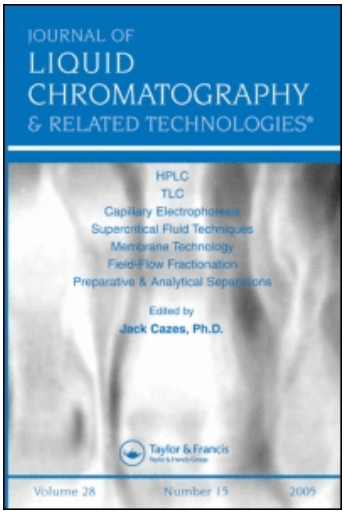

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CAPILLARY ELECTROPHORETIC METHOD FOR THE DETERMINATION OF ETODOLAC IN PHARMACEUTICAL TABLET FORMULATION

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ABSTRACT

Etodolac (ETO) is a nonsteroidal anti-inflammatory drug with anti-inflammatory, analgesic, and antipyretic activities. A capillary electrophoretic method for the determination of etodolac in a pharmaceutical preparation is described. ETO and diflunisal as an internal standard (IS) were well migrated in the background electrolyte of 10 m*M* borate at pH 9.3, using a fused silica capillary. The separation was achieved by applying 25 kV, detecting at 226 nm, and injecting the sample for 0.5 s. The average migration times t_m (relative standard deviation percentage) of ETO and IS were 7.1 (0.4) and 8.3 (0.5) min, respectively. Highly repeatable results were also obtained for areas of the peaks and peak normal-

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ization ratio (PN_{ETO}/PN_{IS}). Well-correlated linearity was found in a concentration range of $1 \times 10^{-5} - 2 \times 10^{-4}$ *M*. Intraday and interday calibration studies were performed, and reliable results were obtained. Limit of detection and limit of quantitation were 3.2×10^{-6} and 9.7×10^{-6} *M*, respectively. The proposed method was successfully applied for the analysis of etodolac in the pharmaceutical tablet formulation. The method proved to be simple, reproducible, precise, and fast, since analysis can be performed in less than 10 min.

INTRODUCTION

Etodolac (ETO, 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-*b*]-indole-1-acetic acid) (Fig. 1) is a nonsteroidal anti-inflammatory drug that is used in the therapy of rheumatic disease and postoperative pain (1). Its pharmacological actions are related to inhibition of prostaglandin biosynthesis at the site of inflammation. Etodolac is rapidly metabolized to its acyl glucuronide, 6-hydroxyetodolac, 7-hydroxyetodolac, 8-(1-hydroxy ethyl)etodolac, and their respective acyl glucuronides (2).

There are several methods reported for the analysis of etodolac in human urine and plasma, including high-performance liquid chromatography (HPLC) (3–6), gas chromatography (GC)-mass spectrometry (MS) (7), and capillary electrophoresis (CE)-MS (8). It has been reported that the determination of etodolac in pharmaceutical tablets has been performed using the techniques of spectrophotometry and spectrofluorometry (9), high-performance thin-layer chromatography (10,11), and HPLC (12,13).

It is also of interest to mention that several reports were published for the analysis of etodolac enantiomers using GC (14,15) and HPLC (16–19). However, no capillary electrophoretic method has been reported so far for the determination of etodolac in pharmaceutical tablets.

This paper describes a rapid, low-cost, selective, and validated method for the determination of etodolac in tablets by capillary electrophoresis. The proposed method is suitable for the routine quality control analysis of etodolac pharmaceutical formulations containing etodolac.

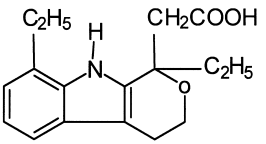

Figure 1. The chemical structure of etodolac.

EXPERIMENTAL

Apparatus

CE experiments were conducted using a Spectrophoresis 100 system equipped with a modular injector, high voltage power supply, and a model Spectra FOCUS scanning CE detector (Thermo Separation Products, San Jose, CA, USA), cabled to an Etacomp 486 DX 4-100 computer processing the data using PC 1000 (Version 2.6) working under the OS/2 Warp program (Version 3.0). The analysis was performed in the total length of 88 cm and effective 58 cm fused silica capillary, having 75 μ inside diameter (ID) (Phenomenex, Torrance CA, USA).

The pH values of the solutions were measured by using a Multiline P4 pH meter with a model SenTix glass electrode (WTW, Weilheim, Germany).

All the solutions used during the experiments were filtered through a Phenex microfilter (25 mm, 0.45 μm) (Phenomenex), and degassed using a B-220 ultrasonic bath (Branson Ultrasonic Corp., Danbury, CT, USA).

Chemicals

Etodolac and its pharmaceutical preparation Etol 300 (containing 300 mg of active material) and diflunisal [internal standard (IS)] were generously provided by Nobel İlaç Sanayi ve Ticaret A.Ş. (Istanbul, Turkey) and Sanovel İlaçlari A.Ş. (İstanbul, Turkey), respectively. Acetonitrile (HPLC grade), hydrochloric acid, sodium hydroxide, and borax were from Merck (Darmstadt, Germany).

