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Enantiomeric separation of bupropion enantiomers by electrokinetic chromatography: Quantitative analysis in pharmaceutical formulations☆

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ABSTRACT

The first CE method enabling the quantitation of the two enantiomers of bupropion was developed in this work. Electrokinetic chromatography (EKC) mode using cyclodextrins as chiral selectors was employed. A study on the enantiomeric separation ability of different neutral and anionic CDs was carried out. Sulfated-β-CD was shown to provide the highest values for the enantiomeric resolution. The influence of some experimental conditions, such as pH, chiral selector concentration, temperature, and separation voltage on the enantiomeric separation of bupropion was also studied. The use of 10 mM sulfated-β-CD in 50 mM borate buffer (pH 9.0) with an applied voltage of 30 kV and a temperature of 30 °C enabled the separation of the enantiomers of bupropion with high resolution (R_s > 7) and short analysis time (~3.5 min). Finally, the method was successfully applied to the quantitation of bupropion in two pharmaceutical formulations.
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1. Introduction

Bupropion (2-(*t*-butylamino)-3′-chloropropiophenone), also known as amfebutamone [1], is a "second generation" antidepressant which is in clinical use from several years ago. It is a monocyclic aminoketone and a weak inhibitor of dopamine reuptake or of monoamine oxidase activity [2]. Bupropion is an atypical antidepressant that has also usefulness as a smoking-cessation aid [3] and it has been studied for a number of other uses such as bipolar disorder, attention-deficit hyperactivity disorder and weight loss [4]. It is formulated and used clinically as a racemate, but there is a paucity of data available on the properties of the individual enantiomers [5]. The enantiomers have been shown to rapidly racemize in phosphate buffers (pH 7.4, 25 °C) [4]. This drug is extensively metabolized, with <0.5% reported to be recovered intact in urine [4]. Stereochemistry may be important for bupropion therapeutic effects. The potency of bupropion enantiomers *in vitro* does not differ from that of the racemate, although racemization at physiological conditions may explain the lack of stereoselectivity [4].

A revision of the literature revealed that several methods have been developed for the chiral analysis of bupropion enantiomers by HPLC [2,4,6,7]. Thus, a coupled achiral–chiral liquid chromatographic technique was employed to separate and quantitate the enantiomers of bupropion and its phenylmorpholinol metabolite in human plasma [2]. Bupropion enantiomers were baseline-resolved in less than 10 min, using an ovomucoid (OVM) chiral column with a mobile phase composition of 40 mM ammonium acetate, pH 5.5, and 12.5% methanol [6], or using a α_1-acid glycoprotein (AGP) chiral column with a mobile phase of 20 mM citric acid, pH 5.5 and 10% methanol [7] but no application was reported. Coles and Kharasch [4] developed and applied a stereoselective LC–MS–MS assay for the analysis, in human plasma and urine, of bupropion enantiomers and hydroxybupropion diastereomers in a single assay. No references were found reporting the determination of bupropion enantiomers in pharmaceutical formulations by HPLC.

The importance of enantioseparations in the pharmaceutical and biomedical fields has prompted that several big pharmaceutical companies consider CE a technique of choice for chiral separations because if offers interesting advantages (fast screening, high peak efficiency, and flexibility) for the detection of very fine enantioselective effects. In fact, chiral CE has been the subject of much attention and has been applied with success to the enantiomeric separation of numerous chiral compounds [8–10].

Abbreviations: CD, cyclodextrin; HP-β-CD, 2-hydroxypropyl-β-cyclodextrin; M-β-CD, methyl-β-CD; TM-β-CD, heptakis-2,3,6-tri-*O*-methyl-β-CD; CM-β-CD, carboxymethyl-β-cyclodextrin; Ac-β-CD, acetyl-β-cyclodextrin; CE-β-CD, carboxyethylated-β-cyclodextrin; Succ-β-CD, succinylated-β-cyclodextrin.

