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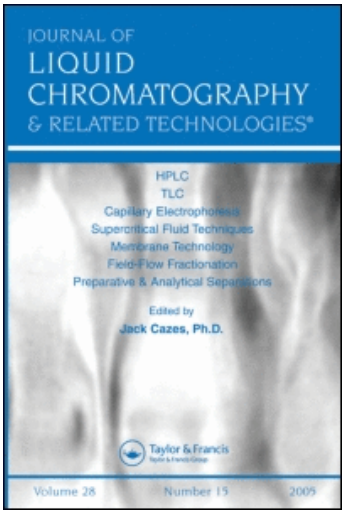

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Validated Capillary Electrophoresis Study for the Determination of Cetirizine in Pharmaceutical Forms

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Abstract: A capillary electrophoretic method for the determination of cetirizine is described in this study. The method was developed by using a running buffer consisting of 10 mM of 10% methanol with pH 8.5, employing a fused silica column with a total length of 85 cm, an effective length of 65 cm, and internal diameter of 75 μm. 28 kV were applied, which produced signals that were detected at 200 nm. Under these conditions, cetirizine and phenobarbital sodium as an internal standard appeared at 6.7 and 8.9 minutes, respectively. The limits of detection and quantification were found to be 5.45×10^{-6} M and 1.60×10^{-5} M, respectively. The repeatability and linearity of the method were validated by intra-day and inter-day precision. Then, the proposed method was applied to Zyrtec® tablet, syrup, and oral drop. The results indicate that the method is simple, accurate, and precise for the analysis of cetirizine.

Keywords: Capillary electrophoresis, Cetirizine, Determination, Pharmaceutical analysis, Method development, Method validation

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INTRODUCTION

Cetirizine (CTZ) [2-(2-{4-[(4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) acetic acid] is a selective peripheral H_1-receptor antagonist in the cyclizine class of compounds. CTZ is orally active and an active metabolite of hydroxyzine that is included into the first generation H_1-receptor antagonist. It represents negligible penetrations into the brain and does not affect the H_1-receptors. Therefore, CTZ lacks the depressant behavior frequently encountered in antihistamines. CTZ is a potent, well tolerated, and non-sedating anti-histamine for the treatment of allergic rhinitis and chronic urticaria,[1–3]

CTZ HCl salt is used in pharmaceutical dosage forms. The chemical structure of CTZ is represented in Fig. 1.

Methods for the determination of CTZ include: Acid base titration and TLC or HPTLC,[4–7] HPLC,[8–16] spectrophotometry/colorimetry,[17–20] and other sophisticated methods such as LC-MS/MS.[21–24] These methods are used pharmaceutically for bulk material;[7] only tablets;[5,9,14,19,20] tablets, syrup, and oral drops;[11,12,18] pharmacokinetic studies,[6,11,16,22,24] and process related substances.[23]

Certain conclusions can be drawn regarding the methods used for the determination of CTZ. However, no studies using CE have been conducted for determining CTZ in pharmaceuticals or bodily fluids. CE is a new and extremely powerful analytical technique for instrumentation and separation methodologies. Studies incorporating CE have been reported in many diverse fields, including chemical, biotechnological, environmental, and pharmaceutical analyses.[25] CE has specific advantages over other methods: It is fast, selective, needs very little volume, and no further purification is required.[25,26]

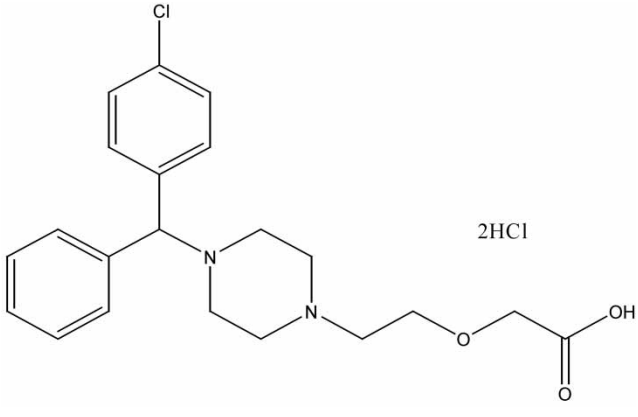

Figure 1. The chemical structure of CTZ.

