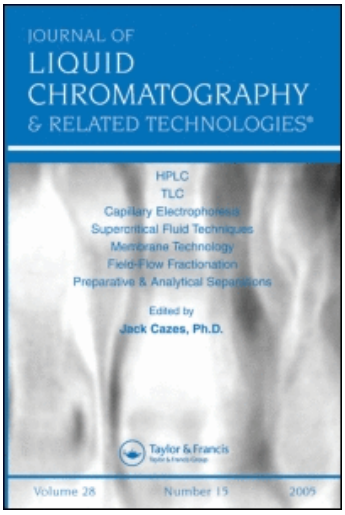

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Robert Hartman[a]; Ahmed Abrahim[a]; Andrew Clausen[a]; Bing Mao[a]; Louis S. Crocker[a]; Zhihong Ge[a]
[a] Analytical Research, Merck Research Laboratories, Rahway, New Jersey, USA

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Development and Validation of an HPLC Method for the Impurity and Quantitative Analysis of Etoricoxib

Robert Hartman,* Ahmed Abrahim, Andrew Clausen, Bing Mao, Louis S. Crocker, and Zhihong Ge

Analytical Research, Merck Research Laboratories, Rahway, New Jersey, USA

ABSTRACT

Etoricoxib (5-chloro-6′-methyl-3[4-(methanesulfonyl)phenyl]-2,3′-bipyridine) is a highly active and selective *cyclo*-oxygenase II inhibitor. A single, stability-indicating HPLC method has been developed and validated for both the impurity and quantitative analysis of etoricoxib. Method development incorporated the optimization of stationary phase, pH, temperature, and mobile phase composition for the resolution of thirteen process impurities and three major degradation products. Further optimization of pH and mobile phase composition was aided by the use of DryLab®, a computer-based simulation program. The stability-indicating capability of the method was proven through the identification of photolytic and oxidative decomposition products. Method validation produced excellent results for linearity, precision, limit of quantitation and limit of

*Correspondence: Robert Hartman, Analytical Research, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065-0914, USA; Fax: 732-594-5468.

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detection, specificity, accuracy, recovery, and robustness. The identities of etoricoxib decomposition products were confirmed by UV, LC/MS, and NMR spectra.

Key Words: Etoricoxib; NSAID; HPLC-MS; Validation; Stability-indicating.

INTRODUCTION

A number of selective *cyclo*-oxygenase II inhibitors (COX-2) have recently been introduced into the nonsteroidal anti-inflammatory drug (NSAID) market place.[1–3] The potential use of these COX-2 inhibitors among the general public is extremely high due to their improved safety profile over traditional NSAIDs.[4] Traditional NSAIDs such as aspirin and ibuprofen, inhibit both the COX-1 and COX-2 enzymes.[5] The COX-1 enzyme, which is expressed in essentially all tissues, has been found to play a role in the homeostasis of the gastrointestinal tract and kidneys, while the COX-2 enzyme is absent unless induced by an inflammatory event. Consequently, side effects of chronic use of traditional NSAIDs include gastrointestinal ulceration and bleeding.[6] Etoricoxib, a highly selective COX-2 inhibitor, was developed in order to address the safety issues associated with traditional NSAIDs, while providing pain relief from inflammatory illness such as osteo- and rheumatoid arthritis.[7]

In order to provide quality control over the manufacture of any Active Pharmaceutical Ingredient (API), it is essential to develop highly selective analytical techniques. Reverse-phase HPLC is one of the most widely accepted techniques used to monitor the quality of APIs. Therefore, a highly selective, stability-indicating reverse phase HPLC method was developed for etoricoxib.

EXPERIMENTAL

Chemical and Reagents

Etoricoxib and the *N*-oxide analog were obtained from Merck Research Laboratories (Rahway, NJ). HPLC grade acetonitrile and water were purchased from Fisher Scientific (Fair Lawn, NJ). Analytical grade phosphoric acid, dihydrogen phosphate, *N*,*N*-dimethylformamide, and acetic acid were obtained from Aldrich Chemical Co., Inc. (Milwaukee, WI).

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Apparatus and Chromatographic Conditions

Analytical HPLC

Method development and validation was performed on an Agilent (Wilmington, DE) 1100 HPLC system, consisting of an auto-injector, quaternary pump, variable wavelength detector, and diode array detector.

Initial method development for column selection was performed using a binary mobile phase consisting of component A, 5 mM KH_2PO_4 adjusted to pH 2.5 with 5 mM H_3PO_4, and component B, acetonitrile. A flow rate of 1 mL min^{-1} with a linear gradient from 20% B to 90% B over 50 min was employed.