Procedure for CE Instrumentation

Fused silica capillary tubing was filled with the background electrolyte (pH 9.3; 10 m*M* borate). Both ends of the tube were dipped into the reservoir (8 mL) and vial (1.8 mL) filled with background buffer. The end part, in which the sample (side of vial) was introduced, was connected with a platinum electrode at the positive high-voltage side of the power supply. The reservoir side at the detector end was connected with a platinum electrode to ground. Samples at a concentration of 1×10^{-4} *M* for the optimization of CE parameters were introduced by 0.5 s of vacuum injection corresponding to almost 25 nL.

A washing program was applied before each run. The capillary was purged for 2 min with acetonitrile followed by 2 min with double-distilled water. Then it was equilibrated by passing through the background electrolyte for 2 min before analysis.

Procedures

A stock solution of ETO was prepared by weighing about 28.3 mg of ETO and dissolving it in 100 mL of distilled water. The dilutions were made in the range of 1×10^{-5} and 2×10^{-4} *M*, each containing 1 μmol of IS. All the dilutions were prepared in the background electrolyte.

The best background electrolyte consisted of 10 m*M* borate buffer at pH 9.3, and it was used throughout the studies. The sample was injected for 0.5 s and detection was made at 226 nm.

Application of Method to ETO Tablets

Ten ETO tablets were accurately weighed. The average weight of one tablet was calculated, and then they were finely mixed in a mortar. An amount of tablet powder equivalent to 45 mg of ETO was accurately weighed, transferred to a 100-mL flask, and made up to volume by distilled water. It was magnetically stirred for 10 min and made up to the final volume with distilled water. The solution was centrifuged at 5000 *g* for 10 min. The supernatant and fixed amounts of IS solutions were diluted with background electrolyte and were injected for CE.

RESULTS AND DISCUSSION

Since ETO has a carboxylic group, it carries a negative charge, which changes depending on the pH of the medium. Therefore, the pH of the background electrolyte was adjusted to effect a negative charge on the molecule. The most suitable electrolyte consisted of 10 m*M* borate at pH 9.3 and the signals were detected at 226 nm. At these conditions, the analysis ends within 10 min. The peaks of ETO and IS were shown at 7.1 and 9.3 min, respectively. The migration times of ETO varied, depending on pH, concentration of buffer components, and applied voltage. The electropherogram of standard ETO and IS is shown in Figure 2a.

The peaks of ETO and IS are almost sharp and symmetrical with 1.28 and 1.26 asymmetry factors, respectively. The results show the selectivity and separation efficiency of the proposed method.

The precision of the experiments was tested by applying eight injections. The repeatability, which corresponds to relative standard deviation percentage (RSD%), was tested by using the results of the integration parameters of the eight successive injections. Table 1 shows the mean (RSD%) values of migration times, area, peak normalization, and ratio of the peak normalization values of ETO to IS.