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The aim of this study was to develop a simple and validated CE method to analyze CTZ, for use in routine analyses of pharmaceutical formulations such as CTZ Tablets, syrup, and oral drops.

EXPERIMENTAL

Apparatus

A CE-L1 injection and power supply module separated the compounds and a Class Elegance Station (CE Resources Pte Ltd., Ayer Rajah Crescent, Singapore) provided the signals. SPD-M10 a VP Diode Array Detector (DAD) (Shimadzu, Kyoto, Japan) detected the signals, and Class VP software (Shimadzu, Kyoto, Japan) processed the data. An uncoated fused silica capillary (Unimicro Technologies Inc., California, USA) having an ID of 75 μm was used for resolution. A UV-VIS spectrophotometer model UV-2101 (Shimadzu, Kyoto, Japan) with 1 cm matched quartz cells was also used. A Sonorex Ultrasonic Bath (Bandelin, Berlin, Germany) degassed all of the solutions after centrifugation.

A Model pH 301 pH/Ion meter with a Hanna HI 1131 glass electrode measured the solution's pH (Hanna Instruments, Sarmeola di Rubano, Italy). A Supelclean LC-18 (Supelco Inc., Beilefonte, PA, USA) solid phase column performed syrup analysis.

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Chemicals

Cetirizine.2HCl (CTZ) and Zyrtec® Tablets, Zyrtec® Syrups, and Zyrtec® Drops were supplied by UCB Pharma A.Ş. (Istanbul, Turkey). Analytical grade sodium phenobarbital (IS), borax, methanol, and sodium hydroxide were provided by Merck GmbH (Darmstadt, Germany). All water was double distilled in glass apparatus in our laboratory.

Procedures

Preparation of the Solutions

A stock solution of 1.15×10^{-3} M CTZ was prepared in an aqueous methanol (10%, v/v) solution. Dilutions were prepared from the stock solution using the electrolyte solution for CE. A 1.01×10^{-3} M concentration of sodium phenobarbital (internal standard, IS) was dissolved in water. Although there were no reports of photosensitivity, all solutions were stored in light free conditions.

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Running Buffer

Borate, 10 mL of 100 mM and 10 mL of methanol were combined in a beaker of 70 mL of double distilled water. The pH was adjusted to 8.5 by the addition of 1 M HCl. Double distilled water was added for a total of 100 mL. It was then degassed in a sonicator for five minutes and transferred to vials.

CE Conditions

An uncoated fused silica capillary (total and effective lengths of 85 cm and 65 cm, respectively, and internal diameter of 75 μm) was used throughout the study. The capillary was conditioned and cleaned with solutions of 0.1 M sodium hydroxide (2 min.), water (2 min.), and a separation buffer (3 min.). All experiments were conducted with an applied voltage of +28 kV (330 $V \cdot cm^{-1}$); the resulting current in the capillary was around 24 μA. A sample was injected through the capillary for 10 seconds at low hydrodynamic injection mode, and separated for 10 minutes in the separation running buffer. Signals were recorded at 200 nm.

Solid Phase Extraction (SPE) Procedure

The solid phase extraction of Zyrtec Syrup was conducted using a Supelclean LC-18 solid phase column. The column was conditioned according to the manufacturer's specifications.

To extract the CTZ, 2–3 drops of diluted NaOH solution was added to 5 mL of Zyrtec syrup®, which was then passed through the LC-18 solid phase (SP) column. The column was then washed with double distilled water. Methanol, 5 mL, was used to elute the materials from the column. The CTZ resulting solution was collected, and 5 mL of water was added. A 0.5 mL aliquot of the recovered syrup was withdrawn and transferred to a test tube. IS, 1 mL, and 8.5 mL of buffer solution were added, the entire combination was vigorously shaken, and then injected to the CE.

