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Short communication

Development and validation of a capillary electrophoresis method for the simultaneous determination of impurities of escitalopram including the *R*-enantiomer

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Abstract

A stereospecific capillary electrophoresis assay for the simultaneous determination of related substances and the enantiomeric purity of escitalopram was developed by a central composite face-centered factorial design and subsequently validated. Separations were carried out in a 50 μm, 47/40 cm fused-silica capillary. The optimized conditions included 20 mM phosphate buffer, pH 2.5, containing 0.5 mg/ml β-cyclodextrin and 22 mg/ml sulfated β-cyclodextrin as background electrolyte, an applied voltage of −20 kV and a temperature of 28 °C. Salicylic acid was used as internal standard. The assay was validated for the (*R*)-enantiomer of citalopram and the enantiomers of the impurity citadiol in the range of 2.5–150 μg/ml and 2.5–50 μg/ml, respectively. The limit of detection was 0.02% for all compounds, the limit of quantitation 0.05%, relative to a concentration of escitalopram of 5 mg/ml. Intraday precision of migration time and peak area ratio were in the range of 0.17–0.44% and 1.64% and 6.25%, respectively. Relative standard deviations of interday precision ranged between 0.84% and 1.85% in the case of migration times and between 5.20% and 9.28% for peak area ratio. The assay was applied to the determination of the purity of escitalopram in bulk drug and tablets. (*R*)-Citalopram and (*S*)-citadiol were detected as impurities.

Keywords: Escitalopram; Citadiol; Related compounds; Chiral separation; Cyclodextrin

1. Introduction

Citalopram (1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile) is a selective serotonin reuptake inhibitor used as an antidepressant drug [1]. The compound is also applied to treat panic, anxiety and obsessive compulsive disorders of pathological laughing and crying [2]. The pharmacological activity is associated with the (*S*)-(+)-enantiomer (escitalopram, Fig. 1) while the (*R*)-(−)-enantiomer ((*R*)-citalopram, Fig. 1) is essentially inactive [3] and even counteracts the activity of escitalopram [4,5]. The key intermediate in the synthesis of citalopram is citadiol (Fig. 1) which is cyclized to yield the dihydroisobenzofuran moiety. Escitalopram is produced from (*S*)-citadiol which is obtained either by preparative chromatographic enantioresolution of racemic citadiol [6] or more frequently by fractionated crystallization of citadiol using, for example, (+)-di-*p*-toluoyl-D-tartaric acid [7,8]. Thus, the chiral purity of escitalopram depends on the purity of starting material (*S*)-citadiol.

The analytical enantioseparation of citalopram has been reported by enantioselective high-performance liquid chromatography (HPLC) for studying the stereoselective pharmacokinetics and metabolism of citalopram [9–12]. HPLC has also been applied to determine the enantiomeric purity of escitalopram in bulk drug and tablets [13]. The separation of the enantiomers of citadiol by HPLC using a Chiralpack AD-H column has been reported recently [14]. Capillary electrophoresis (CE) has been used to study the enantiomeric composition of citalopram and its metabolites in plasma [15] and urine [16] using sulfated β-CD and carboxymethyl-γ-CD, respectively, as chiral selectors. Sulfated β-CD was used for the simultaneous enantioseparation of citalopram and its *N*-demethyl analogs [17] while carboxymethyl-γ-CD was applied to the determination

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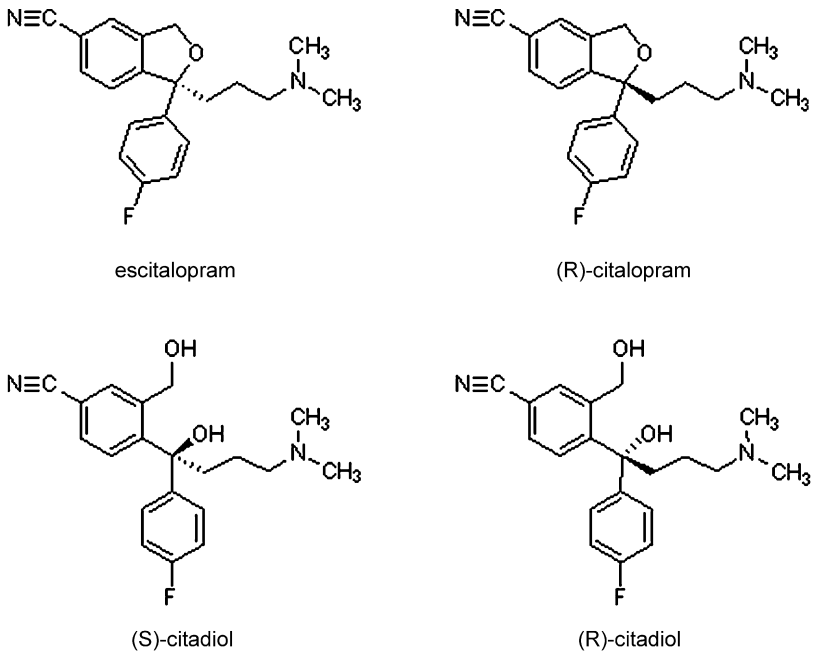