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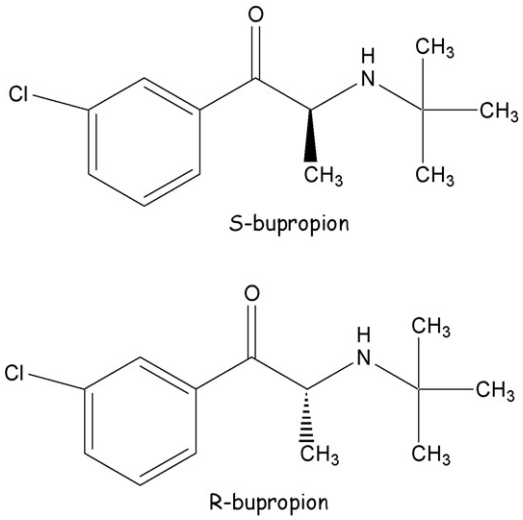

Fig. 1. Structure of bupropion enantiomers.

Regarding CE, no references have been found related to the quantitation of bupropion under achiral or chiral conditions. In fact, only the enantiomeric separation of bupropion has been investigated in some papers in which a systematic screening is achieved for different groups of compounds (including bupropion) using different neutral [11,12] and commercialized and non-commercialized anionic CDs [11–18] in order to characterize these chiral selectors. Among the neutral CDs employed, heptakis-(2,3-*O*-methyl)-β-CD, and hydroxypropyl-α, β and γ-CDs, the best chiral separation of bupropion enantiomers was obtained using phosphate buffer (pH 2.5) containing hydroxypropyl-β-CD as chiral selector (R_s = 2.2) in times lower than 20 min [11]. With regards to the use of commercialized anionic CDs (octakis(2,3-diacetyl-6-sulfate)-γ-CD, octakis(2,3-dimethyl-6-*O*-sulfo)-γ-CD, highly sulfated-α, and β-CDs, and sulfated-β-CD), the use of sulfated-β-CD in an acid buffer, allowed only to achieve a low enantioseparation for bupropion (R_s ∼1 or 1.6) [11,13], while the use of highly sulfated-β-CD in phosphate buffer (pH 2.5) enabled to obtain a high resolution (R_s = 9.78) in less than 30 min [12]. On the other hand, among the non-commercialized CDs investigated (hexakis(2,3-di-*O*-acetyl-6-*O*-sulfo)-α-CD, hexakis(6-*O*-sulfo)-α-CD, heptakis(2-*O*-methyl-3-*O*-acetyl-6-*O*-sulfo)cyclomaltoheptaose, heptakis(2-*O*-methyl-6-*O*-sulfo)cyclomaltoheptaose), heptakis(2-*O*-methyl-3-*O*-acetyl-6-*O*-sulfo)cyclomaltoheptaose enabled a good enantiomeric separation (R_s = 3.3) in a short time (3.0 min) [17]. Finally, there are some references in the literature in which the enantioseparation of bupropion enantiomers has been achieved using NACE with commercialized and non-commercialized anionic CDs [17,19–21].

The main objective of this work was the development of a rapid and simple electrokinetic chromatography (EKC) method using CDs as chiral selectors for the separation of bupropion enantiomers and their quantitation in pharmaceutical formulations.

2. Experimental

2.1. Reagents and samples

All reagents employed for the preparation of the BGE were of analytical grade. Acetic acid was supplied from Riedel-Hägen (Seelze, Germany). Boric acid was purchased from Fluka (Buchs, Switzerland). Sodium hydroxide was from Merck (Darmstadt, Germany). β-CD, (2-hydroxy)propyl-β-CD (HP-β-CD, degree