The final validated HPLC method for the separation of etoricoxib API from process impurities and degradation products was performed on a 15 cm × 4.6 mm i.d., 3 μm particle YMC (Wilmington, NC) AQ-ODS column. The flow rate was 1 mL min^{-1} and the column temperature was 35°C. The binary mobile phase consisted of component A, an aqueous solution of 10 mM KH_2PO_4 adjusted to pH 3.1 with 2.2 mM H_3PO_4, and component B, acetonitrile. An initial isocratic hold of 28% B for 11 min was followed by a linear gradient from 28% B to 70% B over 19 min, then from 70% B to 90% B in 5 min. Samples of etoricoxib (0.1 mg mL^{-1}) were dissolved in 50/50 water–acetonitrile and injected at a volume of 10 μL. Detection was by UV at 220 nm and UV spectra were collected by photodiode array from 200 to 400 nm.

Preparative HPLC

Preparative scale separations for the isolation of the photodegradation products were performed on a Shimadzu (Kyoto, Japan) Preparative HPLC system consisting of an LC-8A pump, an SPD-10A detector, SIL-10A auto-injector, FRC-10A fraction collector, and an SCL-10A controller. Separations were carried out by gradient elution at a flow rate of 5 mL min^{-1}. A 250 × 10 mm i.d., 5 μm Phenomenex (Torrance, CA) Inertsil 5 ODS-2 semi-preparative column was used at ambient temperature. The precipitated photodegradation products were dissolved in *N*,*N*-dimethylformamide at a concentration of 0.5 mg mL^{-1} and injected at a volume of 2 mL. A mobile phase consisting of component A, an aqueous solution of 0.1% (v/v) glacial acetic acid and component B, acetonitrile, employed a linear gradient from 50% B to 90% B over 15 min.

HPLC-MS

LC-MS data was collected with an Agilent LC-MSD 1100 consisting of an auto-injector, quaternary pump, and diode array detector. Separations

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were performed on a 15 cm × 4.6 mm i.d., 3 μm particle YMC AQ-ODS column. The flow rate was 1 mL min^{-1} with a column temperature of 35°C. A mobile phase consisting of component A, an aqueous solution of 0.1% (v/v) glacial acetic acid and component B, acetonitrile, employed a linear gradient from 20% B to 70% B over 30 min. Stressed sample solutions of etoricoxib (0.1 mg mL^{-1}) were injected at a volume of 10 μL. Electrospray ionization was employed in the positive scan mode with a simultaneous fragmentor voltage of 100 and 230 V. The source temperature was 350°C with nitrogen gas flow of 13 L min^{-1} for nebulization and a pressure of 60 psi for drying.

NMR Analysis

Proton NMR was performed on a Bruker (Fermont, CA) Avance-600 spectrometer. Proton spectra were run in trifluoroacetic acid-*d* and referenced to internal tetramethylsilane ($\delta = 0.0$ ppm).

Photolysis

Photolytic stress of etoricoxib was carried out in an Environmental Specialties Inc. (Raleigh, NC) ES-2000 photostability chamber.

Preparation of Etoricoxib Degradation Products

A 125 mg sample of etoricoxib was dissolved in 50 mL of 0.1 N HCl (50/50, v/v% water–acetonitrile) and exposed simultaneously to 1.2 million lux hours of cool white fluorescent light and 200 watt hours/square meter of near ultraviolet light. The resulting precipitate was vacuum filtered and the solids were collected on a sintered glass funnel. The solids were triple washed with 1 M potassium carbonate and de-ionized water, then vacuum dried overnight.

Computer Simulations

Optimization of mobile phase composition and pH was aided by the use of DryLab® (LC-Resources, Walnut Creek, CA) 2000 Version 3.00.04.

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RESULTS AND DISCUSSION

Method Development

An understanding of the nature of the API (functionality, acidity, or basicity), the synthetic process and related impurities, and the possible degradation pathways and their degradation products is needed for successful method development in reverse-phase HPLC. In addition, successful method development should result in a robust, simple, and time efficient method that is capable of being utilized in a manufacturing setting.

Column Selection

Several columns were initially investigated in order to obtain a single method for the separation and quantitation of etoricoxib. The columns investigated included an Inertsil ODS-3, a Waters symmetry C-8 and C-18. Each column had the dimensions of 250 × 4.6 mm with a 5 μm particle size. In each case, poor retention and peak tailing were observed for the etoricoxib peak. In order to avoid the use of ion-paring reagents or amine modifiers to improve retention and peak shape, a YMC basic and a YMC ODS-AQ column were investigated. The design of these columns makes them suitable for the analysis of basic organic compounds in the presence of highly aqueous eluents.[8] Consequently, improved retention and peak shape were observed with these stationary phases. The AQ column produced the best peak shape and was, therefore, used for the remainder of the method development process. Additionally, by using a 150 × 4.6 mm, 3 μm particle column, all peaks of interest were eluted within 30 min.