Spectrophotometric Studies

A standard stock solution of CTZ was prepared in an aqueous solution of methanol (20%, v/v). The calibration solutions were prepared in the range of 9.68×10^{-6}– 7.74×10^{-5} M by diluting the stock solution maintaining the proportions of water to methanol. Their absorbance values were read individually at 231.3 nm. The calibration equation was plotted by the absorbance values against the concentration of CTZ. The regression equation was fitted to the [$A = 15479\ C\ (M) + 0.0125$; $r^2 = 0.9998$] formula. Here, A and C (M) symbolize the absorbance and concentration as molarity, respectively.

RESULTS AND DISCUSSION

Efficiency of the Method

The solubility of compounds is very important during the method development for analytical studies. Since CTZ has low solubility in aqueous solutions, its stock solution was prepared by adding methanol to prevent turbidity to standard CTZ, shaken vigorously, and then the volume increased with double distilled water.

By varying the concentration of the buffer component and pH, 10 mM borax was determined to be an appropriate electrolyte concentration for the resolution of CTZ. Because it has a greater viscosity than water, methanol was added to minimize the time necessary for analysis.

Ultimately, an electrolyte mixture consisting of 10 mM borate and 10 percent methanol (at pH 8.5), and a low hydrodynamic injection mode of 10 seconds proved to be best.

A standard CTZ solution was applied to the instrument, and appeared at 6.7 min. Several possibilities for IS were investigated; phenobarbital sodium produced the best results for the goals of this study with a peak appearing at 8.9 min. The electroosmosis signal consistently appeared at around 5.3 min. In the above mentioned conditions, the mobility of the analytes was calculated to be 0.012 and $0.023\,mm^2.s^{-1}.V^{-1}$ for CTZ and IS, respectively.

An electropherogram of CTZ (1.15×10^{-4} M) and IS (2.01×10^{-5} M) is shown in Fig. 2.

The reasonable time burden of the analysis deemed the conditions as optimal for the study's goals and the validity of the method was realized.

Repeatability

The precision tests were conducted by preparing fixed concentrations of CTZ and IS, which were injected into the CE on consecutive days. Based on the results, the area of the peaks and peak normalizations (PN = peak area/peak retention time), and the rate of the peak normalizations ($R = PN_{CTZ}/PN_{IS}$) were evaluated. The experiments' precision increased in accordance with the rate of normalization. This can be attributed to the fact that the use of peak normalization and the processing of the internal standard become more repeatable by the use of the internal standard method. The results of repeatability tests, executed as intra-day and inter-day precision, are demonstrated in Table 1.

The RSD values, which represent the repeatability, were almost perfect. In the analytical studies, these values were proven in the range precision tests.

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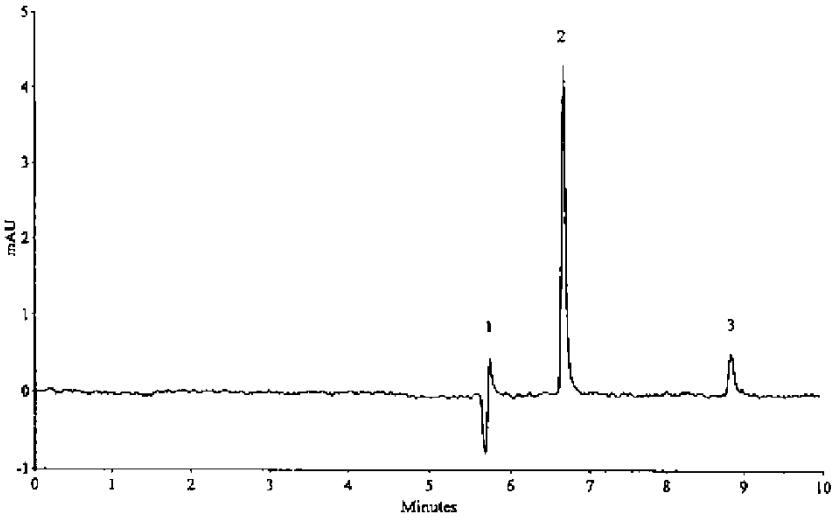