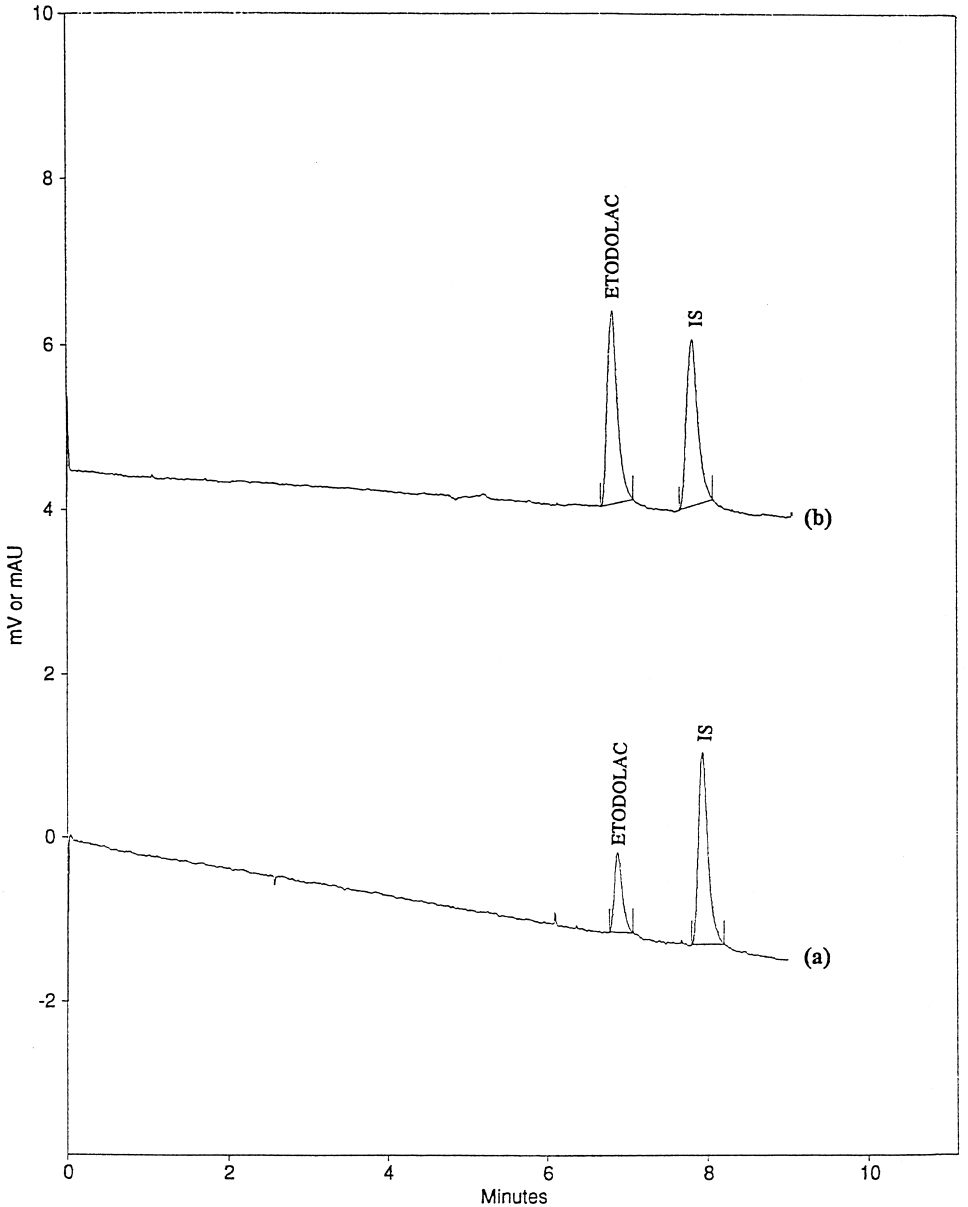

Figure 2. The electropherograms of standard ETO and IS (diflunisal). The conditions: running buffer 10 m*M* borate (pH 9.3), applied potential +25 kV; injection time 0.5 s hydrodynamically, detection wavelength 226 nm, capillary length 86 cm of total and 58 cm to detector, with 75 µm ID. a) Standard solution of ETO (2.5×10^{-5} *M*) and IS (1×10^{-4} *M*). b) ETO recovered from tablet and IS (1×10^{-4} *M*) added.

Table 1. Precision Tests of Migration Time, Area, Peak Normalization, and Ratio of Peak Normalization of ETO to IS

	Mean (RSD%) Values (n = 8)			
	Migration Time	Area	Peak Normalization	PN_{ETO}/PN_{IS}
ETO	7.11 (0.38)	21,815 (2.85)	3,069 (2.93)	1.50 (0.91)
IS	8.30 (0.49)	16,992 (2.75)	2,048 (3.03)	

Table 2. Some Capillary Electrophoretic Parameters Including ETO and IS

	ETO	IS
Mobility ($cm^2 \bullet V^{-1} \bullet s^{-1}$)	2.3×10^{-4}	3.0×10^{-4}
Capacity factor	13.0768	15.3073
Peak width at base (min)	0.213	0.247
Plates	17,501	17,444
Resolution	4.85	5.12

Table 3. Linearity and Accuracy of the Method

Parameters	Intra-Day Precision (k = 1; n = 5)[a]	Inter-Day Precision (k = 3; n = 15)
Slope ± SD	15,567±93	15,750±357
Intercepts	−0.027	-0.021
Correlation coefficient (r)	0.9999	0.9997
Slope± CL (p = 0.05)	15,567±88	15,750±196

[a]*k,* number of sets; *n*, number of determinations.

Table 4. Assay of Etol Tablets[a]

Mean (mg)	300.2
SD	1.35
RSD%	0.45
Confidence limits	300.2±1.04

[a]Contains 300 mg of active material.

The RSD% values are lower than 3, which indicates that the method has good repeatability. Good results are obtained by using the peak normalization ratio values. The capillary electrophoretic parameters are shown in Table 2.

The limit of detection at a signal/noise ratio (S/N) = 3.3 and limit of quantitation at S/N = 10 were 3.2×10^{-6} *M* and 9.7×10^{-6} *M*, respectively.

Linearity

The intraday and interday accuracy of the proposed method is shown in Table 3. Insignificant differences are observed for both intraday and interday accuracy.

Application of the Method to the Pharmaceutical Tablets

The determination of ETO in tablets was carried out using the proposed method described. Analysis was performed using the optimum conditions. Eight independent experiments were performed, and the content of the tablets was determined. It was observed that there was no interference from the inactive ingredients (excipients). The electropherogram of tablet solution containing ETO is shown in Figure 2b. The results obtained were statistically evaluated as shown in Table 4.

The results indicate that the repeatability is 0.45%, which shows the precision of the determinations.

In summary, the proposed method is efficient, precise, simple, fast, and of low cost, which makes it suitable for application in quality control analysis.

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