Mobile Phase Composition/Column Temperature

The composition of the mobile phase was next examined using an initial isocratic hold followed by a linear gradient. The objective of this approach was to provide elution of the etoricoxib peak during the isocratic segment for better quantitation, followed by gradient elution for simultaneous purity analysis. An initial hold of 20% acetonitrile followed by a linear gradient to 70% acetofnitrile, at pH 2.5, was found to give the best peak shape and retention without sacrificing resolution. The critical pair under these conditions was etoricoxib and compound 6 (Fig. 1). With these parameters, compound 6 eluted close to the tail of the etoricoxib peak. Further optimization was performed by varying column temperature. As would be expected, a decrease in retention was observed with increasing temperature. However, no significant improvements

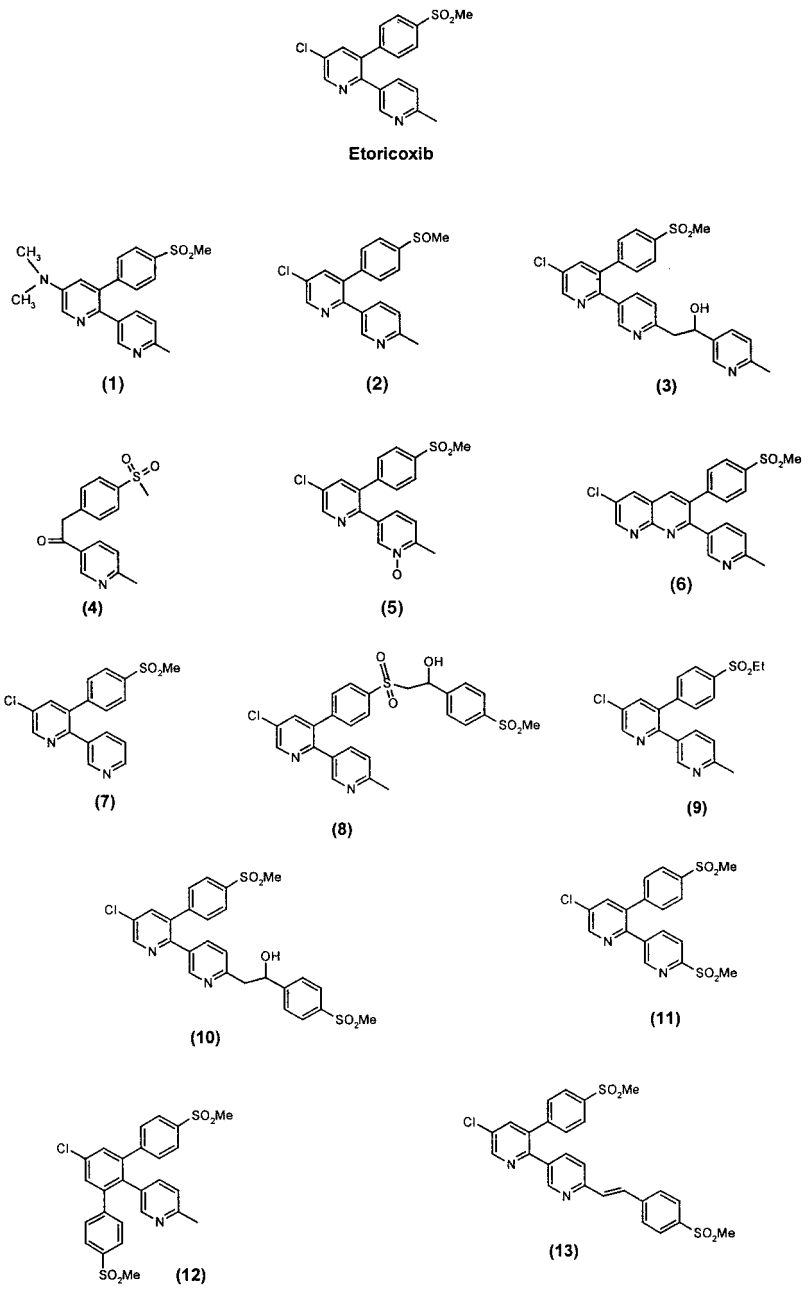

Figure 1. Structure of etoricoxib and 13 potential process impurities.

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in resolution were observed with changes in temperature. Temperatures lower than 25°C resulted in high back pressure while resolution of several other impurities was sacrificed at temperatures above 40°C. As a result, a column temperature of 35°C was chosen for further method development.