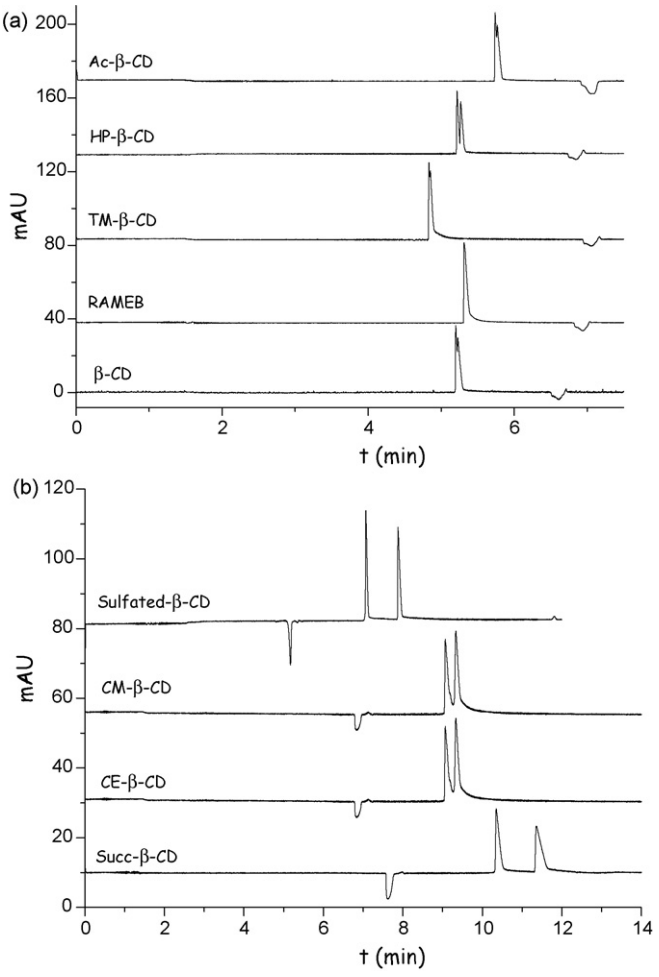

Fig. 2. Chiral separation of racemic bupropion (200 mg L^{-1}) using as chiral selector different CDs. (a) 10 mM β-CD or neutral derivatized β-CDs in 50 mM acetate buffer (pH 5.0); (b) 10 mM anionic derivatized β-CDs in 50 mM borate buffer (pH 9.0). Experimental conditions: uncoated fused-silica capillary, 50 μm i.d. × 50 cm (58.5 cm to the detector); injection by pressure at 50 mbar × 4 s, applied voltage, 20 kV; temperature, 20 °C; and detection at 210 ± 2 nm.

of substitution (DS), average number of substituents on one CD ring, ∼4.2), randomly methyl-β-CD (RAMEB, DS ∼ 12-13), heptakis-2,3,6-tri-*O*-methyl-β-CD (TM-β-CD), carboxymethyl-β-CD (CM-β-CD, DS ∼ 3), and sulfated-β-CD (DS ∼ 12) were supplied from Fluka (Buchs, Switzerland). Acetyl-β-cyclodextrin (Ac-β-CD, DS ∼ 7), carboxyethylated-β-CD (CE-β-CD, DS ∼ 3), and succinylated-β-cyclodextrin (Succ-β-CD, DS ∼ 3.5) were from Cyclolab (Budapest, Hungary). Water used to prepare solutions was purified through a Milli-Q system from Millipore (Bedford, MA, USA). Bupropion was supplied from Sigma (St. Louis, MO, USA). The structure of this basic drug is shown in Fig. 1. The pharmaceutical formulations analyzed were commercially available and acquired in a pharmacy of Alcalá de Henares (Spain). Both tablets were composed of bupropion hydrochloride (150 mg per tablet) and excipients (cellulose microcrystalline, hypromelose, cystein hydrochloride monohydrate, magnesium stearate, macrogol 400, titanium dioxide E171, carnauba wax, and black iron oxide E172).

