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Spectrophotometric Determination of Etodolac

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A simple, sensitive and reproducible spectrophotometric method for the determination of etodolac was described. This method based on the oxidation of the studied drugs by Fe^{3+} in the presence of *o*-phenanthroline (*o*-phen) medium. The formation of *tris*-complex upon reactions with Fe^{3+}-*o*-phen in an acetate buffer solution of the optimum pH-values was demonstrated at 510 nm with *o*-phen. The concentration ranges are from 0.5-20 µg/mL for this method. For more accurate analysis, Ringbom optimum concentration ranges were calculated. The molar absorptivity, Sandell sensitivity, detection and quantification limits were also calculated. The developed method was successfully applied to the determination of etodolac in bulk and pharmaceutical formulations without any interference from common excipients. The relative standard deviations were ≤ 0.76 % with recoveries 99-101 %.

Key Words: Etodolac, *o*-Phenanthroline, Spectrophotometry, Pharmaceutical formulations.

INTRODUCTION

Etodolac (ETD) (Fig. 1) is nonsteroidal anti-inflamatory antirheumatic drugs[1]. A survey of the literature revealed that there have been few methods for the determination of etodolac in biological fluids, pharmaceutical formulations and in presence of its enantiomer. The techniques used in this connection include only HPLC, GC, spectrofluorimetric and spectrophotometric methods[2-8]. Extensive literature survey revealed that no method is available for simultaneous determination of etodolac in pure form and in pharmaceutical formulations by oxidation-reduction reaction.

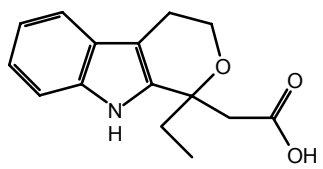

Fig. 1. Chemical structure of etodolac

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The aim of the present study was apply redox reactions to develop simple, accurate, sensitive and reproducible methods of analysis of etodolac in pure form and in pharmaceutical formulations by use of Fe^{3+} with *o*-phenanthroline (*o*-phen).

EXPERIMENTAL

A UV-160 A spectrophotometer (Shimidzu Corporation, Tokyo, Japan) equipped with 1 cm cells was used for all absorbance measurements. The pH values were determined with a Beckman Φ-200 pH meter (Beckman Instruments, Fullerton, CA, USA).

All chemicals and materials were of analytical grade and all solutions were freshly prepared in bidistilled water. Etodolac pure grade supplied by Fluka Corporation and its pharmaceutical formulations (Napilac capsules, 200 mg etodolac/capsule) and (etodine capsules, 300 mg etodolac/capsule) was provided by Kunming Pharmacy Corporation. Stock standard solution of etodolac was prepared by dissolving 100 mg pure drug in methanol and completed to 100 mL with the same solvent to obtain a standard solution of 1.0 mg/mL. Working solutions were prepared by an appropriate dilution of the stock standard solution. The iron(III)-*o*-phenanthroline was prepared by mixing 0.198 g of 1,10-phenanthroline monohydrate (Fluka, Swiss), 2.0 mL of 1.0 mol/L HCl and 0.16 g of ferric ammonium sulphate dodecahydrate (Fluka, Swiss) and diluted with bidistilled water to the mark in 100 mL calibrated flask. The acetate buffer solutions, buffers in pH range from (2.56-5.60) were prepared by mixing appropriate quantities of 0.2 mol/L sodium acetate with 0.2 mol/L acetic acid to get the desired pH as recommended previously.

Transfer aliquots (0.05-2.0 mL) of standard solutions (100 µg/mL) in a series of 10 mL calibrated flasks. Added 1.0 mL Fe^{3+}-*o*-phen or reagent solutions and 4.0 mL acetate buffer solution of pH 4.5 and heated on a water bath at 80 ºC for 10 min. The mixture was cooled to room temperature (25 ± 1 °C) and the volume was made up to the mark with bidistilled water. The coloured complex formed was measured at 510 nm against a reagent blank treated similarly.

Analysis of pharmaceutical formulations: 10 Tablets were accurately weighed and powdered. An accurately weighed quantity equivalent to 20 mg etodolac was dissolved in 20 mL methanol and transferred to a 100 mL calibrated flask. The contents of the flask was shaken for 10 min and then made up to the mark with methanol. The general procedure was then followed in the concentration ranges already mentioned above.