Figure 2. The electropherogram of CTZ (1.15×10^{-4} M) and phenobarbital as IS (2.01×10^{-5} M) in the electrolyte solution consisting of 10 mM borate and 10% methanol at pH 8.5, injecting the sample 10 seconds at low pressure, applying potential of 28 kV (direct polarity), detecting at 200 nm. 1— EOF; 2— CET; 3— IS.

Linearity

The linearity was examined in the concentration range of 2.30×10^{-5} and 1.15×10^{-4} M CTZ. Three sets having a fixed amount of IS (2.01×10^{-5} M) and five dilutions (with increasing concentrations of CTZ) were prepared. On consecutive days, each set was injected into the instrument and their electropherograms were recorded in the optimum conditions. The peak normalization values were calculated as normal and the data were

Table 1. The repeatability results of 1.15×10^{-4} M CTZ and 2.01×10^{-5} M IS regarding rate of peak normalization values (PN_{CTZ}/PN_{IS}) for intra and inter-day

	Intra-day results (n = 6 each)			Inter-day results (n = 18)
	First day	Second day	Third day	
$\bar{X}$	7.90	7.84	7.70	7.84
SD	0.21	0.30	0.21	0.21
RSD %	2.60	3.79	2.70	2.71
$\pm$CL ($p = 0.05$)	0.22	0.31	0.22	0.11

Abbreviations: $\bar{X}$ is mean, SD is standard deviation, RSD % is relative standard deviation, CL is confidence limits at (p = 0.05).

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evaluated as intra and inter-day results. The results of the linearity and their statistical elements are shown in Table 2.

Limit of Detection (LOD) and Limit of Quantification (LOQ)

After gathering the results of repeatability and linearity, it is possible to calculate the values of the limit of detection (LOD) and the limit of quantification (LOQ). These can be achieved by multiplying [standard deviation of regression equation, $(SD)_r$/slope of the calibration equation, a] by 3.3 and 10, respectively. They were found to be 5.45×10^{-6} M for the LOD and 1.60×10^{-5} M for the LOQ.

The LOD values of all the methods,[4–20] except the LC-MS,[21–24] are in the range of 0.1 and 5 $\mu g \cdot mL^{-1}$, and this study's result (2.4 $\mu g \cdot mL^{-1}$) is in this range.

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Accuracy of the Method for the CTZ Tablet

By preparing a synthetic recipient composition, the accuracy and precision, (corresponding to the effect of the inactive ingredients of the tablet formulation on the determination of CTZ) were examined.

The Zyrtec® Tablet contains titanium dioxide in addition to other common ingredients (detailed under 'application of the method CTZ preparations'). To examine the accuracy, individual tubes of three concentrations (2.1×10^{-5}, 4.24×10^{-5} M and 7.00×10^{-5} M) of CTZ were combined with IS, diluted with run buffer, shaken, and injected into the CE system (n = 8). Three duplicate amounts of CTZ solution were spiked into individual tubes containing inactive ingredients, shaken, and left undisturbed for 30 minutes. Then, IS was added, the mixture was diluted with run buffer, and injected into the CE system (n = 8). Using a calibration equation, the

Table 2. Calibration results of CTZ (M) regarding rate of peak normalization values of PN_{CTZ}/PN_{IS} against concentration of CTZ (10 sec injection at low pressure, applying 28 kV, in the direct polarity, detecting at 200 nm)

	Intra-day			Inter-day
	Day 1 (n = 5)	Day 2 (n = 5)	Day 3 (n = 5)	Whole days (n = 15)
a	73650 ± 329	73000 ± 2431	71170 ± 1657	72610 ± 990
b	−0.12	−0.13	−0.08	−0.11
r	0.9999	0.9983	0.9991	0.9988

data were determined; from the equation of the absolute value of the [(found concentration-spiked concentration)/spiked concentration × 100], the accuracy was calculated. The results are shown in Table 3.