2.2. Apparatus

An $HP^{3D}CE$ system from Agilent Technologies (Palo Alto, CA, USA) equipped with an on-column diode array detector (DAD) was employed. Instrument control and data acquisition were performed

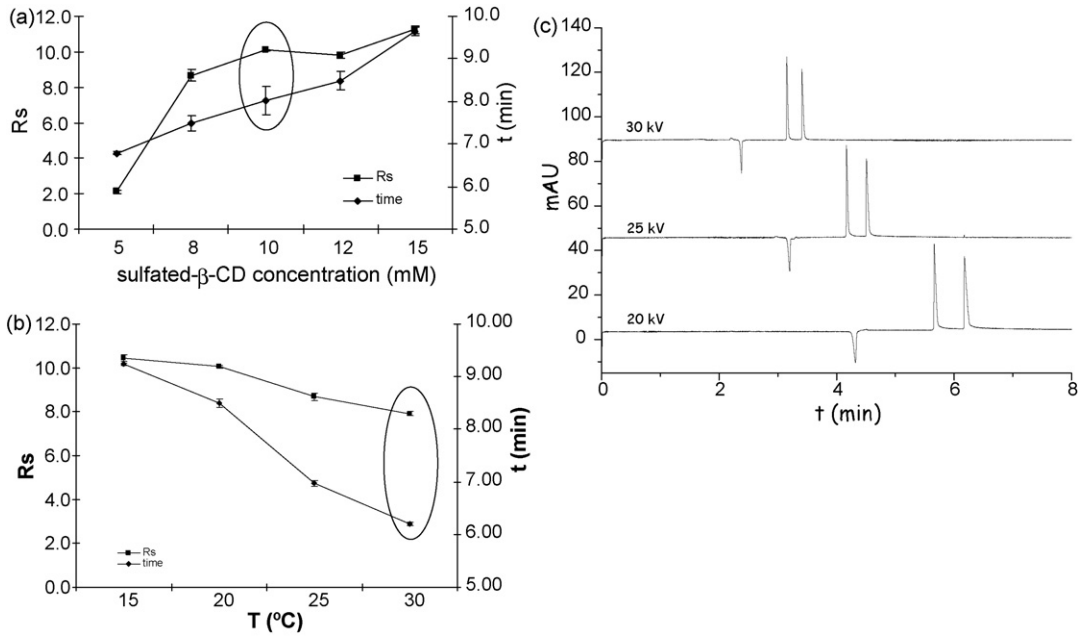

Fig. 3. Variation of the enantiomeric resolution and migration time for bupropion (200 mg L^{-1} racemic mixture), in three consecutive analyses, as a function of: (a) sulfated-β-CD concentration; (b) temperature; and (c) applied voltage. Error bars as mean ± standard deviation are shown. Experimental conditions: BGE, 50 mM borate buffer (pH 9.0), uncoated fused-silica capillary, 50 μm i.d. × 50 cm (58.5 cm to the detector); injection by pressure at 50 mbar × 4 s; and detection at 210 ± 2 nm.

with the HP^{3D}CE ChemStation software. Separations were performed on uncoated fused-silica capillaries of 50 μm i.d. (375 μm o.d.), with a total length of 58.5 cm (50 cm to the detector) purchased from Composite Metal Services Ltd. (Worcester, England). A 744-pH-meter from Metrohm (Herisau, Switzerland) was used to adjust the pH of the separation buffers.

2.3. Procedure

Before first use, a new capillary was rinsed with 1 M NaOH for 30 min, followed by 5 min with water, and conditioned with the buffer (see below) for 60 min and BGE for 15 min. Between runs, the capillary was rinsed with BGE for 2 min.

The selected instrumental conditions were: capillary temperature, 30 °C; injection by pressure, 50 mbar for 4 s; applied voltage, 30 kV; and UV detection at 210 nm with a bandwidth of 4 nm, and a response time of 0.1 s.

Buffer solutions were prepared dissolving the appropriate amount/volume of boric/acetic acids in Milli-Q water, adjusting the pH to the desired value (pH 9.0 or 5.0, respectively) with 1 M NaOH before completing the volume with water to get the desired buffer concentration (50 mM). Finally, BGEs were prepared dissolving the appropriate amount of the different CDs in the buffer solution.