RESULTS AND DISCUSSION

This method is based on the formation of *tris*(*o*-phenanthroline)-iron(II) chelate upon the reaction of etodolac with the Fe^{3+}-*o*-phen reagent. The reaction proceeds through the reduction of Fe^{3+} to Fe^{2+} and the subsequent formation of an intensive orange-red colouration of the complex. The absorption spectra of the coloured complex species in the proposed methods at the optimum conditions was scanned in the double beam mode against a reagent blank in the range 400-600 nm and recorded in the general procedures show a characteristic λ_{max} at 510 nm (Fig. 2).

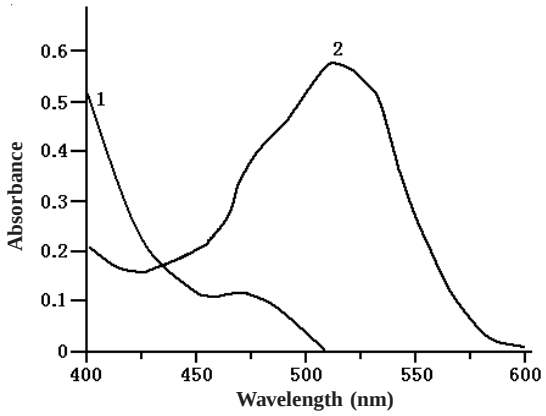

Fig. 2. Absorption spectra (1) Fe(III)-1,10-phenanthroline with etodolac (5.0 µg/mL) against reagent blank (2) Reagent blank against water

Effect of acidity: An acetate buffer solution was the optimal one of those examined (universal, phosphate, borate and acetate). The pH adjustment is necessary especially in acidic medium because the reaction was affected by the change of the pH in the range of (2.5-5.6). The optimum pH value was 3.5-5.0 for this method. Moreover, 4.0 mL of a buffer solution was sufficient for complete colour development as shown in Fig.3.

Effect of reagent concentration: The addition of 1.0 mL Fe^{3+}-*o*-phen reagent solutions was sufficient to obtain the maximum and reproducible absorbance for 20 $\mu g/mL^{-1}$ of etodolac. Smaller amounts give incomplete complex formation. Whereas a larger concentration had no effect on complex formation, although the absorbance increased slightly due to the background of the reagent used. The results are shown in Fig. 4.

Effect of temperature and heating time: The effect of temperature and heating time on the formation of the coloured complex were studied. The reaction of etodolac with the reagent proceeds very slowly at room

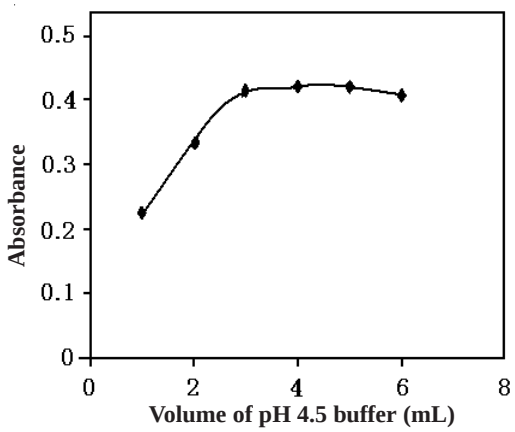

Fig. 3. Effect of buffer (pH 4.5) solution on the absorbance of complex (etodolac 20 µg/mL + Fe^{3+}-*o*-phen)

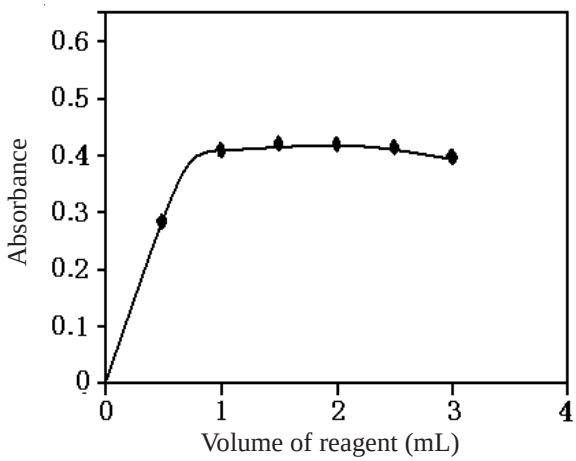

Fig. 4. Effect of reagent concentration with (20 µg/mL etodolac + 4.0 mL buffer) on the absorbance of complex

temperature. Higher temperature was used to accelerate the reaction. Maximum absorbance was obtained after heating for about 10 min with Fe^{2+}-*o*-phen coloured complexes on a water bath at 80 ºC. Further heating caused no appreciable change in the colour. The obtained complex was very stable for at more than 12 h.