Fig. 1. Structures of escitalopram, (*R*)-citalopram and citadiol enantiomers.

of citalopram and escitalopram in tablets [18]. Moreover, separation of the enantiomers of citalopram upon addition of dextrin to the background electrolyte has been reported [19].

No study has been published describing the simultaneous determination of related substances as well as the analysis of the chiral purity of escitalopram. Generally, CE has been recognized as a versatile analytical technique also allowing the simultaneous analysis of chiral compounds with closely related structures [20–22]. Thus, the aim of the present study was the development and validation of a chiral CE assay for escitalopram allowing the simultaneous determination of the (*R*)-enantiomer as well as the synthetic intermediate citadiol.

2. Experimental

2.1. Chemicals and reagents

All chemicals were of analytical grade. Sulfated β-CD sodium salt was obtained from Sigma–Aldrich (Taufkirchen, Germany), β-CD was from Wacker-Chemie GmbH (Burghausen, Germany), sodium hydroxide solution was from Fisher Scientific (Schwerte, Germany) and phosphoric acid was from Carl Roth GmbH (Karlsruhe, Germany). Salicylic acid was purchased from Fluka Chemie AG (Buchs, Switzerland) and methanol from VWR International (Bruchsal, Germany). Escitalopram oxalate, citalopram hydrobromide, racemic citadiol were produced by Hygro Chemical Pharmtek Pvt. Ltd. (Hyderabad, India) and donated by Dr. Ramisetti Nageswara Rao (Indian Institute of Chemical Technology, Hyderabad, India). Escitalopram and citalopram tablets were also gifts by Dr. Nageswara Rao.

2.2. Instrumentation

All analyses were carried out on Beckman P/ACE 5510 instrument (Beckman Coulter GmbH, Unterschleißheim, Germany) equipped with a diode array detector using 50 μm i.d., 360 μm o.d. fused-silica capillaries (BGB Analytik, Schloßböckelheim, Germany). The total length of the capillary was 47 cm with an effective length of 40 cm. Detection was carried out at 205 nm. The optimized background electrolyte consisted of 20 mM phosphate buffer, pH 2.5, containing 0.5 mg/ml β-CD and 22 mg/ml sulfated β-CD. The applied voltage was −20 kV, the capillary was operated at a temperature of 28 °C. A new capillary was treated with 1 M sodium hydroxide for 10 min, 0.1 M sodium hydroxide for 20 min, 0.1 M phosphoric acid and water for 10 min each. At the beginning of the day, the capillary was rinsed with water, 0.1 M sodium hydroxide and 0.1 M phosphoric acid for 5 min each followed by flushing with water for 10 min. Prior to the injections, the capillary was washed subsequently with 0.1 M sodium hydroxide and water for 2 min each followed by a rinse with the background electrolyte for 5 min. At the end of the day, the capillary was flushed with water for 2 min, 0.1 M sodium hydroxide for 10 min, water for 1 min, 0.1 M phosphoric acid for 5 min and water for 10 min. Prior to storage, the capillary was purged with nitrogen for 5 min. Samples were introduced by hydrodynamic injection at 0.5 psi for 6 s. Normalized peak areas were used for quantitative determinations.

2.3. Standard and sample preparation

Stock solutions of escitalopram oxalate, citalopram hydrobromide and citadiol were prepared in water and diluted to the appropriate concentrations. Salicylic acid was diluted in

water and added to the samples to give a final concentration of 21.7 μg/ml.