Stock standard solutions were prepared by dissolving the appropriate amount of bupropion in Milli-Q water up to a final concentration of 2000 mg L^{-1}. This solution was stored at 4 °C and different aliquots were diluted in water to get solutions with different concentrations of racemic bupropion ranging from 20 to 200 mg L^{-1} for the calibration by the external standard method.

To prepare sample solutions of the two pharmaceutical formulations analyzed, the content of five tablets was weighed, powdered, and mixed homogeneously. About 0.1 g of the powder obtained was weighed and dissolved in 25 mL of Milli-Q water to achieve a final concentration of about 2000 mg L^{-1} in bupropion (taking into account the labeled amount of bupropion in the formulation). Dissolution was performed by ultrasonication for 30 min followed by filtration. Finally, sample solutions were diluted with water to 100 mg L^{-1}.

For calibration by the standard additions method three increasing concentrations of racemic bupropion standard (20, 40, and 80 mg L^{-1}) were added to a solution of each pharmaceutical formulation with 100 mg L^{-1} of racemic bupropion. The resulting solutions were directly injected in the electrophoretic system.

All these solutions (buffers, standards, and samples) were filtered through 0.45 μm pore size nylon filter membrane before their use in the CE system.

2.4. Data treatment

The values of resolution between adjacent peaks for the bupropion enantiomers were obtained from the corresponding migration times and their peak widths at half height using the ChemStation software.

Corrected peak areas (Ac) were used to compensate fluctuations in electrophoretic conditions and to obtain a good reproducibility of data [22].

Limits of detection (LOD, 3.3 s_a/b) and quantitation (LOQ, 10 s_a/b) were determined from the standard error of the intercept (s_a) and the slope (b) of the calibration curve obtained by ANOVA [23].

Experimental data analysis, and composition of graphs with different electropherograms were carried out using Excel Microsoft XP, Statgraphics plus 5.0, and Origin 6.0 software.

3. Results and discussion

3.1. Development of an enantioselective method for bupropion by EKC

The first step to develop a chiral analytical methodology by CE is the selection of the most appropriate chiral selector. Taking into account the pK_a value for bupropion (pK_a = 7.4 [24]), three main strategies were designed to attempt the enantiomeric separation:

Table 1
Analytical characteristics of the method developed for the determination of bupropion enantiomers by EKC

	First-migrating enantiomer	Second-migrating enantiomer
Linearity		
Linear range	10–100 mg L^{-1}	10–100 mg L^{-1}
Linear equation	$y = -0.199 + 0.138x$	$y = -0.196 + 0.135x$
Standard errors	$s_a = 0.075$, $s_b = 0.001$	$s_a = 0.076$, $s_b = 0.001$
Correlation coefficient (r)	0.9995	0.9995
p-value of ANOVA	0.938	0.742
LOD	1.8 mg L^{-1}	1.8 mg L^{-1}
LOQ	5.1 mg L^{-1}	5.2 mg L^{-1}
Precision		
Instrumental repeatability ($n = 6$)		
Ac, R.S.D (%)	3.2	2.7
t, R.S.D. (%)	0.6	0.7
Method repeatability ($n = 9$)		
Ac, R.S.D. (%)	2.1	2.6
t, R.S.D. (%)	1.3	1.3
Intermediate precision ($n = 9$)		
Ac, R.S.D. (%)	3.8[a], 4.5[b], 5.7[c]	4.0[a], 4.8[b], 5.2[c]
t, R.S.D. (%)	2.0[a], 1.3[b], 3.1[c]	2.0[a], 1.5[b], 3.3[c]
Accuracy		
Mean recovery (%)	103 ± 3[b], 100 ± 7[c]	102 ± 4[b], 101 ± 7[c]
Study of matrix interferences		
p-value of t-test	0.059[b] 0.052[c]	0.065[b] 0.117[c]

