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# Development and validation of a HPLC method for the determination of cetirizine in pharmaceutical dosage forms

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A rapid, simple and accurate HPLC method is described for the assay of cetirizine in commercial dosage forms. Methanol was found to be a suitable extraction solvent for tablets and for preparing solutions from drops and oral liquids. The samples were chromatographed on a Nova-Pak C18 column and UV detected at 227 nm. The elution was achieved isocratically with a mobile phase of 0.067 M phosphate buffer pH 3.40/acetonitrile (1 : 1, v/v). Ketotifen was applied as an internal standard. The method was validated for linearity, precision, accuracy and limit of detection. The recovery (mean ± SD) for tablets was 100.88% ± 0.8967, for drops 100.35% ± 0.4062 and for solutions 101.20% ± 1.1698.

## 1. Introduction

Cetirizine, 2-[4-(4′-chlorophenyl)-phenylmethyl-1-piperazinyl]-ethoxyacetic acid belongs to the antihistaminic drugs of second generation and was introduced into medical practice in 1989. This drug is an antagonist of the $H_1$ receptor, similarly to the first generation compounds in efficacy and clinical utility but its advantage lies in a lower side effect profile. Cetirizine inhibits the preliminary phase of the allergic reaction mediated by histamine, and reduces migration of demaged cells and releases/the inflammatory reaction. Also, because of its physical properties, it is excluded from the CNS to a large extent. Cetirizine does not bind to serotonin, muscarine or alpha-adrenergic receptors [1, 2].

Several methods have been used for the determination of cetirizine substance and pharmaceutical preparations. Horaguchi [3] proposed spectrophotometric and titration methods in non-aqueous media. A spectrophotometric method for the evaluation of cetirizine in syrup was elaborated also by Garg et al. [4].

For the determination of cetirizine in tablets differential spectrophotometry [5] and potentiometric [6] methods have been elaborated.

Three HPLC methods [5, 7, 8] have been employed for the estimation of cetirizine in tablets. Suryanarayana [7] described a HPLC method, where a μBondapak $C_{18}$ column and the mobile phase acetonitrile/0.01 M dihydrogen phosphate potassium (7 : 3, v/v) was used. The detector wavelength was set at 230 nm and the internal standard was 4-chlorobenzophenone. In another HPLC method acetonitrile/0.01 M dihydrogen phosphate ammonium containing 0.1% tetrabutylammonium hydrogen sulphate adjusted to pH 3.0 was used as the mobile phase; the detection was carried out at 230 nm and salicylic acid was used as an internal standard [8]. Zarapkar [5] used water/acetonitrile/triethylamine (63 : 37 : 0.2, v/v/v) as the mobile phase, set at pH 7.5 by adding orthophosphoric acid.

The purpose of this paper is to present a simple and rapid reverse phase HPLC method with UV detection for the determination of cetirizine in pharmaceutical products.

## 2. Investigations, results and discussion

A reversed-phase isocratic procedure is proposed as a suitable method for the analysis of cetirizine in tablets, drops and solutions for oral use. A mixture of 0.067 M phosphate buffer pH 3.40/acetonitrile (1 : 1, v/v) at a flow rate of 1.5 ml/min was found to be an appropriate mobile phase allowing adequate and rapid separation of analyte and internal standard (ketotifene) (retention times 2.76 min and 3.98 min, respectively). As shown in the Fig. the substances were eluted forming well shaped, symmetrical single peaks, well removed from the solvent front. The internal standard was clearly separated from cetirizine.

For quantitative application a linear calibration curve was obtained over the concentration range 5–50 μg/ml. The parameters of the calibration graph were $y = 0.01988x - 0.00180$; where y, peak area ratio of cetirizine to that of the I.S., and x, concentration of cetirizine in μg/ml; correlation coefficient $r = 0.9999$. Methanol was chosen both for the extraction of cetirizine from tablets and for dilution of the pharmaceutical preparations (drops and solution).

The selectivity of this method is shown by the fact that the excipients from tablets, drops and solution did not interfere in determining the substances analysed. The precision of the HPLC system was determined using the coefficient of variation (C.V.) of the peak areas for six injections of the standard solution. The C.V. was less than 1%. The precision of the elaborated method was determined from one lot of the finished products. The results of determinations are shown in Table 1. In order to verify the accuracy of the described method, recovery studies were carried out by analyzing model mixtures of cetirizine. The recovery of cetirizine was evaluated from 50 to 150% of the labelled tablet, 1 ml of drops and 1 ml of solution. The accuracy of the method is given in Table 2.