Calibration curve and sensitivity: The calibration curve shows that Beer's law is obeyed in the concentration range of 0.5-20 µg/mL. The linear regression equation obtained was: A = 0.00628 + 0.0596 C (r = 0.9999). The molar absorptivity was calculated to be 1.83×10^4 L mol^{-1} cm^{-1} and the

Sandell sensitivity was found to be 15.74 ng/cm^2. The relative standard deviation at a concentration level of 6.0 µg/mL (11 repeat determination) was 0.58 %. The detect limit, based on (LOD = 3s/k) is 0.062 µg/mL. The limits of quantitation, LOQ, defined as (LOQ = 10 s/k) was found to be 0.22 µg/mL.

Precision and recovery: The intra-day precision and inter-day precision were calculated from data obtained during a 7-day validation, solutions containing four different concentrations of etodolac were prepared and analyzed in seven replicates. Precision of the assay was determined by repeatability (intra-day) and intermediate precision (inter-day). To assess intraday variation (repeatability), calibration curve was prepared seven times on the same day. Intermediate precision was assessed by comparing the assays on different days (7 d, n = 7 at each concentration). The results showed that the relative standard derivation of overall intra-day variations were less than 0.52 % and the relative standard derivation of inter-day variations were less than 0.76 %.

The recovery test of the proposed method was prepared by adding a known amount of standard at three different levels (1.0, 2.0 and 8.0 µg/mL) to the pre-analyzed sample. The results shown that the recoveries (n = 7) were ranged from 99-101 %.

Effects of interference: The criterion of interference was an error of not more than ± 3.0 % in the absorbance. To test the efficiency and selectivity of the proposed analytical method to pharmaceutical formulations, a systematic study of additives and excipients (*e.g.* lactose, glucose, dextrose, talc, calcium hydrogen phosphate, magnesium stearate and starch) that usually present in dosage forms. Experimental showed that there was no interference from additives or excipients for the examined method as shown in Table-1.

TABLE-1
DETERMINATION OF ETODOLAC IN PRESENCE OF ADDITIVES OR EXCIPIENTS

Material	Amount (mg)	Recovery (%)* ± SD**
Lactose	50	99.6 ± 0.8
Glucose	50	98.8 ± 0.6
Dextrose	50	99.3 ± 0.7
Magnesium stearate	30	99.2 ± 0.7
Calcium hydrogen phosphate	50	99.5 ± 0.9
Talc	40	99.8 ± 0.6
Starch	50	100.0 ± 1.1

*6.0 µg/mL of ETD was taken; **Average of five determinations;
SD = Standard deviation.

Analytical applications: The proposed methods were successfully applied to determine etodolac in its pharmaceutical formulations. They could be used easily for the routine analysis of pure etodolac and its dosage forms. Moreover, to check the validity of the proposed methods, dosage form [Napilac capsules (200 mg etodolac per capsule) and etodine capsules 300 mg etodolac per capsule)] were tested for possible interference with standard addition method. The performance of the proposed methods was assessed by calculation of the t-test (for accuracy) and a variance ratio F-value (for precision) compared with the reference method (potentiometric titrate with tetrabutylammonium hydroxide) (for 95 % confidence level with five degrees of freedom. The results showed that the t- and F-values were less than the critical value, indicated that there was no significant difference between the proposed and reference method for etodolac. Because the proposed methods were more reproducible with high recoveries than the reference method, they can be recommended for the routine analysis in the majority of drugs quality control laboratories.

Conclusion

The proposed method is simpler, less time consuming and more sensitive than the published methods. The proposed method was advantageous over other reported visible spectrophotometric method with respect to their higher sensitivity, simplicity, reproducibility, precision, accuracy and stability of the coloured species for ≥ 12 h. The proposed method is suitable for the determination of etodolac in pure form and in pharmaceutical formulations without interference from excipients such as starch and glucose or from common degradation products, suggesting applications in bulk drug analysis.

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