[a] Standard.
[b] Tablet A.
[c] Tablet B.

the use of acetate buffer at pH 5.0, where the analyte under study was cationic, with (i) neutral CDs or (ii) anionic CDs, and (iii) the use of borate buffer at pH 9.0, where the analyte was neutral, with anionic CDs. In these experiments, all CDs were tested using a 10 mM concentration in 50 mM of the corresponding buffer, with a separation voltage of 20 kV, a temperature of 20 °C, and a concentration of racemic bupropion of 200 mg L^{-1}.

The use of RAMEB (neutral CD) as chiral selector in acetate buffer (pH 5.0), did not enable the chiral separation of bupropion enantiomers, while the use of other neutral CDs such as β-CD, HP-β-CD, TM-β-CD, and Ac-β-CD, enabled a partial enantiomeric separation, being HP-β-CD the selector that gave rise to the highest enantiomeric resolution ($R_s = 0.7$), as it can be observed in Fig. 2a. On the other hand, the use of anionic CDs, such as CM-β-CD, sulfated-β-CD, CE-β-CD, and Succ-β-CD, in borate buffer (pH 9.0), showed a high discrimination power for the enantiomers (see Fig. 2b). Among these CDs, sulfated-β-CD provided the best enantioseparation ($R_s > 9.0$) in the lowest analysis time (~9 min), probably owing to the higher negative charge of this CD. The use of this CD in acetate buffer (pH 5.0), where the analyte was cationic showed an increase both in the resolution ($R_s \sim 14$) and the analysis time (~21 min). According to these results, sulfated-β-CD was chosen as chiral selector in borate buffer (pH 9.0) in order to develop a rapid chiral method for the analysis of bupropion.

Due to the fact that the concentration of the chiral selector affects the affinity of the enantiomers for the selector [9,25–27], the influence of the concentration of sulfated-β-CD on the chiral separation of bupropion was investigated in the range from 5 to 15 mM (5, 8, 10, 12, and 15 mM values were tested). As shown in Fig. 3a the resolution gradually improved when the concentration increased up to 15 mM. The increase in the CD concentration also produced an increase in the migration times, due to a decrease in the mobility of drug–CD complexes, which are more stable at high concentrations [9]. For this reason, establishing a compromise between these two parameters, a 10 mM concentration of sulfated-β-CD was chosen for further experiments (the resolution obtained was about 9.0 with an analysis time of 8 min).

Using a 10 mM concentration of sulfated-β-CD, the variation of the enantiomeric resolution and the migration time for the two bupropion enantiomers as a function of the temperature was also studied. The results obtained when this parameter ranged from 15 to 30 °C (15, 20, 25, and 30 °C were investigated) are shown in Fig. 3b. This figure shows that the enantiomeric resolution increased when decreasing the temperature, but migration

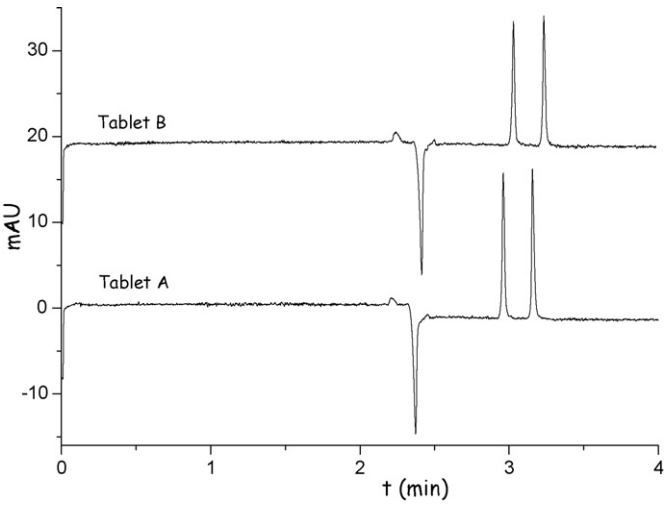

Fig. 4. Electropherograms corresponding to the two pharmaceutical formulations analyzed using 10 mM sulfated-β-CD in 50 mM borate buffer (pH 9.0). Experimental conditions: uncoated fused-silica capillary, 50 μm i.d. × 50 cm (58.5 cm to the detector); injection by pressure at 50 mbar × 4 s; applied voltage, 30 kV; temperature, 30 °C; and detection at 210 ± 2 nm.