The acceptance criterion for the accuracy is not higher than 15% deviation from the nominal value, and for precision not more than a 15% coefficient of variance (C.V.).[27] As the accuracy and precision results obtained are in accordance with this criterion, it can be concluded that the ingredient of the Zyrtec® Tablet does not interfere with the proposed method.

Based upon the results of validation, precise determination of CTZ could be achieved, in the conditions outlined.

Application of the Method to CTZ Preparations

Capillary Electrophoretic Studies

The CE method developed in this study was applied to Zyrtec® Tablets, Syrups, and Oral Drops. In addition to CTZ, the ingredients for these products include, titanium dioxide in the tablets, methylparaben, propylparaben, sorbitol, saccharine sodium, and a fragrance in the syrup; and methylparaben, propylparaben, and saccharin sodium in the oral drop.

A tablet was dissolved in an aqueous solution 10% methanol and centrifuged. A specified amount of the resulting liquid was removed, blended with a fixed amount of IS and buffer solution, and injected into the CE system. Using integration outputs, a very clear and well defined electropherogram appeared and quantification was realized.

In a similar trial, after the syrup preparation was diluted, IS was added and injected into the capillary electrophoresis.

Unrepeatable electropherograms for the syrup samples resulted from the presence of sorbitol and/or fragrance. To accommodate this, a common solid phase extraction (SPE) was made, and the recovered sample was injected in the same way. In return, after the application procedure, a peak relating to CTZ, methylparaben, propylparaben, IS, and saccharine sodium appeared, and very good integration was obtained.

Table 3. The results of accuracy and precision of CTZ by CE (n = 8)

Added CTZ (M)	Found CTZ (M) (mean ± SD)	Recovery %	Accuracy %	RSD %
2.10×10^{-5}	$1.98 \times 10^{-5} \pm 1.3 \times 10^{-6}$	94.8	−5.2	0.87
4.24×10^{-5}	$4.28 \times 10^{-5} \pm 2 \times 10^{-7}$	100.9	0.9	3.21
7.00×10^{-5}	$6.75 \times 10^{-5} \pm 1.1 \times 10^{-6}$	96.4	−3.6	4.36

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No difficulties were encountered in the determination of CTZ in the oral drop. A dilution was made, IS was added and as with previous trials, it was injected. No interference was evident.

Regarding the CTZ forms, the CE method is directly applicable to tablet and oral preparations. For quantification, slight cleaning of the syrup form is required. Peaks were detected in the electropherograms of the oral drop and the syrup forms of CTZ. These showed the following: CTZ, propylparaben, methylparaben, phenobarbital IS (added during trials) and saccharin sodium. The electropherograms of the tablet, syrup, and oral drop are shown in Fig. 3.

Spectrophotometric Studies

Though there is a risk of absorbing UV light in wavelengths under 254 nm, the determination of CTZ in tablets was realized at 231.1 nm. By using the calibration equations, their concentrations were calculated. The producer of CTZ preparations (Zyrtec® tablet, syrup, and drop) confirms the ingredients as mentioned above.