Effect of pH

The effect of pH on resolution of the critical pair was examined next. Separations of pharmaceutical compounds containing basic functionality can be challenging due to the complexity of interactions with the stationary phase.[9] In addition, pH effects can add to this complexity when impurities generated during processing possess a wide range of pK_as. Etoricoxib, a phenyl bipyridine, contains two ring nitrogens and, therefore, is expected to have two different pK_as. In addition, thirteen potential process impurities were identified, each possessing one to three ring nitrogens (Fig. 1). Several studies on the effect of mobile phase modifier, buffer concentration, and counter-anion on resolution and retention of basic compounds in HPLC have been reported.[10] However, many buffer and counter-anion additives are unsuitable for trace analysis in gradient reverse-phase HPLC due to low (wavelength) UV absorbing impurities. Therefore, the pH of the mobile phase was varied with a phosphate buffer in order to avoid these additives.

In order to elucidate the effect of pH on resolution, a computer simulation program was utilized. DryLab, a computer-based software program, allows for the mapping of retention and resolution without having to perform large sets of analyses.[11] Multiple parameters can be varied simultaneously during a single run, resulting in faster method development.[12] The effect of pH and percent organic, in an isocratic separation, was modeled in the six run mode. Using the results from the initial development strategy, 20% and 28% organic were used in combination with pH values of 2.5, 3.1, and 3.7. The column temperature was maintained at 35°C for all six runs. The resolution map (Fig. 2), generated by the retention time data entered into DryLab, shows the three-dimensional plot of resolution against the two other separation variables, pH and percent organic. Resolution, as represented by the color shading of the map, is plotted for the etoricoxib peak and compound 6. The resolution ranges from 0 to 31, as shown in the regions of darker and lighter shade, respectively. By crossing the dark region on any point on the map, the order of peak elution is reversed for the etoricoxib and compound 6 peaks. This region presented the most useful information for our goal. Through a change in pH and percent organic, we were able to not only improve resolution but also to move the compound 6 peak so that it eluted before the etoricoxib peak (Fig. 3). The benefits of reversing elution order were two fold. First, any tailing of the etoricoxib peak

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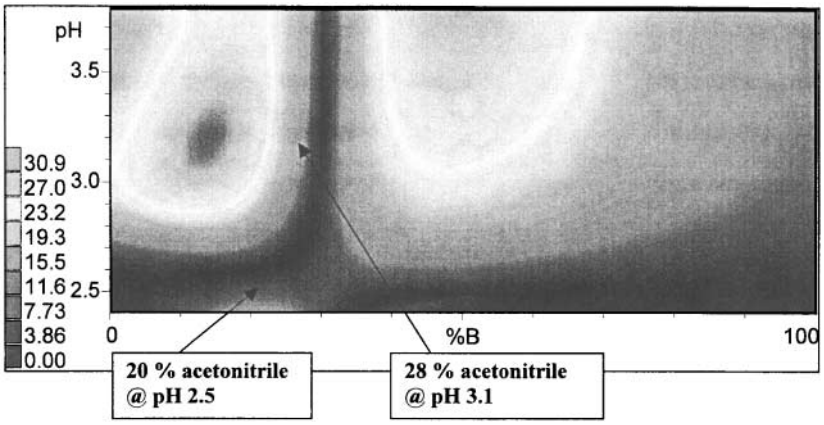

Figure 2. Resolution map of pH vs. percent organic (%B) for etoricoxib and compound 6. Sufficient resolution was obtained at 28% acetonitrile and pH 3.1 without sacrificing run time or peak shape.

would not interfere with the quantitation of compound 6, and second, isolation of compound 6 by preparative HPLC was now attainable. Through careful analysis of the resolution map, it was shown that an initial isocratic hold of 28% acetonitrile at pH 3.1 gave the best separation without sacrificing peak shape or analysis time.

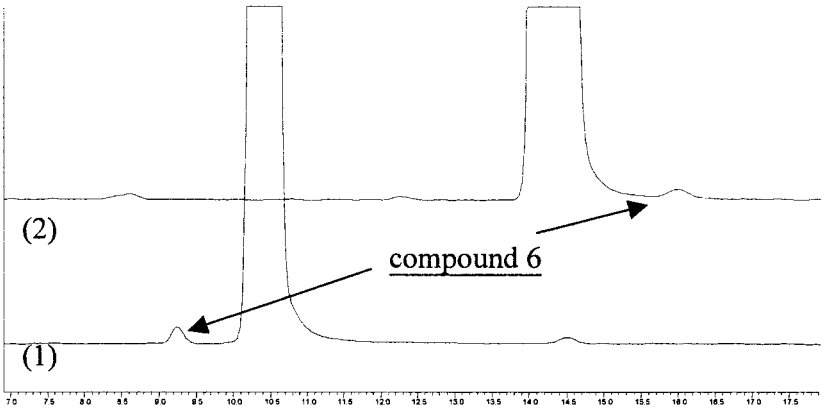

Figure 3. Chromatograms showing reversal of elution order for etoricoxib and compound 6 with change in pH and percent organic. (1) 28% acetonitrile, pH 3.1; (2) 20% acetonitrile, pH 2.5.