The limit of detection was 20 ng/ml (coefficient of variation C.V.= 4.3%). The presented HPLC method is precise,

**Table 1: Precision of the method**

| No | Amount found of cetirizine (mg) | | |
|---|---|---|---|
| | in one tablet | in 1 ml drops | in 1 ml solution |
| 1 | 10.09 | 10.02 | 1.012 |
| 2 | 10.26 | 9.98 | 0.993 |
| 3 | 10.07 | 10.00 | 1.027 |
| 4 | 10.11 | 10.02 | 1.030 |
| 5 | 10.00 | 10.12 | 0.998 |
| 6 | 9.99 | 10.05 | 1.015 |
| 7 | 10.05 | 10.07 | 1.010 |
| 8 | 10.20 | 10.04 | 1.020 |
| 9 | 9.99 | 10.00 | 1.005 |
| 10 | 10.12 | 10.05 | 1.012 |
| Mean | 10.088 | 10.035 | 1.012 |
| SD | 0.0897 | 0.0406 | 0.0117 |
| C.V. (%) | 0.89 | 0.40 | 1.16 |

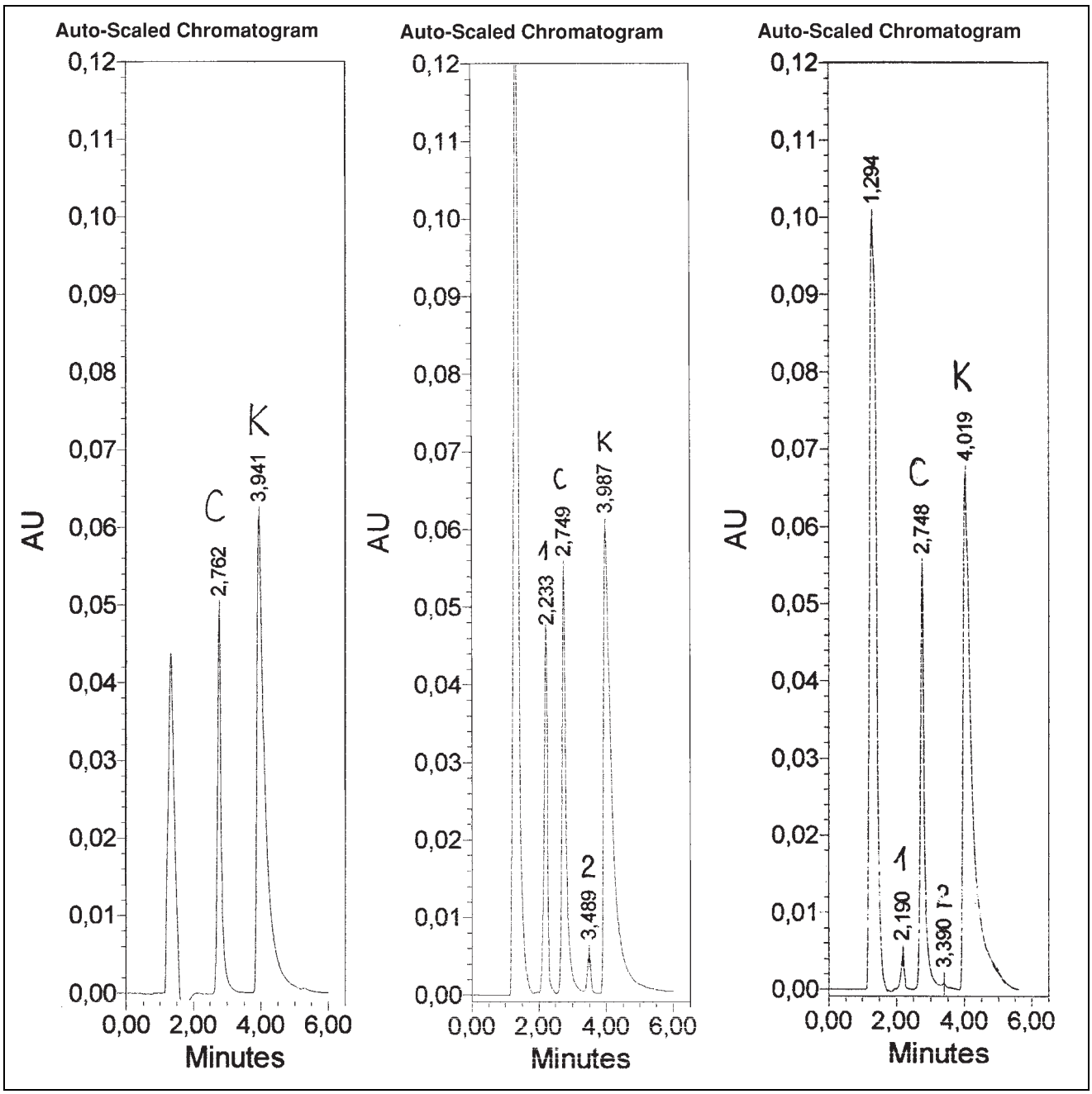


Fig.: a – Chromatogram of cetirizine after isolation from tablets; b – Chromatogram of solution for use orally; c – Chromatogram of drops for use orally; C – cetirizine, K – ketotifen (I.S.), 1,2 – undentified peaks

sensitive and accurate. The advantages of the proposed method are its short analysis time and a simple procedure for sample preparation. The elaborated method was equally applicable to the quantitative analysis of liquid and solid dosage forms. The satisfying recoveries and low coefficients of variation confirm the suitability of the proposed method for the routine analysis of cetirizine in pharmaceuticals.