Table 2
Average amount of bupropion enantiomers and total bupropion determined in the two pharmaceutical formulations analyzed (average ± confidence interval ($t\,s/n^{1/2}$ at 95% confidence level, $n = 3$)

Pharmaceutical formulation	Amount of first-migrating enantiomer (mg) ± $t\,s/n^{1/2}$	Amount of second-migrating enantiomer (mg) ± $t\,s/n^{1/2}$	Total amount determined (mg) ± $t\,s/n^{1/2}$	Total labeled (mg)
Tablet A	72 ± 7	72 ± 9	144 ± 16	150
Tablet B	69 ± 14	69 ± 7	138 ± 21	150

time also increased due to the increment in solution viscosity or enatiomer–CD interactions [9]. A temperature of 30 °C was chosen as working temperature since it enabled the separation of bupropion enantiomers with high resolution (R_s ~8) in a short analysis time (~6.2 min).

Finally, under the above selected conditions (10 mM sulfated-β-CD concentration and a temperature of 30 °C), the influence of the applied voltage from 20 to 30 kV was investigated. Fig. 3c depicts the electropherograms obtained for 20, 25, and 30 kV. It can be observed that an increase in the separation voltage originated a decrease in the migration time and also in the resolution. However, a value of 30 kV gave rise to the shortest migration time (~3.5 min) with enough resolution (R_s ~7.5) with an acceptable current intensity (~100 μA). Then, it was the separation voltage selected to obtain a rapid enantiomeric separation of bupropion enantiomers.

The optimized separation conditions enabled the best enantiomeric separation of bupropion (the highest enantiomeric resolution) in the shortest migration time when comparing these results with those previously obtained by other authors (see Section 1).

3.2. Quantitative analysis of bupropion enantiomers in pharmaceutical formulations

Before studying the analytical characteristics of the chiral method developed for the analysis of bupropion enantiomers, the possibility to carry out an interchange of inlet and outlet vials after each run to improve the reproducibility was performed. Taking into account the migration of the charged CD, this fact could avoid the decrease CD concentration in the inlet vial and the increase the concentration in the outlet vial [28]. Thus, R.S.D. values for five consecutive injections of racemic bupropion using a preconditioning with BGE (2 min) were 3.6 and 5.7 for corrected peak areas of first and second-migrating enantiomers, and 1.1 and 1.2 for migration times of first and second enantiomer. When using the same preconditioning with interchange of vials, the R.S.D. values were 3.3 and 2.6 for corrected peak areas of the first and second-migrating enantiomers, and 1.2 for migration time for both enantiomers. Since R.S.D. values for corrected peak areas were lower using interchange of vials, this procedure was selected to carry out the chiral analysis of bupropion enantiomers.

The analytical characteristics of the developed method were evaluated in terms of linearity, LODs, LOQs, precision, accuracy and selectivity in order to demonstrate the method suitability for routine determination of bupropion enantiomers.

Linearity was determined by plotting the corrected peaks areas (Ac) as a function of the bupropion concentration in mg L^{-1}. Thus, five standard solutions containing racemic bupropion from 20 to 200 mg L^{-1} (20, 50, 100, 150, and 200 mg L^{-1} of racemic bupropion, each one injected in triplicate) were prepared and checked for linearity during 3 days. The chiral method enabled to study separately each enantiomer, whose concentrations ranged from 10 to 100 mg L^{-1}. The linear equation for each enantiomer as well as standard errors of the intercept (s_a) and the slope (s_b), and the correlation coefficient (r) are shown in Table 1. In addition, ANOVA analysis enabled to confirm that experimental data fit properly to linear models for both enantiomers (p-values of 0.938 and 0.742 for the first- and second-migrating enantiomers, respectively).