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Stability-Indicating Capability

In order to develop the stability indicating power of the assay, stress-testing was carried out under extreme acidic, caustic, oxidative, thermal, humid, and photolytic conditions. Oxidative stress, using a $0.1\,mg\,mL^{-1}$ solution of etoricoxib dissolved in 50/50 water–acetonitrile containing 5% H_2O_2, was shown to generate three impurities (Fig. 4). The major impurity was identified by retention time of an authentic sample, UV and MS spectra as the *N*-oxide of etoricoxib (compound 5, Fig. 1). The presence of this impurity under oxidative stress was expected, as it has been previously identified as a metabolite of etoricoxib.[13] Stress testing under the acidic, caustic, thermal, humid, and photolytic conditions failed to generate any impurities. These results were rationalized from an understanding of the intrinsic stability of etoricoxib. Synthesis of etoricoxib using acid- or base-induced enolization has shown this compound to be extremely stable to acidic and caustic environments.[14] Also, testing of etoricoxib through process development has shown the compound to be non-hygroscopic and stable under various thermal and mechanical stresses.

The photolytic stress was expected to generate some degradation based on the photochemical behavior of similar compounds. Rofecoxib, another COX-2 inhibitor, has previously been reported to undergo *cis*-stilbene like photocyclization.[15,16] In addition, many structurally comparable compounds, such as *o*-terphenyls and other arene analogs of stilbene, have been shown to undergo photocyclization.[17]

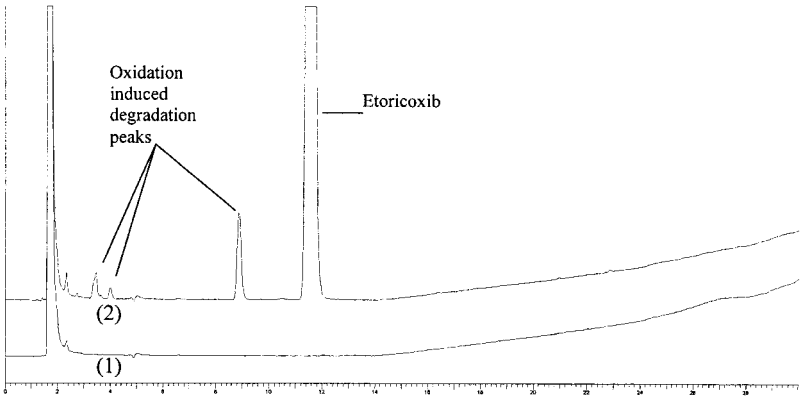

Figure 4. Stability indicating performance for oxidative stress. (1) Blank 50/50 water–acetonitrile with 5% H_2O_2; (2) Oxidative stress with *N*-oxide of etoricoxib as major impurity.

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In order to understand the stability of etoricoxib toward photolytic stress and consequently establish the stability-indicating capacity of the method, a number of possible forced degradation pathways were investigated. Etoricoxib in the solid state was the focus of our initial investigation. The International Conference on Harmonization (ICH) has established guidelines for the photolytic stress of APIs.[18] In accordance with these guidelines, etoricoxib was simultaneously exposed to 1.2 million lux hours of cool white fluorescent light and 200-watt hours/square meter of near ultraviolet light. Analysis of stressed and control samples showed no changes in the impurity profile. Additionally, a 0.1 mg mL^{-1} solution of etoricoxib in 50/50 water–acetonitrile, exposed to ICH photolytic conditions, did not produce any degradation peaks in the impurity profile.

As stated previously, several analogs of stilbene have been reported to undergo photocyclization. Some of these compounds required reaction conditions varying from that of *cis*-stilbene. Most notable are the reactions of heterocyclic systems, which contain one or more ring nitrogens. Many of these compounds have been reported to undergo photocyclization only under acidic conditions.[19–22] Therefore, the photostability of etoricoxib was investigated using a 50/50 water–acetonitrile solution containing 0.1 N HCl. Two solutions of etoricoxib were separately prepared in clear and amber (control sample) volumetric flasks, at a concentration of 0.1 mg mL^{-1}, and exposed to near ultraviolet light. Analysis of the clear volumetric preparation revealed a single degradation peak at 23 min. Due to the apparent low solubility in the assay diluent, the photodecomposition product precipitated from solution after 24 hours at room temperature. The resulting precipitate was filtered, washed, and analyzed by ^{1}H NMR.