**Table 2: Recovery values obtained for the determination of cetirizine in model mixtures**[a]

| Model mixture (%) | Tablets | | Drops | | Solution | |
|---|---|---|---|---|---|---|
| | Found | C.V. (%) | Found | C.V. (%) | Found | C.V. (%) |
| I (50) | 100.30 | 0.90 | 99.77 | 0.52 | 100.40 | 1.15 |
| II (100) | 99.85 | 1.10 | 100.12 | 0.78 | 100.26 | 1.06 |
| III (150) | 100.10 | 0.76 | 100.33 | 0.90 | 100.13 | 0.86 |

[a] Results are the average of five determination and are expressed as a percentage of the cetirizine added

## 3. Experimental

### *3.1. Reagents*

Cetirizine dihydrochloride (subst.) was obtained from Pharmaceutical Works "Pliva" (Krakow, Poland). Zyrtec® (10 mg of cetirizine) tablets, Zyrtec® (10 mg/1 ml) drops for use oral and Zyrtec® (1 mg/ml) solution for oral use were purchased from UCB S.A. Pharma Sector – Chemin du Foriest (Braine l'Alleud, Belgium). Ketotifen hydrogen-fumarate was purchased from Pharmaceutical Works "Polfa" (Tarchomin, Poland). Acetonitrile and methanol LiChrosolv® for chromatography (E.Merck, Darmstadt, Germany) were applied. All the other reagents were of analytical grade. The water needed in the experiment was double distilled.

### 3.2. Instrumentation

A Waters HPLC system (Milford, MA, USA) consisting of a Model 515 high-pressure pump, and a Model 2487 variable wavelength detector (UV-VIS) dual λ absorbance was used. Manual injections were made using a Rheodyne injectable valve (20 µl loop). The detector wavelength was set at $\lambda = 227$ nm. The chromatographic separations were performed at ambient temperature on a Nova-Pak C18 column (250 mm × 4.6 mm; dp = 4 µm) (Waters, Milford). The mobile phase was a mixture of acetonitrile/0.067 M phosphate buffer pH 3.40 (1 : 1, v/v), filtered and degassed prior to use, and flowing at the rate of 1.5 ml/min. The data were collected and analyzed with Millenium 32 system software on a Pentium MMX 166 MHz computer.

### 3.3. Solutions

Stock solutions (1.0 mg/ml) of cetirizine and ketotifene (I.S.) were prepared by dissolving appriopriate amounts of there substances in methanol. These solutions were stable for at last 2 months at 4 °C.

### 3.4. Chromatographic method

#### 3.4.1. Calibration procedure

From the working solution of cetirizine, volumes of 0.05–0.5 ml were pipetted. 0.4 ml of the working solution of ketotifene (I.S.) was added to each sample and made up with methanol to 10.0 ml. A volume of 20 µl of each sample was injected into the column. All measurements were repeated five times for each concentration. The calibration curve was constructed by plotting the peak area ratios of analyte to I.S. versus the respective drug concentration.

#### 3.4.2. Extraction from tablets and quantification

Ten tablets were weighed and powdered. An accurately weighed portion of the powder about 0.11 g (equivalent about of 0.010 g of cetirizine after a declaration) was extracted with methanol in a 50 ml flask by means of a reciprocating shaker for 20 min. Filtered 1.0 ml volumes of the extracts were transfered to a 10 ml measuring flask, 0.40 ml of I.S. solution (1 mg/ml) was added and made up to the mark with methanol. Then, 20 µl of sample solution was injected into the column. The procedure was repeated six times.

#### 3.4.3. Determination of cetirizine in solution for oral administration

Zyrtec solution for oral use (0.20 ml, according to the declaration 1 mg of substance/1ml) was pipetted into a 10 ml volumetric flask and 0.40 ml of I.S. solution (1 mg/1 ml) was added and made up to the mark with methanol. Then 20 µl of sample solution was injected into the column. The procedure was repeated six times.

#### 3.4.4. Determination of cetirizine in drops

Zyrtec drops (1 ml, according to the declaration 10 mg of substance/1 ml) was pipetted into a 10 ml volumetric flask and made up to the mark with methanol. From this solution, 0.2 ml were transfered to a 10 ml volumetric flask, 0.40 ml of I.S. solution (1 mg/1 ml) was added and made up to 10 ml. Then, 20 µl of the sample was injected into the column. The procedure was repeated six times.

### 3.5. Precision

The precision the elaborated method has been estimated by means of ten determinations of cetirizine in tablets, drops and solution for oral administration.

### 3.6. Accuracy

The accuracy of the method was shown by analyzing model mixtures which were obtained by adding known amounts of cetirizine to pharmaceutical preparations. The model mixtures contained 50 (I), 100 (II) and 150% (III) of cetirizine compared to the labelled drug amount. For each model mixture five determinations of cetirizine were made.

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