Citalopram (1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3-dihydro-5-isobenzofurancarbonitrile, Figure 1) is a "second generation" antidepressant drug whose pharmacological activity is based on the selective serotonin reuptake inhibition. Its efficacy is comparable to tricyclic antidepressants but it is better tolerated and is characterized by a lower risk of causing adverse effects (1). Citalopram is effective and safe for the treatment of depressive symptoms even in children and adolescents (2).

Literature data on the analysis of citalopram mostly describe the determination of citalopram in biological fluids (3). There are only a few publications concerning the determination of citalopram in pharmaceutical formulations. Gas chromatography method with flame ionization detection (4), HPLC and densitometric HPTLC methods (3) were used in this case.

In this study three new simple analytical methods for the determination of citalopram in commercial dosage forms were developed and compared.

**EXPERIMENTAL**

**Chemicals**

Citalopram hydrobromide and Cipramil tablets containing 20 mg of citalopram (quantitation for a base) were obtained from H. Lundbeck A/S (Copenhagen, Denmark). Methanol HPLC grade from E. Merck (Darmstadt, Germany) was used. All the other chemicals were of analytical grade, water was double distilled.

**Apparatus**

A Prince Technologies B.V. CE System (Emmen, Netherlands) with a Bischoff Lambda 1010 UV-VIS detector (Leonberg, Switzerland) placed at cathodic side of uncoated fused-silica capillary (Prince Tech.) with a total length of 82.0 cm (effective length 65.0 cm) and 75 µm I.D. was used. The background electrolyte (BGE) was 67 mM phosphate buffer pH 7.0. The sample solutions were loaded into the capillary by pressure injection at 20 mbar for 0.1 min. The power supply was operated in the constant-voltage mode at 30 kV and the capillary was kept at 30.0°C. The detection was carried out at λ = 239 nm. The data were recorded and analyzed with Dax software.

Before use the new capillary was purged with 0.1 M sodium hydroxide for 10 min, 0.1 M sodium hydroxide for 10 min and water for 5 min. Every day at the start and the end of the work the capillary was rinsed with 0.1 M sodium hydroxide for 10 min. Before each electrophoretic run the capillary was rinsed with 0.1 M sodium hydroxide for 2 min and with BGE for 2 min.

The spectrophotometric analyses were performed on a Perkin-Elmer GmbH (Rodgau-Jugelsheim, Germany) double-beam spectropho-
tometer using 1 cm quartz cuvettes. The measurements were carried out at the wavelength of 239 nm in the case of direct spectrophotometry and at 210 nm in the case of derivative spectrophotometry. In derivative spectrophotometric method the second derivative of the absorbance spectra and peak-zero (P-0) technique of measuring were used.

**Analytical procedure**

Citalopram stock solution at a concentration of 1.0 mg/mL (as a base) was prepared by dissolving appropriate amount of citalopram hydrobromide in methanol. This solution was stable for at least three months at 4°C. The working solutions of citalopram at a concentration of 0.1 mg/mL were prepared by diluting the stock solution with the double distilled water for CZE method and with the 0.1 M HCl for spectrophotometric methods.

**Capillary zone electrophoresis**

From the working solution of citalopram the volumes of 0.5-5.0 mL were pipetted to a 10 mL volumetric flasks and filled up to the mark with double distilled water. Next, the samples were injected into the CE system. All the measurements were repeated six times for each concentration and the calibration curve was set up by plotting the peak area values against the drug concentration.

The extraction of citalopram from tablets was made by using twenty Cipramil tablets. The tablets were accurately weighed and triturated to fine powder and amount equivalent to 11 mg of citalopram (as a base) was extracted with methanol in a 25 mL volumetric flask. 0.5 mL volume of the filtered extract was transferred into a 10 mL volumetric flask and filled up to the mark with 0.1 M HCl. The procedure was repeated six times and the samples were measured similarly as the standard solutions.

**Spectrophotometric methods**

From the working solution of citalopram the volumes of 0.2-1.2 mL were pipetted to 10 mL volumetric flasks and filled up to the mark with 0.1 M HCl. Next, the samples were measured at \( \lambda = 239 \) nm (direct spectrophotometry) and at \( \lambda = 210 \) nm (derivative spectrophotometry – second order) and the calibration curves were set up by plotting absorbance and derivative of absorbance against the drug concentration. All measurements were repeated six times for each concentration.

The amount equivalent to 8 mg of citalopram (as a base) was extracted from Cipramil powdered tablets with the mixture of methanol – 0.1 M HCl (50:50, v/v) in a 25 mL volumetric flask. 0.2 mL volume of the filtered extract was transferred into a 10 mL volumetric flask and filled up to the mark with 0.1 M HCl. The procedure was repeated six times and the samples were measured similarly as the standard solutions.

**Precision**

The precision of the elaborated methods was estimated by the means of six determinations of citalopram in powdered tablets. The percentage relative standard deviations (RSD%) of the data obtained were calculated.

**Accuracy**

The accuracy of the methods was evaluated by analyzing the model mixtures which were obtained by adding known amount of citalopram to a known amount of the powdered Cipramil tablets. The model mixtures contained 50, 100 and 150% of citalopram compared to the labeled tablet amount. The mean recoveries of the data obtained were calculated.