Analysis by NMR revealed the presence of two compounds in the filtered precipitate at a ratio of 3 : 5. These degradation products were identified as the substituted triphenylene isomers of photocyclized etoricoxib (Fig. 5). Initially, it was assumed that the two positional isomers had coeluted as a single peak in the HPLC assay. However, attempts to resolve the two impurities by varying several method parameters failed to produce more than one peak. As a result, the gradient was extended an additional 5 min and ramped from 70% to 90% organic. A second peak, in the filtered precipitate, was then observed at 33 min. Integration of the two peaks gave an area percent of 37% for peak 1 and 63% for peak 2, or a ratio of 3 : 5. The two degradation products were then isolated by preparative HPLC and individually analyzed by ^{1}H NMR.[a] The

[a]Spin–spin coupling constants (J) are reported in hertz.
1. ^{1}H NMR (600.03 MHz, tfa-d) δ10.65 (s, 1H), 9.79 (s, 1H), 9.54 (s, 1H), 9.50 (s, 1H), 9.29 (s, 1H), 9.17 (d, $J = 8.6$, 1H), 8.74 (d, $J = 8.6$, 1H), 3.50 (s, 3H), 3.23 (s, 3H).
2. ^{1}H NMR (600.03 MHz, tfa-d) δ10.28 (d, $J = 8.7$, 1H), 9.99 (s, 1H), 9.61 (s, 1H), 9.41 (s, 1H), 9.28 (d, $J = 8.7$, 1H), 8.77 (d, $J = 8.7$, 1H), 8.42 (d, $J = 8.7$, 1H), 3.53 (s, 3H), 3.39 (s, 3H).

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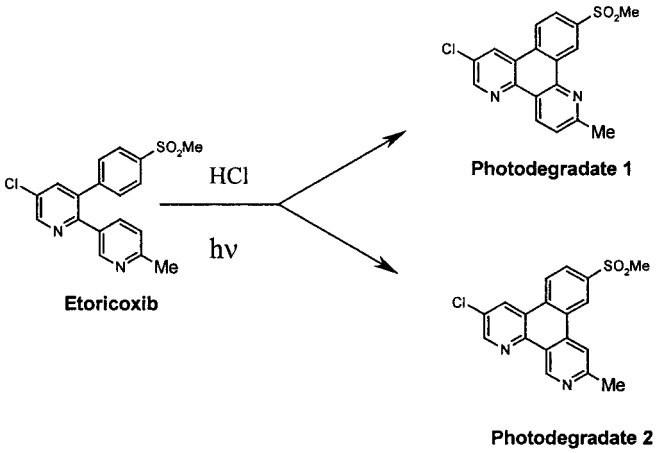

Figure 5. Schematic of the photocyclization of etoricoxib.

degradation product at relative retention time 2.12 (23 min), is labeled as Photodegradate 1 and the degradation product at relative retention time 2.97 (33 min), is labeled as Photodegradate 2 (Fig. 6).

Method Validation

Linearity

The linearity of the method was determined by making triplicate injections of etoricoxib API over the range of 0.02% to 120% for the target concentration of 0.1 mg mL^{-1}. The UV detector response was shown to be linear over this range with a correlation coefficient of 0.99997. The linearity of the detector response for potential impurities was also demonstrated. Compounds 4 and 7 were spiked into a typical batch of etoricoxib API over the range of 0.03 to 0.51 wt.%, for the target assay concentration of 0.1 mg mL^{-1}. The detector response was found to be linear with a correlation coefficient of 0.9997 and 0.9996 for compounds 4 and 7, respectively.

Precision

Injection precision was determined for six replicate injections of a representative batch of etoricoxib API at the target concentration of 0.1 mg mL^{-1}. The RSD of the response factors of the etoricoxib peak was

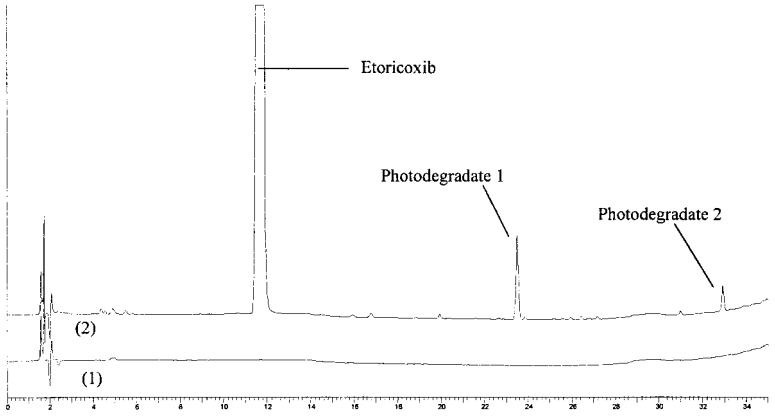

Figure 6. Stability indicating performance for acid-photolytic stress. (1) Blank 50/50 water–acetonitrile with 0.1 N HCl; (2) Acid-photolytic stress with Photodegradate 1 as major impurity.

0.07% for the six injections. In addition, the RSD for the area percent of two impurities at 0.04% and 0.07% were 3.9% and 2.5%, respectively.