LODs and LOQs for bupropion enantiomers were calculated from the calibration line. For the first-migrating enantiomer a LOD of 1.8 mg L^{-1} and a LOQ of 5.1 mg L^{-1} were obtained, while for the second-migrating enantiomer the values were 1.8 and 5.2 mg L^{-1} for LOD and LOQ, respectively (see Table 1).

Precision was evaluated considering the instrumental and method repeatability as well as the intermediate precision. Instrumental repeatability was determined from six repeated injections of a standard solution of 150 mg L^{-1} racemic bupropion. As it can be observed in Table 1, R.S.D. values obtained were lower than 3.2% for corrected peak areas and lower than 0.7% for migration times. The method repeatability was assessed with three replicate standard solutions of 150 mg L^{-1} of racemic bupropion injected each one in triplicate on the same day. R.S.D. values lower than 2.6 and 1.3% for corrected peak areas and migration times, respectively, were obtained (see Table 1). The intermediate precision of the method was calculated taking into account the mean value obtained each day for three replicate standard solutions of 150 mg L^{-1} of racemic bupropion injected in triplicate for 3 consecutive days. In this case, R.S.D. values for corrected peak areas and migration times were lower than 4.0 and 2.0%, respectively. Intermediate precision was also determined for tablets A and B from the mean value obtained each day for three individual sample solutions (about 100 mg L^{-1} concentration of racemate) injected in triplicate for three consecutive days. R.S.D. values for corrected peak areas were lower than 5.7% and lower than 3.3% for migration times.

Accuracy of the method was evaluated as the recovery obtained for bupropion enantiomers when spiking the two pharmaceutical formulations (50 mg L^{-1} concentration for each enantiomer) with known concentrations of bupropion enantiomers (10, 20, and 40 mg L^{-1} of each enantiomer). Table 1 shows that the mean recovery values obtained for both tablets ranged from 100 to 103%.

Appropriate separation selectivity was observed for the developed method as shown in Fig. 4 since the bupropion enantiomers were well-separated and there was no evidence of interferences from other components present in the pharmaceutical formulations. In addition, the comparison of the slopes obtained when using the external standard calibration method and the standard additions calibration method was used to investigate the existence of possible matrix interferences. The results obtained by the t-test (p-value >0.05) showed that there were not statistically significant differences between the slopes obtained by the external standard and the standard additions calibration methods for both enantiomers (see Table 1). Therefore, the external standard calibration method can be used to achieve the quantitation of bupropion enantiomers in pharmaceutical formulations.

The average amount of bupropion enantiomers and total bupropion determined in the two pharmaceutical formulations analyzed is shown in Table 2 together with the total labeled amount for each pharmaceutical formulation. Confidence intervals are also included in this table showing that there were not statistically significant differences between determined and labeled contents.

4. Concluding remarks

A method enabling the rapid enantiomeric separation and quantitation of bupropion was developed in this work. The method improved the results obtained previously in terms of resolution and analysis time. Moreover, it is the first CE method enabling the quantitation of bupropion enantiomers and the first method enabling the quantitation of bupropion enantiomers in pharmaceutical formulations. The method was based on the use of 50 mM borate buffer at pH 9.0 with 10 mM sulfated-β-CD, a temperature of 30 °C, and 30 kV as the separation voltage and enabled the chiral separation of bupropion enantiomers with a high resolution (>7) and in a short analysis time (3.5 min). LODs of 1.8 mg L^{-1} for each bupropion enantiomer were achieved, and the method was successfully applied, for the first time, to the quantitative determination of bupropion enantiomers in pharmaceutical formulations.

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