer model 2202.

Standard drug solution:

Accurately weighed 100mg of etodolac was dissolved in 5 ml of ethanol and volume was made up to 100ml with distilled water to give a concentration of 1mg/ml. The final concentration was brought to 50 and 20 µg/ml for Methods A and B respectively.

Reagents:

Method A:

- 1.25% p-dimethylaminocinnamaldehyde
- 1% perchloric acid

Method B:

- 2 % ferric chloride hexahydrate
- 6 % hydrogen peroxide

Assay procedure for the determination of Etodolac:

Method A: 1ml, 2ml, 3ml, 4ml, 5ml, 6ml of working standard of Etodolac were added in seven different volumetric flask. Then 1.5 ml 1.25% of PDAC solution and 1ml of 1% perchloric acid were added and heated on boiling water-bath for 10 min. Volume was made up to mark with distilled water. The absorbance was measured at 526.8nm (Fig:1) against reagent blank which shown nil absorbance at corresponding wave length. The calibration curve was prepared to calculate the amount of the drug.

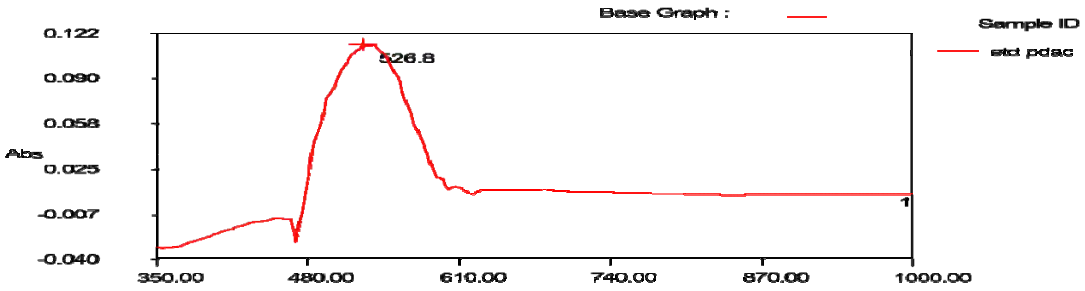

Fig: 1 Absorption spectrum of colored chromogen in method A

Method B: 1ml, 2ml, 3ml, 4ml, 5ml, 6ml of working standard (20µg/ml) of Etodolac were added in seven volumetric flask. To each flask, 1.5ml of 2% FeCl3.6H2O and 1ml of hydrogen peroxide were added. The volume in flask was made up to the mark with distilled water. The absorbance was measured against the reagent blank at 537.2 nm. The calibration curve was prepared to calculate the amount of the drug.

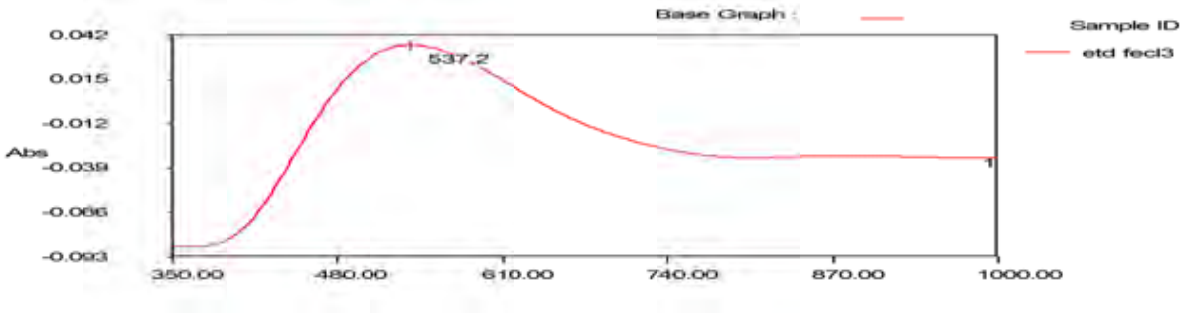

Fig: 2 Absorption spectrum of colored chromogen in method B

Assay of pharmaceutical formulations

Weighed accurately tablet powder equivalent to 100mg and transferred into 100ml volumetric flask and etodolac was extracted in 10ml of ethanol. The solution was then filtered and filtrate was then made up to 100ml with distilled water to get 1000µg/ml concentration. This solution was further diluted to get concentration of 50µg/ml. To keep an additional check on accuracy of developed assay method, analytical recovery experiments were performed. The different solutions of different concentrations were prepared in case of both pure drug solution and the formulation extract solution and these solutions were subjected to analysis by above developed methods. Six such samples were prepared and average of that readings taken for calculation of % recovery. Results of recovery studies are reported in table 2.

TABLE - 2.Assay and Recovery of Etodolac in Pharmaceutical Formulations

Method	Sample	Labeled amount (mg)	Amount found (mg)	% Recovery
Method A	Etova	400	396.64	99.16
Method B			393.08	98.27

Results and Discussion:

The proposed method A involve the condensation reaction between etodolac and p-dimethylaminocinnamaldehyde. The secondary amine of the cyclic imine group of the drug reacts with PDAC in non-aqueous acidic condition forming intense coloured species which shows maximum absorbance at 526.8 nm. In method B, etodolac is oxidized in presence of ferric chloride hexahydrate and hydrogen peroxide, which shows maximum absorbance at 537.2 nm. Iron (III) is reduced to Iron (II) by a molecule of hydrogen peroxide, forming hydroperoxyl radical and a proton. Iron (II) is oxidized by another molecule of hydrogen peroxide, forming hydroxyl radical and a hydroxide ion in the process. The net effect is a disproportion of hydrogen peroxide to create two different oxygen-radical species, with water as a by-product. The free radicals generated by this process engage in oxidation of the drug moiety.

TABLE – 1 Optical Characteristics, Precision and Accuracy of Proposed Methods

Parameters	***Method A***	***Method B***
λmax (nm)	526.8	537.2
Beer's law limit (µg/ml)	5-30	2-12
Regression Equation* (y)	0.0275x+0.0043	0.0825x+0.0244
Slope(b)	0.0275	0.0825
Intercept(a)	0.0043	0.0244
Correlation coefficient (R2)	0.999	0.9966
Accuracy (% Recovery)	97.79	96.84
Precision (% RSD)		
I. Method Precision	0.40	0.48
II. Intermediate Precision		
a. Intra-day	0.87	0.2
b. Inter-day	0.94	0.48
Limit of Detection (µg/ml)	0.0824	0.0230
Limit of Quantitation (µg/ml)	0.2498	0.0699

y = bx + a, where y is the absorbance and x is the concentration of etodolac in µg/ ml.

Conclusion:

Proposed methods make use of simple reagents, which an ordinary analytical laboratory can afford. The methods were found to be simple, precise, economic and less time consuming. The methods have been statistically evaluated and results obtained are accurate, precise and sensitive and can be applied to routine analysis.

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