Intermediate precision was evaluated over a three day period using a representative batch of etoricoxib API. Samples were freshly prepared each day using triplicate weighing, with triplicate injections of each solution. The solutions were then assayed against freshly prepared standard solutions. The RSD based on the weight percentage of the etoricoxib peak and the area percent of two impurities at 0.04% and 0.06% was 0.1%, 0.9%, and 1.4%, respectively.

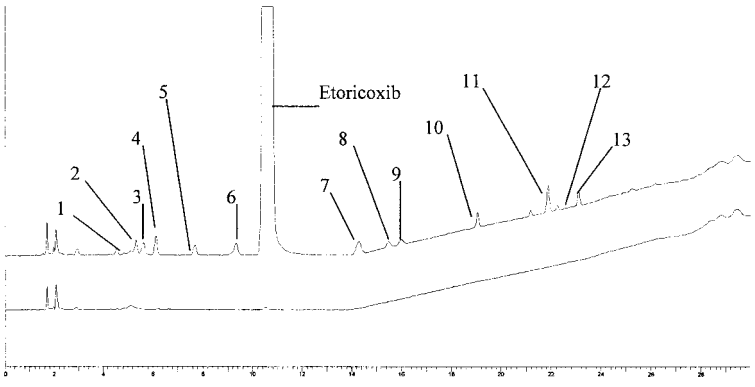

Figure 7. Specificity showing resolution of 13 potential process impurities.

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Detection and Quantitation Limit

The limit of detection was established at 0.02 wt.% of the 0.1 mg mL^{-1} target etoricoxib concentration based upon the signal-to-noise ratio of approximately 29.

A limit of quantitation (LOQ) of 0.04 wt.% was determined by evaluating signal to noise ratio, precision, and linearity at this concentration. The signal to noise ratio at the 0.04% level of etoricoxib was 56. The injection precision at 0.04% was determined to be acceptable with a relative standard deviation of 7.4%. The relative standard deviation of the response factor at the LOQ, as compared to five times the LOQ level, was found to be acceptable at 5.4%.

Specificity

The specificity of the method was demonstrated by spiking known potential impurities into a sample of etoricoxib API. The chromatogram of

Table 1. Specificity, relative retention times of impurities and degradates.

Compound	RR_t
Oxidation Imp. 1	0.30
Oxidation Imp. 2	0.35
Compound 1	0.43
Compound 2	0.50
Compound 3	0.53
Compound 4	0.58
Compound 5 (*N*-oxide of etoricoxib)	0.72
Compound 6 (Compound of critical resolution)	0.88
Etoricoxib	1.00
Compound 7	1.35
Compound 8	1.46
Compound 9	1.51
Compound 10	1.80
Compound 11	2.06
Compound 12	2.20
Compound 13	2.10
Photodegradate 1	2.12
Photodegradate 2	2.97

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Table 2. Robustness with respect to four critical method parameters.

Method parameter	Etoricoxib (wt.%)	Number of impurities detected (number $\geq 0.04\%$)	Resolution of compound 6 and etoricoxib[a]	Tailing factor[b]
Percent acetonitrile				
26	100.3	6 (4)	4.4	1.0
28	100.2	6 (4)	2.8	0.9
30	100.0	6 (4)	4.9	0.9
Mobile phase pH				
2.9	99.4	6 (4)	3.6	0.9
3.1	100.3	6 (4)	2.8	1.0
3.3	99.6	6 (4)	4.9	0.9
Column temperature (°C)				
32	100.4	6 (4)	2.6	1.1
35	100.3	6 (3)	2.8	1.0
38	100.3	6 (3)	3.0	1.1
Flow rate ($mL\,min^{-1}$)				
0.8	99.8	6 (4)	3.0	1.0
1.0	100.3	6 (3)	2.8	1.0
1.2	99.9	6 (4)	2.9	1.1
Injection volume (μL)				
5	100.3	6 (4)	3.3	1.0
10	100.3	6 (3)	2.8	1.0
15	100.2	6 (4)	3.0	0.9

[a]Resolution calculated by equation $Rs_2 = (2(Rt_2 - Rt_1)/(W_2 + W_1))$.
[b]Tailing factor calculated by equation $Tf = W_{0.05}/2f$.

the spiked solution, provided in Fig. 7, shows the resolution of these potential impurities from the etoricoxib peak. The relative retention times (RR_t) for potential impurities and degradation products are listed in Table 1.

Accuracy

Method accuracy was determined by a comparison to the weight percent obtained from titration by standardized perchloric acid. Analysis of three typical batches of etoricoxib resulted in a relative percent difference of 0.3, 1.2, and 0.5 for the three determinations, respectively. The method accuracy was further demonstrated by spiking known amounts of two potential impurities into etoricoxib drug substance. The recoveries of compounds 4

and 7 spiked into etoricoxib over the range of 0.03 to 0.51 wt.% ranged from 92% to 105%.