Four different commercial brands, three containing escitalopram oxalate and one containing citalopram hydrobromide, were investigated. Five tablets were weighed and ground to a fine powder. An equivalent of the powder corresponding to 10 mg of the drug was extracted with 10 ml methanol by sonication for 15 min. The solutions were filtered and the filtrates were evaporated to dryness under a gentle stream of nitrogen at 40 °C. The residue was reconstituted in 1 ml water and filtered through a 0.2 μm PET membrane filter. Two hundred and fifty microliters of the filtrate were added to 250 μl water containing 43.4 μg/ml salicylic acid and vortexted.

2.4. Chemometrics

Chemometrics for method optimization was carried out by central composite face-centered factorial design using MODDE 7.0 (Umetrics, Umea, Sweden). Four variables were applied, i.e. concentration of sulfated β-CD, buffer concentration, separation temperature, and applied voltage. The experiments were run in a randomized order. The data were fitted by partial least square (PLS) regression.

For each model, interaction and quadratic terms were included. The fraction of variation of the response that can be explained by the model (R^2 = (total sum of squares − sum of squares for residuals)/total sum of squares) and the fraction of variation of the response that can be predicted by the model (Q^2 = 1 − (prediction residual sum of squares/total sum of squares)) were subsequently examined. For a good model, R^2 and Q^2 are as close to 1 as possible. The model estimated the coefficients (b_n), which represent half the effect of a factor. The confidence interval of each coefficient (95% of confidence) was studied to see if the factors had any effect on the responses. Some of the coefficients (interaction or quadratic terms) that did not have a significant effect were subsequently removed from the current model, and a new model was calculated. If R^2 and Q^2 decreased following the removal of an insignificant coefficient, the coefficient was added to the model again. To identify outliers, a normal probability plot of the residuals was examined. The observed response versus predicted plot was examined to evaluate the predictability of each model and the observed response versus run order plot was examined to ensure the absence of systematic errors. A logarithmic transformation of the responses improved the model.

2.5. Method validation

The assay was validated for concentrations that referred to a range of 0.05–3.0% for (*R*)-citalopram (5–300 μg/ml racemic citalopram) and 0.05–1.0% for the citadiol enantiomers (5–100 μg/ml racemic citadiol) based on a final concentration of escitalopram of 5.0 mg/ml. Method validation was conducted according to ICH guideline Q2(R1) [23] with regard to range, linearity, limit of detection and quantitation, and precision. Precision was determined at a low concentration (0.1% for each compound) and a high concentration (0.6% for citadiol and 2% for (*R*)-citalopram). Linearity was estimated by unweighted linear regression using the least square method. Detection and quantitation limits were based on signal to noise ratio, 3:1 and 10:1, respectively. Intraday precision was calculated from six replicate injections in the same day while interday precision was based on six injections on three consecutive days.

3. Results and discussion

3.1. Selection of cyclodextrins and initial conditions

Based on the published enantioseparations of citalopram which were performed in the pH range 2.5–7 [15–18] where citalopram is positively charged, several neutral CD derivatives such as α-CD, β-CD, γ-CD, 2-hydroxypropyl-β-CD and 2,6-dimethyl-β-CD as well as the negatively charged sulfated β-CD were screened for the chiral resolution ability for the enantiomers of citalopram and citadiol in the pH range 2.3–6.2. Baseline separation of the analyte enantiomers was observed using 5 mg/ml sulfated β-CD in 20 mM phosphate buffer, pH 2.5, but especially the peaks of the citalopram enantiomers revealed strong tailing. This has also been observed previously [17]. The peak shape could not be improved substantially by a variation of the CD concentration. Mandrioli et al. exploited the carrier ability of sulfated β-CD under reversed polarity conditions to separate the enantiomers of citalopram and its *N*-demethylated metabolites [17]. Thus, a background electrolyte consisting of 15 mg/ml sulfated β-CD in 35 mM phosphate buffer, pH 2.5, and reversing the polarity of the applied voltage was studied. Generally, good separation of the enantiomers was observed ($R_S \geq 2$) but the peaks showed considerable fronting. Peak shape improved significantly when 0.5–1 mg/ml β-CD was added to the sulfated β-CD containing background electrolyte as also observed by Mandrioli et al. [17]. It has been shown in many examples that dual CD systems based on combinations of charged and neutral CDs can result in efficient chiral CE separations [24–26]. Essentially the same effect on the peak shape was observed when α-CD or γ-CD was added instead of β-CD. Employing short end injection using a citrate buffer, pH 5.5, as described as a fast method for the chiral separation of citalopram by Mandrioli et al. [17] did not result in satisfactory separations as citalopram and citadiol migrated too close to achieve a simultaneous enantioseparation of both compounds. As citalopram is typically marketed as the oxalate or hydrobromide salts the migration times of oxalic acid and bromide were also recorded. Using 35 mM sodium phosphate buffer, pH 2.5, containing 15 mg/ml sulfated β-CD and 0.5 mg/ml β-CD as background electrolyte the anionic compounds migrated in front of the citalopram and citadiol resulting in the migration order bromide > oxalate > (*R*)-citalopram > escitalopram > (*S*)-citadiol > (*R*)-citadiol. Oxalate and bromide peaks were identified by injection of solutions of oxalic acid and potassium bromide. The migration order of the citadiol enantiomers was tentatively assigned due to the fact that a small impurity with the migration time of the (*S*)-citadiol was found in escitalopram substance as well as tablets.