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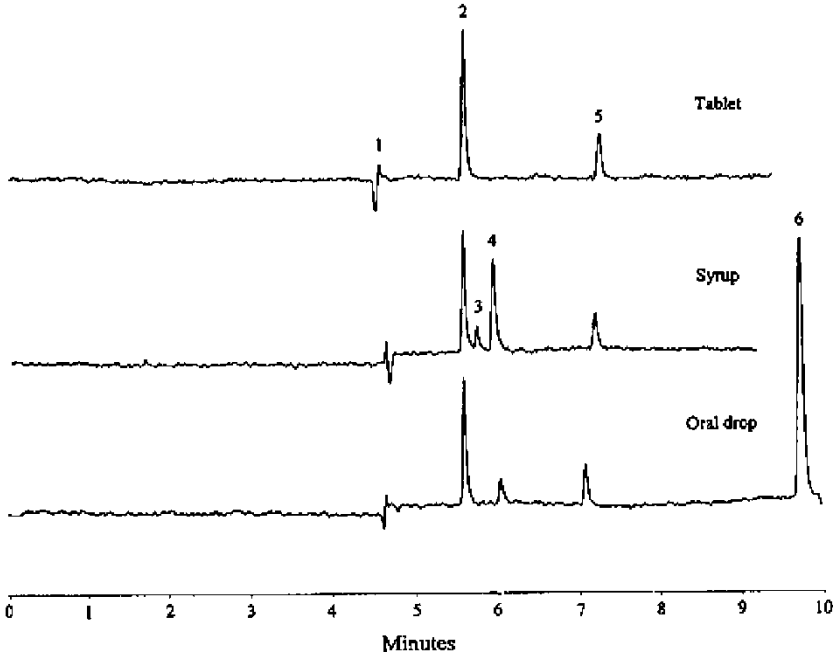

Figure 3. The electropherogram of tablet, syrup and oral drop and phenobarbital as IS (2.01×10^{-5} M) in the run buffer solution consisting of 10 mM borate and 10% methanol at pH 8.5, injecting the sample 10 seconds at low pressure, applying potential of 28 kV (direct polarity), detecting at 200 nm. 1—EOF; 2—CET; 3—Propylparaben; 4—Methylparaben; 5—IS; 6—Saccharine.

At the indicated wavelength, the tablets containing titanium dioxide and the ingredient do not affect the determinations of CTZ. Zyrtec® Syrup and Drops, however, have parabens and artificial sweeteners (that have n and π antibonds), which cause absorption far from the ultraviolet region, and thus affect the absorption spectrum of CTZ. As a result, the determination was realized only in the tablet form.

The complete results of the pharmaceutical preparations of CTZ are demonstrated in Table 4.

Satisfactory quantification results were obtained by the presented method. Though the dosage forms of CTZ (such as syrup and oral drops) have certain ingredients as soluble materials that affect the spectrophotometric quantification, no problems were encountered with the tablet form. Since CE is a method that resolves and determines the analyte, quantification was successfully achieved. Therefore, the developed method is extremely effective for analyses of this kind.

EP IV[4] has a monograph for the bulk material of CTZ, which does not contain any suggested limits for the active material of CTZ for the pharmaceutical dosage forms. Therefore, general rules for the quantification of CTZ dosage forms were employed for the acceptance criteria. While whole preparations provide official requirements as uniformity tests, a 10 percent deviation for the 10 mg tablets was allowed.

The method produced here is faster; more efficient, more cost effective, has higher resolution and separations, and has less reagent usage.[26,27] Based upon these findings, this method is an excellent option for the routine analysis of CTZ.

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Table 4. The CTZ contents which were achieved by CE and UV spectrophotometry in zyrtec tablet, syrup and oral drop

	Capillary electrophoresis CTZ preparations (n = 10)			UV-spectrophotometric only for tablets (n = 5)
	Tablet (10 mg/tablet)	Syrup (1 mg/mL)	Oral drop (10 mg/mL)	
$\bar{X}$ as (%)	100.7	98.2	100.2	98.5
SD	3.3	4.4	3.5	1.8
RSD %	3.3	4.5	3.5	1.8
t-test of significance	0.40	—	—	$t_{Table} = 2.13$ ($p = 0.05$)
F-test of significance	0.32	—	—	$F_{Table=} 4.74$ ($p = 0.05$)

Abbreviations: $\bar{X}$ is mean, SD is standard deviation, RSD % relative standard deviation.

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