**RESULTS AND DISCUSSION**

CZE analysis of citalopram was carried out using UV detector set at 239 nm and uncoated fused-silica capillary. The influence of the changes of pH of BGE, as well as the changes of voltage and temperature on the electrophoretical migration of the analyzed substance was tested. The best results were achieved at pH 7.0 and 30 kV voltage at 30°C. Under these conditions the time of analysis was short (lower than 3.8 min) and the peaks were sharp and symmetric. The calibration curve was obtained by plotting the peak area values against citalopram concentration. Excellent linearity was observed in the range of 5-50 \( \mu \)g/mL \( (r = 0.9999) \) and the equation of the calibration line was \( y = 0.00334929x - 0.00000162 \) (error for the slope = 2.4 \( \times \) 10\(^{-5}\); error for the intercept = 7.5 \( \times \) 10\(^{-7}\)), where \( x \) is citalopram concentration expressed as \( \mu \)g/mL. The limit of detec-
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The extraction procedure of citalopram from the tablets by the use of methanol is very simple and effective. No interference from excipients was observed. A typical electropherogram of citalopram obtained from tablets is shown in Figure 2.

The precision of the elaborated methods is given in Table 1 and, as shown, CZE methods is characterized by good intermediate precision (RSD = 2.12%). The accuracy of the described method was verified by analyzing model mixtures of citalopram (Table 2). The results show that the mean recovery value or CZE method was 100.9% with a mean repeatability of 1.94%.

In order to select an optimal solvent for the need of the spectrophotometric methods the spectra of citalopram in methanol, 0.1 M HCl and 0.1 M NaOH were made (Figure 3). The best solvent, as shown, is 0.1 M HCl, because the spectrum of citalopram has two main absorbance bands here, as well as the highest absorbance (λ = 204 nm and λ = 239 nm). The calibration curve for direct spectrophotometry was obtained by plotting absorbance values (at λ = 239 nm against the citalopram concentration in the range of 2-12 µg/mL. A good lin-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CZE</th>
<th>Direct Spectr.</th>
<th>Derivative Spectr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean* (mg)</td>
<td>19.74</td>
<td>19.53</td>
<td>20.12</td>
</tr>
<tr>
<td>Drug found of amount declared (%)</td>
<td>98.7</td>
<td>97.6</td>
<td>100.6</td>
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<tr>
<td>SD</td>
<td>0.4177</td>
<td>0.3976</td>
<td>0.5320</td>
</tr>
<tr>
<td>RSD (%)</td>
<td>2.12</td>
<td>2.04</td>
<td>2.64</td>
</tr>
</tbody>
</table>

* n = 6

Figure 3. Ultraviolet spectrum of a 10 µg/mL citalopram standard solution 1 – in methanol, 2 – in 0.1 M HCl and 3 – in 0.1 M NaOH.
Linearity was found in the examined concentration range \((r = 0.9997)\), the equation of the calibration line was in this case \(y = 0.0573171x - 0.0270533\) (error for the slope \(= 7.3 \times 10^{-4}\); error for the intercept \(= 5.7 \times 10^{-3}\)). The limit of detection was 0.5 \(\mu g/mL\).

In the derivative spectrophotometry assays the first, second and third derivative spectra and the “peak-zero” (P-0) and “peak-peak” (P-P) techniques of measuring were examined. Good results were obtained at \(\lambda = 210-199\) nm (P-P) for the second derivative and at \(\lambda = 239-216\) nm (P-P) and \(\lambda = 216\) nm (P-0) for the third derivative, but the best conditions for quantitative analysis were found at \(\lambda = 210\) nm (P-0) for the second derivative spectra (Figure 4). The calibration curve in this case was obtained by plotting derivative absorbance values against citalopram concentration in the same range as in direct spectrophotometry (2-12 \(\mu g/mL\). The obtained linearity \((r = 0.9999)\) was better than in direct spectrophotometry, and the equation was \(y = 0.140489x + 0.0318133\) (error for the slope \(= 1.1 \times 10^{-3}\); error for the intercept \(= 8.3 \times 10^{-3}\)). The limit of detection (0.3 \(\mu g/mL\)) was also better in comparison with direct spectrophotometry. The proposed extraction procedure (by mixture of methanol – 0.1 M HCl) of citalopram from tablets, similarly to extraction procedure for CZE is simple and effective. In this case also no interference from excipients was observed.

The precision of the two elaborated spectrophotometric methods (Table 1) is good and similar to the precision of CZE method. The accuracy of the direct spectrophotometric method (Table 2) is slightly lower (mean recovery value was 96.4% with a mean repeatability of 2.17%) than the accuracy of derivative spectrophotometry (mean recovery value was 100.7% with a mean repeatability of 1.97%) and capillary electrophoresis methods. However, the comparison of the results obtained by the three elaborated methods by the use of Student’s t-test and ANOVA test (at the 95% confidence level) showed that there was no statistical difference between them.

**CONCLUSION**

The three elaborated methods (CZE, direct and derivative spectrophotometry) of the determination of citalopram in tablets are rapid, simple, precise and quite accurate for routine quality control testing of this drug. CZE and derivative spectrophotometry are more accurate than direct spectrophotometry, but this one is slightly more precise.

**REFERENCES**


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