Table 1
Central composite face-centered factorial design and results

Experiment no.	Run order	Concentration S-β-CD (mg/ml)	Temperature (°C)	Voltage (kV)	Concentration buffer (mM)	R_S, ox/(*R*)-cit	R_S, (*S*)-cit/(*R*)-cit	MT last (min)	Current (μA)
1	15	10	20	15	20	2.73	5.82	15.5	27.5
2	2	30	20	15	20	3.98	6.89	13.8	52.5
3	9	10	30	15	20	2.39	5.35	14.9	33
4	22	30	30	15	20	3.61	5.88	10.9	66
5	13	10	20	25	20	4.13	5.06	9.8	48.5
6	11	30	20	25	20	4.06	8.49	7.0	102.5
7	23	10	30	25	20	2.26	4.62	9.7	60
8	10	30	30	25	20	3.79	6.48	6.6	130
9	1	10	20	15	50	0.93	11.45	28.6	39
10	21	30	20	15	50	5.36	4.56	14.6	79
11	25	10	30	15	50	0.74	7.00	22.0	48
12	27	30	30	15	50	5.00	4.07	12.0	98
13	5	10	20	25	50	0.96	8.52	14.6	72
14	18	30	20	25	50	5.74	4.33	7.9	164
15	16	10	30	25	50	0.39	6.56	17.2	88
16	8	30	30	25	50	4.00	5.43	7.5	195
17	14	10	25	20	35	1.71	6.38	17.3	49.5
18	19	30	25	20	35	3.07	6.95	9.7	92
19	3	20	20	20	35	7.64	8.70	11.8	71.5
20	6	20	30	20	35	3.09	7.26	10.4	88.4
21	4	20	25	15	35	3.06	7.60	14.8	56.5
22	26	20	25	25	35	2.69	6.30	7.9	110.5
23	12	20	25	20	20	3.99	5.43	9.2	63.5
24	7	20	25	20	50	2.78	7.37	12.4	90
25	24	20	25	20	35	3.01	6.87	9.9	81
26	17	20	25	20	35	3.14	6.91	10.5	80
27	20	20	25	20	35	3.16	6.87	10.5	82

3.2. Method optimization

A central composite face-centered factorial design was used for method optimization. Four factors, concentration of sulfated β-CD (10–30 mg/ml), buffer concentration (20–50 mM), applied voltage (15–25 kV) and temperature (20–30 °C), were studied. The concentration of β-CD was kept constant at 0.5 mg/ml as preliminary experiments revealed not significant effect in the range of 0.5–2 mg/ml. Moreover, pH was set at 2.5 and variations were not investigated either as citalopram and citadiol are both basic compounds which are essentially protonated up to pH 7–8. The resolution between the citalopram enantiomers as well as the resolution between oxalate and (*R*)-citalopram, the migration time of the last migrating compound (*R*)-citadiol, and the generated current were initially selected as responses. The current was included because it increased with increasing concentrations of sulfated β-CD. High currents will lead to loss in resolution and instable run conditions due to extensive Joule heating. All experiments were performed in random order to avoid a systematic error. Three experiments (nos. 25–27) were carried out in the center of the design matrix in order to obtain the information about day-to-day variability. The individual experiments and the respective results of the runs are summarized in Table 1. The resolution between the enantiomers of citalopram always exceeded 4.0 and was therefore excluded from further considerations. The resolution between oxalate and (*R*)-citalopram exceeded 2 except for experiments with low concentrations of sulfated β-CD. Thus, essentially only the CD concentration is affecting this value as was also deducted from analysis of the respective coefficients (data not shown). The scaled and centered coefficients of migration time and current are shown in Fig. 2. CD concentration and applied voltage had positive effects on the current while a negative effect on migration time was observed. Upon increase of the buffer concentration migration time as well as current increased.