Robustness

The robustness of the method was demonstrated by showing the impact of changes to key system parameters, such as mobile phase composition, pH, column temperature, flow rate, and injection volume, which can affect retention time, peak shape, and the resolution of closely eluting impurities. The data presented in Table 2 demonstrate that the method is rugged with respect to each of these variations.

CONCLUSION

A single, robust, and time efficient HPLC method has been developed for the impurity and quantitative analysis of etoricoxib. Through an understanding of the intrinsic stability of the API and an understanding of the synthetic process, the method was shown to be specific and stability indicating.

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REFERENCES

1. Talley, J.J.; Brown, D.L.; Carter, J.S.; Graneto, M.J.; Koboldt, C.M.; Masferrer, J.L.; Perkins, W.E.; Rogers, R.S.; Shaffer, A.F.; Zhang, Y.Y.; Zweifel, B.S.; Seibert, K. J. Med. Chem. **2000**, *43*, 775–777.
2. Bosh, J.; Roca, T.; Catena, J.L.; Llorens, O.; Peres, J.J.; Lagunas, C.; Fernandez, A.G.; Miquel, I.; Fernandez-Serrat, A.; Farrerons, C. Bioorg. Med. Lett. **2000**, *10*, 1745–1748.
3. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J.F.; Ford-Hutchinson, A.W.; Gauthier, J.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neill, G.P.; Quellet, M.; Percival, M.D.; Perrier, H.;

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Riendeau, D.; Rodger, I.; Tagari, P.; Therien, M.; Vickers, P.; Wong, E.; Xu, L.J.; Young, R.N.; Zamboni, R. Bioorg. Med. Lett. **1999**, *9*, 1773–1778.
4. Botting, J.H. Drugs of Today **1999**, *35*, 225–235.
5. Cryer, B.; Feldman, M. Am. J. Med. **1998**, *104*, 413–421.
6. Allison, M.C.; Howatson, A.G.; Torrance, C.J.; Lee, F.D.; Russell, R.I. New Engl. J. Med. **1992**, *327*, 749–754.
7. Friesen, R.W.; Brideau, C.; Chan, C.; Charleson, S.; Deschenes, D.; Dube, D.; Ethier, D.; Fortin, R.; Gauthier, J.; Girard, Y.; Gordon, R.; Greig, G.M.; Reindeau, D.; Savoje, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, J.; Young, R.N. Bioorg. Med. Lett. **1998**, *8*, 2777–2782.
8. YMC, 1998–1999 Product Information.
9. Hindriks, R.; Maris, F.; Vink, J. Chromatogr. **1989**, *485*, 255–265.
10. Jones, A.; LoBrutto, R.; Kazakevich, Y. J. Chromatogr. A **2002**, *964*, 179–187.
11. Dolan, J.W.; Lommen, D.C.; Snyder, L.R. J. Chromatogr. **1990**, *535*, 55–74.
12. Schmidt, A.H.; Molnar, I. J. Chromatogr. A **2002**, *948*, 51–63.
13. Chauret, N.; Yergey, J.A.; Brideau, C.; Friesen, R.W.; Mancini, J.; Riendeau, D.; Silva, J.; Styhler, A.; Trimble, L.A.; Nicoll-Griffith, D.A. Bioorg. Med. Lett. **2001**, *11*, 1059–1062.
14. Davies, I.W.; Marcoux, J.F.; Wu, J.; Palucki, M.; Corely, E.G.; Robbins, M.A.; Tsou, N.; Ball, R.G.; Dormer, P.; Larsen, R.P.; Reider, P.J. J. Am. Chem. Soc. **2000**, *65*, 4571–4573.
15. Mao, B.; Abrahim, A.; Ge, Z.; Ellison, D.; Hartman, R.; Prabhu, S.; Reamer, R.; Wyvratt, J. J. Pharma. Biomed. Anal. **2002**, *28*, 1101–1113.
16. Woolf, E.; Fu, I.; Matuszewski, B. J. Chromatogr. B **1999**, *730*, 221–227.
17. Mallory, F.B.; Mallory, C.W. Org. React. **1984**, *30*, 74.
18. Federal Register, 16 May 1997, 62, No. 95, 27115–27122.
19. Glinka, J. Rocz. Chem. **1977**, *51*, 577–581.
20. Glinka, J. Pol. J. Chem. **1978**, *52*, 1039–1044.
21. Mudry, C.A.; Frasca, A.R. Tetrahedron **1974**, *30*, 2983–2991.
22. Mariano, P.S.; Krochmal, E.; Leone, A. J. Org. Chem. **1977**, *42*, 1122–1125.

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