The method was further optimized utilizing the "optimizer" mode of the software (based on the Nelder–Mead simplex method [27]). As resolution between the citalopram enantiomers and between oxalate and (*R*)-citalopram was not really an issue as outlined above, only the migration time of the last migrating citadiol enantiomer (maximum 10 min) and the current (maximum 80 μA) were minimized. Optimized conditions were a 20 mM sodium phosphate buffer, pH 2.5 containing 22 mg/ml sulfated β-CD and 0.5 mg/ml β-CD, at a capillary temperature of 28 °C and an applied voltage of −20 kV. The predicted values for migration time and current of the optimized method were 8.7 min and −73 μA. The observed experimental values of 8.4 min and −68 μA are in reasonable agreement. A typical electropherogram of escitalopram oxalate containing (*R*)-citalopram and citadiol as impurities analyzed under optimized conditions is shown in Fig. 3.

3.3. Method validation

Salicylic acid was used as internal standard in order to compensate for fluctuations of the migration time and injection

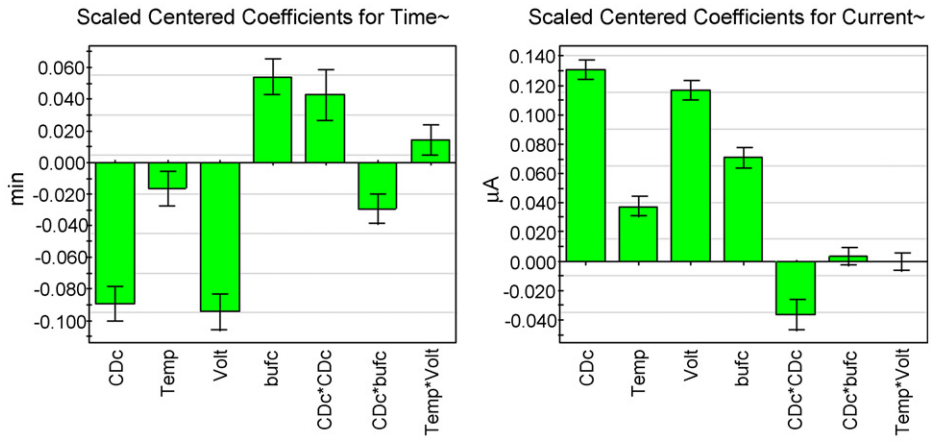

Fig. 2. Scaled and centered coefficients of the logarithms of the migration time of (*R*)-citadiol (left) and electrophoretic current (right). The respective 95% confidence intervals are shown as error bars. Coefficients with 95% confidence intervals including zero are insignificant. CDc: concentration of sulfated β-CD; Temp: temperature; Volt: applied voltage; bufc: phosphate buffer concentration.

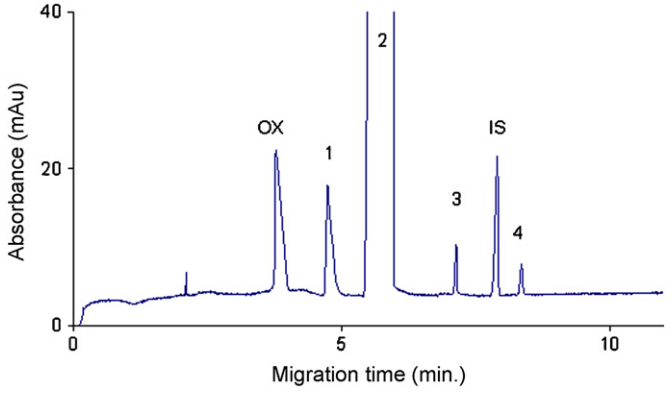

Fig. 3. Electropherogram of 5 mg/ml escitalopram oxalate containing approximately 2.4% of (*R*)-citalopram and 0.1% of the citadiol enantiomers. Experimental conditions: 47/40 cm fused-silica capillary, 50 μm i.d., 20 mM sodium phosphate buffer, pH 2.5, containing 22 mg/ml sulfated β-CD and 0.5 mg/ml β-CD, −20 kV, 205 nm. Peak identification: (1) (*R*)-citalopram; (2) escitalopram; (3) (*S*)-citadiol; (4) (*R*)-citadiol; (IS) internal standard (salicylic acid); (OX) oxalic acid.

errors. The compound was selected from a series of basic and acidic compounds based on the migration between the citadiol enantiomers. Most basic compounds and several acidic compounds which were tested as internal standards migrated either too close or even comigrated with bromide or oxalate.

The final method was subsequently validated according to the ICH guideline Q2(R1) [23] with respect to specificity, linearity range, limit of detection (LOD) and limit of quantitation (LOQ), and precision. With respect to specificity, all compounds were well separated (Fig. 3). When developing assays for the determination of related substances as well as stereoisomeric impurities it is always desirable to validate the impurities in the presence of a large excess of the parent compound. However, this could not be carried out in the present study as the escitalopram substance that was available contained approximately 2.4% (*R*)-citalopram based on peak area normalization. Thus, method validation was performed using racemic citalopram and citadiol in the range of 2.5–150 μg/ml and 2.5–50 μg/ml, respectively, corresponding to a relative range of 0.05–3.0% in the case of (*R*)-citalopram and 0.05–1.0% for the citadiol enantiomers based on a target concentration of escitalopram in the samples of 5 mg/ml (the concentrations refer to the respective enantiomers). At 5 mg/ml the peak shape of escitalopram was still acceptable. The concentration of the internal standard in the samples was 21.7 μg/ml corresponding to a relative concentration of 0.43%. The calibration data are summarized in Table 2. Correlation coefficients of at least 0.9964 were determined. The 95% confidence intervals of the *y*-intercept for all compounds included zero. Thus, a systematic error can be excluded.

The LOD of (*R*)-citalopram and the citadiol enantiomers defined as a signal-to-noise ratio of 3:1 were about 1 μg/ml corresponding to a relative concentration of 0.02% of the compounds based on a concentration of escitalopram of 5 mg/ml. The LOQ defined as the signal-to-noise ratio of 10:1 was 2.5 μg/ml

Table 2
Calibration data: range, linearity, LOD and LOQ

Parameter	(*R*)-Citalopram	(*S*)-Citadiol	(*R*)-Citadiol
Range (μg/ml)	2.5–150	2.5–50	2.5–50
Correlation coefficient	0.9964	0.9992	0.9989
Slope	1.15	1.59	1.55
Intercept	−0.0163	−0.0156	−0.0097
95% confidence interval of intercept	−0.0980 to 0.0653	−0.0321 to 0.0008	−0.0280 to 0.0086
Relative residual S.D. (%)	8.18	3.41	3.90
LOD/LOQ (μg/ml)	1.0/2.5	1.0/2.5	1.0/2.5

Table 3
Assay precision

	(*R*)-Citalopram		(*S*)-Citadiol		(*R*)-Citadiol	
	0.1% level	2% level	0.1% level	0.6% level	0.1% level	0.6% level
Intraday precision						
Concentration (μg/ml)	4.85 (6.25)	97.0 (2.51)	5.45 (4.63)	32.7 (1.64)	5.45 (4.68)	32.7 (1.95)
Migration time (min)	4.49 (0.17)	4.54 (0.19)	6.67 (0.40)	6.73 (0.32)	7.81 (0.44)	7.87 (0.36)
Interday precision						
Concentration (μg/ml)	4.85 (8.56)	97.0 (8.05)	5.45 (9.28)	32.7 (5.90)	5.45 (7.57)	32.7 (5.20)
Migration time (min)	4.54 (1.17)	4.53 (0.84)	6.76 (1.61)	6.64 (1.35)	7.93 (1.85)	7.88 (1.59)

The R.S.D. is listed in parenthesis.

corresponding to 0.05%. The observed LOQ values are identical with the requirement of the reporting limit for impurities as stated by the ICH guideline Q3A "Impurities in New Drug Substances" [28] as well as international pharmacopoeias such as the United States Pharmacopeia [29] or the European Pharmacopoeia [30].

Precision was investigated at a relative concentration of approximately 0.1% and 2.0% or 0.6% in the case of the citalopram and citadiol enantiomers, respectively. The respective concentrations based on the target concentration of 5 mg/ml escitalopram were 9.7 μg/ml and 194 μg/ml for racemic citalopram and 10.9 μg/ml and 65.4 μg/ml in the case of racemic citadiol. Sample solutions were injected six times on 1 day (intraday precision) and on three consecutive days (interday precision). The migration times as well as the concentrations of the compounds are summarized in Table 3. Generally acceptable relative standard deviation (R.S.D.) values of the peak area ratios ranging between 1.64% and 6.25% for intraday precision and between 5.20% and 9.28% for interday precision were observed.

3.4. Method application

The method was applied to determine (*R*)-citalopram and the citadiol enantiomers in escitalopram bulk and tablets. In addition, one tablet containing racemic citalopram was investigated. An electropherogram of an escitalopram tablet is shown in Fig. 4. In bulk drug about 2.30 ± 0.11% (*R*)-citalopram and 0.10 ± 0.01% (*S*)-citadiol could be detected. The results of the tablets are summarized in Table 4. Two brands contained about 0.3–0.4% (*R*)-citalopram and about 0.4–0.5% (*S*)-citadiol. A third brand contained approximately 10-fold higher concentrations of (*R*)-citalopram and 2-fold higher concentrations of (*S*)-citadiol. (*R*)-citadiol could not be detected in any samples of escitalopram. The tablet of racemic citalopram contained only very low levels of both citadiol enantiomers.

In order to estimate the recovery of (*R*)-citalopram and the citadiol enantiomers from the tablets a second extraction of the residue of sample 1 was performed. (*R*)-Citalopram could not be detected while a concentration of (*S*)-citadiol corresponding to about 0.03% was determined. This concentration is below the LOQ but considering the amount of the impurity found in the first extraction this value corresponds to about 7% of the compound not extracted in the first step. Moreover, the tablet residue of the second extraction was spiked at the 0.5% level. Concentrations of 0.49 ± 0.01%, 0.44 ± 0.02% and 0.45 ± 0.02% were determined for (*R*)-citalopram, (*S*)-citadiol and (*R*)-citadiol, respectively. Thus, a sample recovery of at least 88% can be estimated for all compounds so that the analysis of the impurities following a single extraction can be regarded as representative.

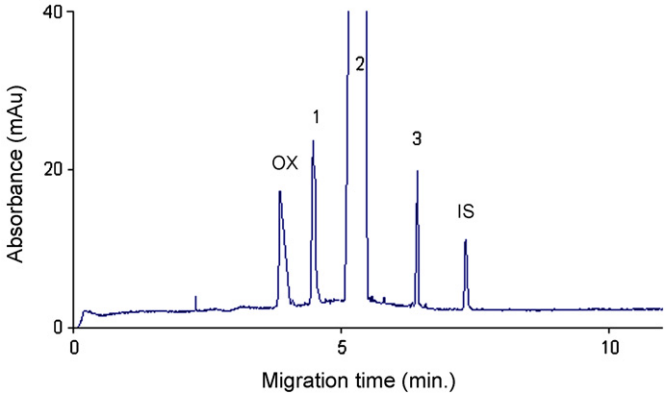

Fig. 4. Electropherogram of an escitalopram tablet (entry 3 in Table 4). For experimental conditions see Fig. 3. Peak identification: (1) (*R*)-citalopram; (2) escitalopram; (3) (*S*)-citadiol; (IS) internal standard (salicylic acid); (OX) oxalic acid.

Table 4
Impurity profile of commercial tablets

Sample	Impurity (%)		
	(*R*)-Citalopram	(*S*)-Citadiol	(*R*)-Citadiol
1	0.37	0.45	ND[a]
2	0.32	0.38	ND
3	2.01	0.72	ND
4[b]	Racemate	0.07	0.03[c]

The amount is listed relative to a concentration of escitalopram of 5 mg/ml (mean of two determinations).
[a] ND: not detected.
[b] Tablet containing racemic citalopram.
[c] Below LOQ.

4. Conclusions

A stereoselective CE method employing a dual CD system has been developed and validated for the analysis of escitalopram with regard to its impurities (*R*)-citalopram and citadiol using chemometrics for method optimization. The assay is specific allowing the detection of the impurities at the 0.05% level relative to escitalopram at a concentration of 5 mg/ml. This is the equivalent of the reporting threshold of the ICH guideline Q3A [28]. The assay was subsequently applied to the analysis of bulk and tablets. The results demonstrated different qualities of the tablets with regard to the impurity profile clearly indicating the necessity of validated assays for purity control. Although not developed and validated for citalopram the assay can also be applied to analyze the racemic drug.

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